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International Union of Basic and Clinical Pharmacology CXIII: Nuclear Receptor Superfamily—Update 2023

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ABBREVIATIONS: 9CDHRA, 9-cis-13, 14-dihydroretinoic acid; AD, Alzheimer's disease; AF1, activation function 1; AF2, activation function 2; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AQ, amodiaquine; AR, androgen receptor; AREs, androgen response elements; AR-V, androgen receptor variant; ATRA, all-trans retinoic acid; BA, bile acid; BMD, bone mineral density; Bmal1, brain and muscle arnt-like protein 1; CBP, chromatin remodeling protein; CDCA, chenodeoxycholic acid; ChIP, chromatin immunoprecipitation; CNS, central nervous system; COUP-TF, chicken ovalbumin upstream promoter transcription factor; CQ, chloroquine; CREB, cyclic-AMP response element binding protein; CRPC, castration-resistant prostate cancer; DAX1, dosage-sensitive sex reversal adrenal hypoplasia congenital critical region on X chromosome; DBD, DNA binding domain; DC, dendritic cells; DES, diethylstilbestrol; DHI, 5, 6-dihydroxyindole; DLPC, dilauroylphosphatidylcholine; DMHCA, *N*, *N*-dimethyl-3β-hydroxy-cholenamide; DR, direct repeat; EAE, experimental autoimmune encephalomyelitis; EGF, endothelial growth factor receptor; EMT, epithelial-to-mesenchymal transition; ER, everted repeat; ERE, estrogen response element; eRNA, enhancer RNA; ERR, estrogen receptor-related receptor; ESC, embryonic stem cell; FDA, Food and Drug Administration; FXR, farnesoid X receptor; GATA, GATA binding protein; GCNF, germ cell nuclear factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GR, glucocorticoid receptor; GRE, glucocorticoid-responsive element; HAT, histone acetyltransferase; HCC, hepatic cell carcinoma; HDAC, histone deacetylase; HDX-MS, hydrogen-deuterium exchange mass spectrometry; HSCs, hematopoietic stem cells; Hsps, heat shock proteins; IBD, inflammatory bowel disease; IDP, intrinsically disordered proteins; IL, interleukin; iPSC, induced pluripotent stem cell; IR, inverted repeat; kbp, kilobase pairs; KO, knockout; LBD, ligand binding domain; LBP, ligand binding pocket; LPS, lipopolysaccharide; LRH-1, liver receptor homolog 1; LXR, liver X receptor; MaSCs, mammary stem cells; MAPK, mitogen-activated protein kinase; MCA, muricholic acid; MoDCs, monocyte-derived dendritic cells; MS, multiple sclerosis; MSCs, mesenchymal stem cells; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NCoR1, nuclear receptor corepressor 1; NFκB, nuclear factor kappa B; NGFI-B, nerve growth factor IB-like receptor; nGRE, negative glucocorticoid-responsive element; NMR, nuclear magnetic resonance; NOR1, neuron-derived orphan receptor 1; NR, nuclear receptor; NRL, neural retina leucine zipper factor; NTD, N-terminal domain; NurRE, Nur response element; NURR1, nuclear receptor-related factor 1; OPCs, oligodendrocyte precursor cells; PDX, patient-derived xenograft; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1 α; PGC-1β, peroxisome proliferator-activated receptor γ coactivator-1 β; PKC, protein kinase C; PL, phospholipid; PML, promyelocytic leukemia protein; polyQ, polyglutamine; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; PRE, progesterone response element; PTM, post-translational modification; RANKL, receptor activator of NFκB ligand; RAR, retinoic acid receptor; RARA, retinoic acid receptor alpha; RE, response element; REV-ERB, reverse-Erb receptor; RNAPII, RNA polymerase II; ROR, retinoid-related orphan receptor; RORE, retinoid-related orphan receptor response element; RTK, receptor tyrosine kinases; RXR, retinoid X receptor; SAR, structure-activity relationship; SARMs, selective modulators of androgen receptors; SCA, statistical coupling analysis; SCN, suprachiasmatic nucleus; SCN^{GABA}, suprachiasmatic nucleus GABAergic neurons; SHP, short heterodimer partner; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; SPPARMs, selective peroxisome proliferator-activated receptor modulators; SRC, steroid receptor coactivator; SREBP, sterol regulatory element binding protein; StAR, steroidogenic acute regulatory protein; STAT, signal transducer and activator of transcription; SUMO, small ubiquitin-like modifier; T2D, type 2 diabetes; T3, tri-iodothyronine; T4, thyroxine; TADs, topologically associating domains; TBP, TATA-binding protein; TF, transcription factor; TGF-β, transforming growth factor beta; T_H1, T helper 1; T_H9, T helper 9; T_H17, T helper 17; TLR, Toll like receptor; TLX, tailless homolog orphan receptor; TNFα, tumor necrosis factor-alpha; TR, thyroid hormone receptor; Tregs, regulatory T cells; TSS, transcription start site; TZD, thiazolidinedione; UFA, unsaturated fatty acids; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Wnt, Wingless/integrated.

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***Abstract*——The NR superfamily comprises 48 transcription factors in humans that control a plethora of gene network programs involved in a wide range of physiologic processes. This review will summarize and discuss recent progress in NR biology and drug development derived from integrating various approaches, including biophysical techniques, structural studies, and translational investigation. We also highlight how defective NR signaling results in various diseases and disorders and how NRs can be targeted for therapeutic intervention via modulation via binding to synthetic lipophilic ligands. Furthermore, we also review recent studies that improved our understanding of NR structure and signaling.**

***Significance Statement*——Nuclear receptors (NRs) are ligand-regulated transcription factors that are critical regulators of myriad physiological processes. NRs serve as receptors for an array of drugs, and in this review, we provide an update on recent research into the roles of these drug targets.**

I. Introduction

Nuclear receptors (NRs) form a family of 48 transcription factors (TFs) in humans that regulate diverse functions, including homeostasis, metabolism, inflammation, circadian rhythm, differentiation, and reproduction (Table 1). This superfamily of receptors functions as ligand-activated TFs, thereby providing a link between signaling molecules and transcriptional responses. The majority of NRs have known endogenous ligands, and numerous synthetic, pharmacological molecules have been developed, which facilitated their characterization. However, a subset of these receptors identified via sequence similarity have no known natural ligands (Table 1). The physiologic roles of these receptors, classified as orphan NRs, have been characterized using genetic techniques, but their potential for regulation by lipophilic ligands has remained elusive. Since NRs bind small molecules that could be synthetically modified and have roles in the physiology, progression, and molecular mechanism of disease, they are attractive pharmacological targets. Here, we have compiled recent progress in the field of NR function and pharmacology. This report is not a comprehensive review but dynamically integrates key biologic and pharmacological concepts across different sections to illustrate the complexity of NR biology and to focus on recent advances in NR regulation of physiologic and pathologic processes as well as NR-targeted drug development.

Additional details concerning each of the NRs can be obtained by referencing the IUPHAR Guide to Pharmacology website section on NRs (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=695).

A. Nuclear Receptor Architecture

The overall architecture of NRs typically comprises five functional regions, namely A/B, C, D, and E regions (Brélivet et al., 2012) (Fig. 1A). The A/B region is the highly disordered N-terminal domain (NTD), which has not been amenable to structural analysis. The NTD contains the ligand-independent activation function 1 (AF1) that permits cell and promoter-specific transcriptional cofactor—NR interactions (Pawlak et al., 2012). The NTD is a target of numerous post-translational modifications (PTMs), including acetylation, phosphorylation, and SUMOylation, which invokes structural rearrangement that drives or represses transcription activity (Anbalagan et al., 2012). The DNA binding domain (DBD; region C) is the most conserved region across all superfamily members. The DBD comprises two zinc modules or "fingers" that coordinate a zinc ion to create the canonical DNA-binding motifs. The ligand binding domain (LBD;

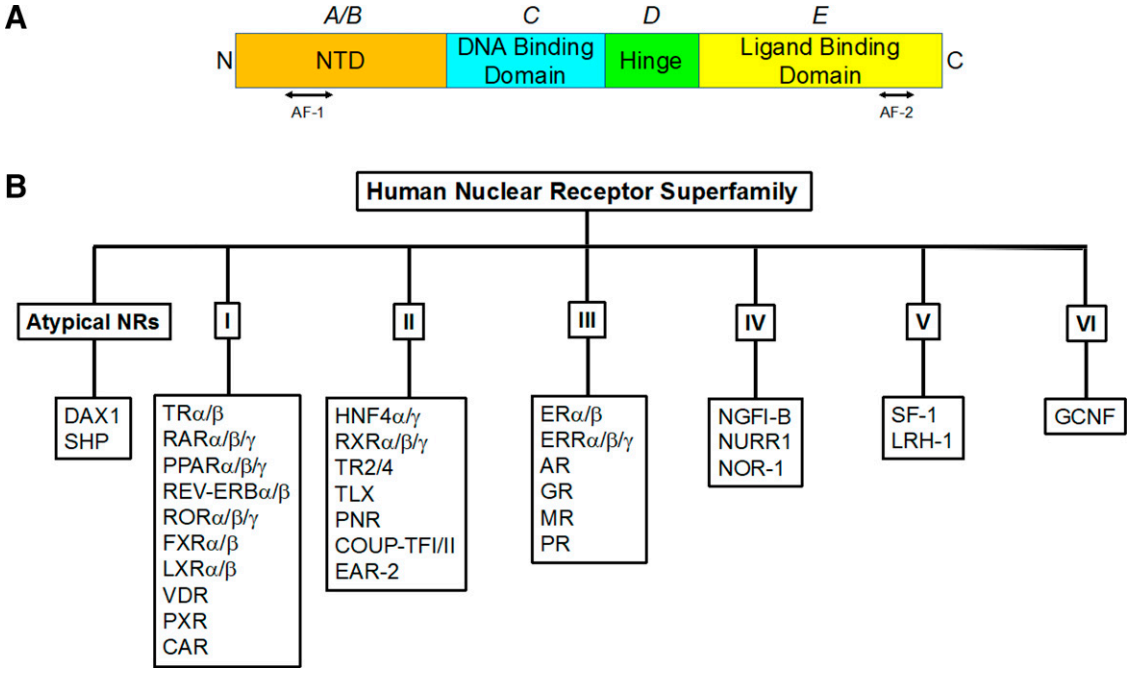

Fig. 1. The human nuclear receptor superfamily and its classification into groups.

region E) is a complex globular domain that binds to small hydrophobic signaling molecules that drive allosteric alterations in this domain that lead to signaling via altered interactions with transcriptional coregulatory proteins. The DBD and LBD are linked by the flexible hinge region (domain D) that often contains a nuclear localization signal (Haelens et al., 2007; Anbalagan et al., 2012). Region E, the LBD, is typically composed of 11 α-helices and 4 β-strands that form an alpha-helical sandwich tertiary structure and create a hydrophobic ligand-binding pocket (LBP) in the interior of the globular domain near the base of an NR LBD (Moras and Gronemeyer, 1998; Weatherman et al., 1999). With a few exceptions, NRs employ a second activation function surface (AF2) consisting of helices 3, 4, and 12 within the LBD that is ligand-dependent. The conformationally dynamic helix 12 (H12), also known as AF2 helix, changes its orientation upon ligand binding, which facilitates the recruitment of various coregulatory proteins (Moras and Gronemeyer, 1998). Most NRs have known endogenous ligands such as lipophilic vitamins (retinoids and vitamin D3), steroids, bile acids (BAs), fatty acids, and thyroid hormones that bind to the LBD, thereby triggering conformational changes to the receptor (Xu and Lambert, 2003).

NRs are directed to their target genes through direct binding to canonical DNA response elements (REs) via their DBD. Depending on the specific NR in question, the NRs may bind to DNA as homodimers, heterodimers [typically with a common NR partner, retinoid X receptor (RXR)], or monomers. NR DNA REs generally are composed of a "half-site" of the sequence 5′-RGKTCA-3′ organized as direct (DR), inverted (IR), or everted (ER) repeats (two copies) linked by a nucleotide spacer of variable length. The organization of the repeats (DR versus IR versus ER) and the spacer length specify the NR that binds to the DNA. Each "half-site" is bound by one NR of the dimer complex, and NRs that bind as monomers bind to only a "half-site" RE, although additional 5′ bases provide a degree of NR specificity. NRs have also been shown to interact with target genes indirectly by tethering to other TFs (Nagy and Schwabe, 2004; Penvose et al., 2019).

NR function is highly dependent on protein–protein interaction with transcriptional coregulators. Most NRs function exclusively as transcriptional activators by associating with transcriptional coactivators such as steroid receptor coactivators (SRC1, SRC2, and SRC3). Other coactivators beyond the SRCs have also been characterized (Lonard and O'Malley, 2007). The standard dogma for NR activation of transcription involves binding a hormone agonist to the LBD, inducing a conformational change that allows the recruitment of coactivators to the target gene. The ligand-induced conformational changes lead to the recruitment or release of various coregulators, allowing for the modulation of transcriptional activity (Tata, 2002; Lonard and O'Malley, 2007). These events typically lead to modification of the chromatin architecture by histone acetyltransferases (HATs) that neutralize positively charged lysine residues on histones, decreasing their association with the negatively charged DNA. This action increases target gene accessibility for transcription and yields "relaxed" and transcriptionally active DNA (Zhu et al., 2015; Papazyan et al., 2016). Many NRs can inhibit transcription through corepressor recruitment, such as the well-characterized

TABLE 1
Human nuclear receptor superfamily

Group	Common Name	Abbreviation	Aliases	Natural Ligand(s)
Atypical NRs	Dosage-sensitive sex reversal-adrenal hypoplasia critical region on chromosome X, gene 1	DAX1	NR0B1, AHC, AHCH, AHX, DSS, GTD, HHG, SRXY2	Orphan
	Short heterodimeric partner	SHP	NR0B2, SHP1	Orphan
I	Thyroid hormone receptor-α	TRα	NR1A1, THRA	Thyroid hormones
	Thyroid hormone receptor-β	TRβ	NR1A2, THRB	Thyroid hormones
	Retinoic acid receptor-α	RARα	NR1B1, RARA	Retinoic acids
	Retinoic acid receptor-β	RARβ	NR1B2, RARB	Retinoic acids
	Retinoic acid receptor-γ	RARγ	NR1B3, RARG	Retinoic acids
	Peroxisome proliferator activated receptor-α	PPARα	NR1C1, PPARA	Fatty acids
	Peroxisome proliferator activated receptor-δ	PPARδ	NR1C2, PPARD, PPARβ	Fatty acids
	Peroxisome proliferator activated receptor−γ	PPARγ	NR1C3, PPARG	Fatty acids
	Reverse-Erb-α	REV-ERBα	NR1D1, EAR1	Heme
	Reverse-Erb-β	REV-ERBβ	NR1D2, EAR-1R	Heme
	Retinoic acid-related orphan-α	RORα	NR1F1, RORA	Sterols
	Retinoic acid-related orphan-β	RORβ	NR1F2, RORB	Sterols
	Retinoic acid-related orphan-γ	RORγ	NR1F3, RORC	Sterols
	Farnesoid X receptor-α	FXRα	NR1H4, BAR, HRR1	Bile acids
	Liver X receptor-α	LXRα	NR1H3, LXRA	Oxysterols
	Liver X receptor-β	LXRβ	NR1H2, LXRB	Oxysterols
	Vitamin D receptor	VDR	NR1I1, PPP1R163	1α,25-dihydroxyvitamin D3
	Pregnane X receptor	PXR	NR1I2, SXR, BXR	Endobiotics, xenobiotics
	Constitutive androstane receptor	CAR	NR1I3, CAR1, MB67	Androstenol, androstanes, xenobiotics
II	Hepatocyte nuclear factor-4-α	HNF4α	NR2A1, HNF4A	Fatty acids
	Hepatocyte nuclear factor-4-γ	HNF4γ	NR2A2, HNF4G	Fatty acids
	Retinoid X receptor-α	RXRα	NR2B1, RXRA	9-cis retinoic acid
	Retinoid X receptor-β	RXRβ	NR2B2, RXRB, RCoR-1	9-cis retinoic acid
	Retinoid X receptor-γ	RXRγ	NR2B3, RXRG, RXRC	9-cis retinoic acid
	Testicular receptor 2	TR2	NR2C1	Orphan
	Testicular receptor 4	TR4	NR2C2, TAK1	Unsaturated fatty acids
	Tailless homolog orphan receptor	TLX	NR2E1, TLL, XTLL	Orphan
	Photoreceptor cell-specific nuclear receptor	PNR	NR2E3, RNR, ESCS	Orphan
	Chicken ovalbumin upstream promoter-transcription factor I	COUP-TFI	NR2F1, COUPTFA, SVP44, COUP-TF1	Orphan
	Chicken ovalbumin upstream promoter-transcription factor II	COUP-TFII	NR2F2, COUPTFB, SVP40, COUP-TF2	Orphan
	V-ErbA-related protein 2	EAR-2	NR2F6, ERBAL2	Orphan
III	Estrogen receptor-α	ERα	NR3A1, ESR1, ESRA	Estrogens
	Estrogen receptor-β	ERβ	NR3A2, ESR2, ESRB	Estrogens
	Estrogen Receptor-related receptor-α	ERRα	NR3B1, ERR1, ESRRA	Cholesterol, estradienolone
	Estrogen Receptor-related receptor-β	ERRβ	NR3B2, ERR2, ESRRB	Orphan
	Estrogen Receptor-related receptor-γ	ERRγ	NR3B3, ERR3, ESRRG	Estradienolone
	Androgen receptor	AR	NR3C4, DHTR, AR8	Androgens
	Glucocorticoid receptor	GR	NR3C1, GCCR, GCR	Glucocorticoids
	Mineralocorticoid receptor	MR	NR3C2, MCR, MLR	Mineralocorticoids and glucocorticoids
	Progesterone receptor	PR	NR3C3, PGR	Progesterone
IV	Nerve growth factor 1B	NGFI-B	NR4A1, NUR77, GFRP1	Unsaturated fatty acids
	Nurr-related factor 1	NURR1	NR4A2, RNR1, NOT	Unsaturated fatty acids, 5,6-dihydroxyindole
	Neuron-derived orphan receptor 1	NOR-1	NR4A3, CHN, CSMF	Orphan
V	Steroidogenic Factor 1	SF-1	NR5A1, FTZ1, ELP	Phospholipids
	Liver receptor homolog-1	LRH-1	NR5A2, FTZ-F1beta	Phospholipids
VI	Germ cell nuclear factor	GCNF	NR6A1, RTR, CT150	Orphan

NR corepressor 1 (NCoR1) or silencing mediator of retinoic acid and thyroid hormone receptor (SMRT).

In contrast to the coactivators associated with HAT activity, the corepressors recruit histone deacetylases (HDACs). The HDACs modify histones to allow positively charged lysine residues on chromatin to attract negatively charged DNA, resulting in densely packed DNA and decreased target gene transcription (Jetten and Cook, 2020). Transcriptional regulation by coregulator recruitment and chromatin accessibility is extensively examined in *Subgroup III*. Many NRs interact with either coactivators or corepressors, even in the absence of ligands displaying constitutive activity at their target genes. Ligand binding may either increase or decrease

binding to the coregulators or even switch the coregulator binding type (from coactivator to corepressor or vice versa). These situations provide a very large dynamic range for NR regulation of the transcription of a target gene.

B. Nuclear Receptor Classifications

The first NRs identified were steroid receptors such as estrogen receptor (ER), progesterone receptor (PR), and glucocorticoid receptor (GR), and their characterization was biochemical in nature, driven by the development of radiolabeled high-affinity ligands. Over several years, it became clear that steroid receptors regulated specific mRNA levels in a hormone-dependent manner, but the field burst with activity with the application of molecular cloning technology in the 1980s and 1990s when the superfamily of highly related receptors (the NR superfamily) was identified. Beyond the steroid receptors, it was found that retinoid, vitamin D, and thyroid hormone receptors (TRs) belonged to the same class of receptors. Furthermore, an array of orphan receptors were identified based on sequence similarity to these receptors that would become the focus of many investigators searching for their natural signaling molecules (Petkovich et al., 1987; Evans, 1988).

NRs are restricted to metazoans, and although 48 NRs have been identified in humans, other species may contain more (e.g., *C. elegans* have >300 and mice have 49) or fewer (e.g., *Drosophila* have 24) members. The NRs are organized into seven families based on homology, and here, we focus on human NRs (Fig. 1B) (Owen and Zelent, 2000; Germain et al., 2006). Group I is composed of a large number of NRs, including the TRs, retinoic acid receptors (RARs), vitamin D receptors, peroxisome proliferator-activated receptors (PPARs), reverse-Erb receptors (REV-ERBs), retinoid-related receptor orphan receptors (RORs), constitutive androstane receptor, pregnane X receptors, farnesoid X receptors (FXRs), liver X receptors (LXRs). Group II includes the RXRs, chicken ovalbumin upstream promoter TFs (COUP-TFs), hepatocyte nuclear factor-4 receptor, tailless homolog orphan receptor, photoreceptor cell-specific NR, and testicular receptors 2 and 4. The Group III subfamily consists of the steroid receptors [ER, androgen receptor (AR), GR, PR, and mineralocorticoid receptor) as well as the ER-related receptors (ERRs). Group IV includes nerve growth factor-induced clone B group of orphan receptors [nerve growth factor IB-like receptor (NGFI-B), nuclear receptor-related factor 1 (NURR1), and neuron-derived orphan receptor 1 (NOR1)]. Group V is a small group that consists of the liver receptor homolog-1 (LRH-1) and steroidogenic factor 1. Group VI is a subfamily with germ cell nuclear factor (GCNF) as the sole member. Group 0 includes the "atypical" receptors that lack a DBD but have a classic LBD and is composed of two members: the dosage-sensitive sex reversal-adrenal hypoplasia congenital critical region on the X chromosome, gene 1 (DAX1) and small heterodimer partner (SHP). Although these two NRs lack a DBD, they appear to bind to other NRs to modulate transcription (Heery et al., 1997; Borgius et al., 2002).

II. Subgroup I

Subgroup I is the largest NR subfamily in which most of the members have known endogenous ligands (Tang and Gudas, 2011; Tyagi et al., 2011; Brent, 2012; Kojetin and Burris, 2014). In this section, we summarize recent developments on TRs, RARs, RORs, REV-ERBs, and PPARs and discuss their physiologic roles and their potential as therapeutic targets for the treatment of various diseases.

A. Thyroid Hormone Receptors (TRα-NR1A1, TRβ-NR1A2)

TRα and TRβ serve as the physiologic receptors for thyroxine (T4) and tri-iodothyronine (T3) produced by the thyroid gland. Thyroid hormones play essential physiologic roles in brain development and function, metabolic homeostasis, sympathetic nervous system activity, and bone growth and turnover. TR signaling abnormalities are frequent and mainly arise from abnormal production of thyroid hormones. Currently approved medications effectively normalize hormone levels and restore most of the affected physiologic functions. Other types of thyroid diseases originate from genetic mutations of one or, in extremely rare cases, both TR isoforms. These conditions are less understood and more difficult to treat. This section emphasizes the importance of TR structural integrity, isoform and tissue-specific functions, and the regulation of their transcriptional activity.

1. Mutations in Human THRA and THRB Genes. TR-encoding genes (Sap et al., 1986; Weinberger et al., 1986) are designated as *Thra* and *Thrb* in mice or *THRA* and *THRB* in humans (*NR1A1* and *NR1A2*, respectively). *Thra* encodes the TRα1 receptor, whereas *Thrb* encodes two receptor isoforms, TRβ1 and TRβ2, which differ only in their NTD upstream of the DBD and LBD. While TRα1 and TRβ receptors play overlapping roles, tissue-specific studies report distinct and even opposite functions.

Abnormalities in the *THRB* gene are implicated in resistance to thyroid hormone syndrome β (Refetoff et al., 1967; Dumitrescu and Refetoff, 2013). Most patients with thyroid hormone syndrome carry a pathogenic variant of the *THRB* gene that leads to a TRβ1 structure unable to bind T3, recruit coactivators, or release corepressors. Given that TRβ1 is a part of the hypothalamic–pituitary axis, its malfunction disrupts the negative feedback loop. This leads to the abnormal release of thyroid hormones available to intact TR isoforms. As a result, these patients present a state of hypermetabolism (elevated resting energy expenditure) (Mitchell et al., 2010).

Several types of mutations in the *THRA* gene were also identified and associated with hypothyroid-like symptoms, including cognitive retardation, delayed bone development, and constipation, although there are only marginal changes in serum levels of thyroid hormone. (Bochukova et al., 2012; van Mullem et al., 2012, 2013; Moran et al., 2013). These hypothyroid-like symptoms arise from a significant loss in T3 binding affinity to TRα1, thus reducing receptor transcriptional activity (Moran et al., 2014). The contrasting phenotype may be explained by TRα1 versus TRβ1 patterns of expression (Saponaro et al., 2020). The mutations in *THRA* and most in *THRB* are heterozygous and are associated with the dominant inheritance of disease. Homozygous or compound heterozygous mutations in *THRB* are rare but, compared to heterozygous mutations, exacerbate defects in the pituitary–thyroid axis and mental and sensory function (Ferrara et al., 2012; Weiss et al., 2012).

2. Functions of TR Isoforms in Mouse Models. TRs promote various tissue and isoform-specific functions. TRβ2 induces cone photoreceptor differentiation, which mediates color vision (Ng et al., 2011). However, TRβ2 also mediates cone cell death if stimulated excessively by T3 (Ng et al., 2010). The role of TRβ2 in cone viability opens a window for novel pharmacological interventions to counter retinal degeneration. With this view, inhibition of thyroid hormone synthesis mitigated cone loss in mouse models of retinal dystrophy (H. Ma et al., 2014). It has also been proposed that human retinoblastoma originates from TRβ2-positive cone-like precursor cells (X. L. Xu et al., 2009).

In the brain, TRα1 promotes diverse functions (Bernal, 2007; Richard et al., 2020), including neurotransmission and electrical activity (Hadjab-Lallemend et al., 2010). In the cerebellum, TRβ1 contributes to structural development (Portella et al., 2010), whereas TRα1 promotes Purkinje cell, Bergman glia (Avci et al., 2012; Fauquier et al., 2014), and oligodendrocyte development (Picou et al., 2012). In the cerebral cortex, TRα1 is more active than TRβ1 (Gil-Ibañez et al., 2013; Chatonnet et al., 2015). TRβ1/2 also promotes cochlear differentiation for the development and maintenance of auditory function (Ng et al., 2015). Brain TRα1 signaling plays an instrumental role in autonomic control of the cardiovascular system (Mittag et al., 2013). At the peripheral level, TRs impact resting energy expenditure by inducing adaptive thermogenesis (Ribeiro et al., 2010; Warner et al., 2013). Interestingly, TRα1 and TRβ isoforms have opposite effects on liver lipid metabolism. Indeed, mutation in TRα1 increased, whereas TRβ mutation decreased liver fat content (Araki et al., 2009).

TRα1 has a more prominent role than TRβ in bone (O'Shea et al., 2012; Bassett et al., 2014). TRα1 promotes both the development and maintenance of bone as *Thra* mutations retard ossification in juveniles but cause osteosclerosis in adults (Bassett et al., 2007). In the intestine, TRα1 can enhance intestinal tumorigenesis (Kress et al., 2010). In the skin, TRα1 and TRβ isoforms modulate keratinocyte proliferation and inflammatory responses (Contreras-Jurado et al., 2011) and act as suppressors of skin carcinogenesis (Martinez-Iglesias et al., 2009).

3. Transcriptional Activities of TR Isoforms. In the absence of T3 or T4, TRs constitutively recruit nuclear corepressors. The hormone binding leads to a conformational shift in the TR LBD that induces corepressor release and coactivator recruitment (Astapova and Hollenberg, 2013). The ratio between corepressors and coactivators determines transcriptional activity (Vella et al., 2014). TRs primarily recruit coregulators through the C-terminal LBD, although evidence suggests that the N-terminus of the TRβ2 isoform recruits alternative coregulators. Thus, the relative abundance of TRβ2 versus other isoforms may contribute to the tissue-specific effect of thyroid hormones (Hahm and Privalsky, 2013).

Differences in the isoleucine-rich CoRNR boxes in NCoR1 and SMRT are thought to promote recruitment to specific NRs (X. Hu and Lazar, 1999). TRs preferentially recruit NCoR1 to suppress transcriptional activity. This has been supported in mice where inactivation of NCoR1 enhances T3 action in many tissues (Astapova et al., 2008; Astapova and Hollenberg, 2013). Although NCoR1 may be the principal corepressor for TR, evidence suggests that SMRT may also modify TR action in the lung in mice (Pei et al., 2011).

In resistance to thyroid hormone syndrome, mutant TRβ isoforms are locked into an unliganded structure, which results in constitutive recruitment of corepressors. This may be a pathogenic mechanism in this disease. This hypothesis was supported by in vivo studies in which thyroid hormone resistance-like syndrome mice were crossed to *Ncor1* mutant mice (Fozzatti et al., 2011). The combined mutations ameliorated the thyroid hormone resistance-like syndrome phenotype. Other studies suggest a role of NCoR1 in TRα1-mediated diseases (Fozzatti et al., 2013). This work has ramifications for the therapy of diseases of resistance to thyroid hormone as it suggests that the recruitment of NCoR1 and HDAC3, the downstream molecular event repressing gene expression, is causative. In this sense, HDAC inhibitors could be therapeutic (D. W. Kim et al., 2014).

The identification of specific genomic binding sites has been limited by TR scarcity in most tissues. To overcome this issue, several genetic models were created. For instance, chromatin affinity selection in TRβ1-overexpressing liver found that most of DNA binding sites were within genes rather than promoters (Ramadoss et al., 2014). In contrast, TR α1 in the HepG2 cell line is enriched near promoters of T3-induced genes (Ayers et al., 2014). Immunoprecipitation assay from mouse tissues reported that T3 treatment stimulated the recruitment of coactivator to chromatin sites and

changes in histone acetylation (Grontved et al., 2015; Praestholm et al., 2020). In vivo experiments also confirmed the ability of ligand-bound TRβ to modify the associations of the receptor with cofactors and, in some cases, promote the recruitment of receptors to chromatin sites (Shabtai et al., 2021).

4. TR Structure and Interactions with Ligands. Structures of the LBD of each TR isoform have been solved in association with T3 and other agonists. T3 occupies a buried LBP in the core of the LBD, which condenses around the hormone to induce an active C-terminal helix 12 position that favors coactivator over corepressor recruitment. TRs can bind to DNA as monomers, homodimers, as well as heterodimers with RXR. A structure of the TRα1/RXR LBD reveals that both receptor subunits bind to cognate ligands and adopt an active conformation but that TRα1 is relatively disordered (Putcha et al., 2012). Mutant TRβ isoforms that arise in resistance to thyroid hormone display general destabilization of LBD organization, leading to decreased ligand binding. TR can accommodate some ligands that are larger than T3, including T4 and the thyromimetic GC-24, without affecting the coactivator binding surface (Togashi et al., 2005).

There are several modes of ligand selectivity for TRβ1/2. Some TRβ-selective ligands display enhanced contacts with LBP amino acids in TRβ1/2 versus TRα1 (e.g., GC-1) (Bleicher et al., 2008), whereas others exploit the selective LBP expansion of TRβ isoforms, resulting in extended ligand contacts (GC-24) or water entry into the LBP with an increased entropic contribution to ligand binding (Triac) (L. Martinez et al., 2009). A synthetic TRα1-selective agonist (CO-23) binds TRα1 and TRβ1/2 with similar affinity but selectively activates TRα1. The structural basis for this effect is not known.

No X-ray structures of TR/antagonist complexes have been solved, but hydrogen/deuterium exchange analysis of TRβ1 with the antagonist NH-3 suggests that TRβ helix 12 is displaced over the coactivator binding site (Figueira et al., 2011). A structure of the TRβ1/2 LBD with a different type of antagonist, which blocks coactivator binding via covalent modification of surface cysteine, reveals a predicted reaction intermediate at the coactivator binding surface (Estebanez-Perpina et al., 2007). T3 and T4 are frequently detected on a functionally important region of the LBD surface, raising the possibility of multiple hormone-binding sites (Souza et al., 2014).

A previous structure of a TRβ1/2 DBD dimerized with that of RXR on a direct repeat (DR) DNA element separated by four nucleotides (DR4) showed that RXR occupied the upstream half-site and revealed the heterodimer contacts (Rastinejad et al., 1995). A TRβ1/2 DBD structure on an IR palindrome element (IR6), which preferentially binds TRβ homodimers, revealed DBD homodimer contacts and evidence for cooperative assembly (Y. Chen and Young, 2010).

As yet, no full-length or multidomain structures of a TR have been reported at high resolution, but low-resolution solution structures suggest that TR DBD-LBD fragments display extended organization with separation between domains. (Figueira et al., 2007). The most recent information regarding TRs and their ligands can be accessed on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=84).

B. Retinoic Acid Receptors (RARα-NR1B1, RARβ-NR1B2, RARγ-NR1B3)

RARs (*NR1B1-3*) serve as the physiologic receptors for retinoic acid, essential vitamin A derivatives, and related retinoid compounds. There are three RAR isoforms: RARα, RARβ, and RARγ. Similar to some other NRs, RARs constitutively bind to REs as heterodimers with RXR. Here, conformational change in the AF2 region upon ligand binding generally results in the dissociation of corepressors and subsequent recruitment of coactivators to activate gene transcription. The RAR isoforms display a range of redundant and nonredundant roles. In this section, we describe isoform-specific biologic functions of RARs in development, differentiation, proliferation, and apoptosis of immune, cancer, and adult stem cells. A comprehensive report on RAR biology may be accessed in a previously published review (di Masi et al., 2015).

1. Cistromic and Binding Site-Specific Regulation of RAR. RARs predominantly heterodimerize with RXRs to bind retinoic acid REs (RAREs) to exert their biologic effects (R. M. Evans and Mangelsdorf, 2014). RAREs consist of DR 5′-AGGTCA-3′ motifs separated by one (DR1), two (DR2), or five (DR5) nucleotides (Balmer and Blomhoff, 2005; Evans and Mangelsdorf, 2014). Genome-wide studies have revealed a more complex set of noncanonical RAREs that include DR0, DR8, and IR0 (inverted consensus repeats with no separation) (Moutier et al., 2012). The RAR/RXR complex preferentially binds to these noncanonical sites in undifferentiated, pluripotent cells (Moutier et al., 2012). Electrospray ionization mass spectrometry was used to evaluate the stoichiometry of different species of RAR-DBD and RXR-DBD bound to DR0, DR1, DR2, and DR5 oligos. The inclusion of at least 1-bp spacing in the DRs favors RAR/RXR over RAR monomers. Of note, DR0 equally binds all conformations, but the lack of spacing nucleotides reduces stability between RAR and RXR molecules, thus forming "noncooperative" dimers (Osz et al., 2015; Nguyen-Huynh et al., 2016). To evaluate the dynamics of RAR and RXR binding, F9 mouse embryonic carcinoma cells were treated with all-trans retinoic acid (ATRA), an active metabolite of vitamin A that has been identified as a RAR agonist, to analyze changes in binding events at various

stages of stem cell differentiation (Chatagnon et al., 2015). Chromatin immunoprecipitation sequencing (ChiP-seq) analyses revealed that untreated and undifferentiated cells had the most significant number of DR0-overlapping RXR peaks devoid of RAR and ATRA shifted peak distribution from DR0 to DR5-enriched loci in a time-dependent manner. Formaldehyde-assisted Isolation of Regulatory elements sequencing confirmed chromatin remodeling events at some of the new RAR/RXR sites in differentiated cells. Future studies are needed to determine whether the shift from DR0 to DR5 binding sites throughout maturation reflects RAR/RXR switching from fast and transient DNA binding to more binding stability in the presence of ligands and coactivators (Brazda et al., 2014). RARs display both ligand-independent and ligand-dependent interactions with transcriptional coregulators. Microarray assay for real-time coregulator-NR interaction assays simultaneously quantified interactions between RARα-LBD/RARβ-LBD/RARγ-LBD and each of 154 coregulator NR binding motifs (Miro Estruch et al., 2017). This high-throughput analysis revealed that RARβ exhibited the highest number of coregulatory interactions in the apo state while also showing the lowest sensitivity to ATRA ligation (as judged by binding affinity changes with coregulatory motifs). Microarray assay for real-time coregulator-NR interaction assays with concurrent ATRA treatments revealed an unexpectedly high number of dose-dependent interactions. RARα elicited the most promiscuous ATRA-dependent interactions with 126 coregulator motifs. Many of these interactions have not been reported, including those with BRD8, DDX5, MEN1, and MLL2. However, these assays were exclusively conducted in vitro. In the absence of other proteins, these results may not reflect binding events in the whole organism, especially with the screen being limited to high-affinity coregulatory motifs such as the NR-box (LXXLL) and CoRNR-box (LXXI/HIXXXI/L) (Le Douarin et al., 1996; Perissi et al., 1999).

2. RAR Isoform-Specific Roles in Stem Cell Maintenance and Differentiation. RAR signaling plays a critical role in embryonic development. The ability to culture embryonic stem cells (ESCs) and to generate induced pluripotent stem cells (iPSCs) has facilitated a greater understanding of the roles of RARs in these processes. In ESCs/iPSCs, the nongenomic effects of RARγ on PI3K/AKT (L. Chen and Khillan, 2010) and Wnt (De Angelis et al., 2018) signaling promote both the induction of iPSCs from somatic cells and the maintenance of these cells in their pluripotent state (J. Yang et al., 2015). However, overstimulation of RARs by ATRA promotes ESC cell differentiation through the genomic activity of RARα/γ. Activation of these receptor isoforms promotes differentiation into neural progenitors, which eventually become GABAergic medium spiny neurons (Podlesny-Drabiniok et al., 2017). Importantly, phosphorylated RARγ2 is the only isoform that can access DR5/DR7 RAREs, and binding to these sites is required for neural lineage differentiation (Al Tanoury et al., 2014).

RARβ may also play a role in downstream events of this pathway. This is suggested by the observation that *RAR*$\beta^{-/-}$ ESCs have a reduced capacity to differentiate into pancreatic islet cells, and treatment of ESCs with the RARβ-selective agonist EC19 produced epithelial-like cells (Perez et al., 2013; Haffez et al., 2017). RARs also affect the fate of adult stem cells, such as their differentiation into mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). MSCs are mesoderm-derived stem cells that reside in the bone marrow and adipose tissue to give rise to osteoblasts, myocytes, and adipocytes (Wei et al., 2013). RARγ (Shimono et al., 2011; Green et al., 2017), and potentially RARα (Shimono et al., 2010), potently inhibit osteoblastic differentiation from MSCs, and RAR agonists show promise for treating heterotopic ossification that can occur as a result of tissue trauma (Pavey et al., 2016; Uchibe et al., 2017). MSCs also provide a supportive niche for HSCs in the bone marrow. Cre-targeted, selective RARγ knockout in Nestin$^+$ and Prrx1$^+$ MSCs of the bone marrow results in decreased and increased peripheral lymphocyte counts, respectively (C. Joseph et al., 2016; Green et al., 2018). These phenotypic traits are not well understood, although MSC-RAR signaling likely intervenes in HSC differentiation into immune cells. The roles of RARs differ depending on the HCS differentiation stage. In granulocyte-monocyte progenitors, RARα activation promotes granulocytic and, to a lesser extent, monocytic differentiation (Kastner and Chan, 2001; S. J. Collins, 2002). In more primitive HSCs, however, RAR signaling maintains quiescence and prevents stress-induced activation in a small subset of dormant HSCs to prevent exhaustion (G. Brown et al., 2017; Cabezas-Wallscheid et al., 2017). RNA sequencing analyses detected high levels of *RARB* in dormant HSCs, although another study showed that RARα-selective antagonists are sufficient to promote HSC expansion (G. Brown et al., 2017). *RARB* expression may be secondary to RARα activation, although this hypothesis has not been confirmed.

3. Predominant Role of RARα in the Maintenance of Fully Differentiated Cell Types. The contribution of RARs goes beyond stem cell specialization and persists in fully differentiated cells. In models of renal tissue injury, RARα preserves terminal podocyte differentiation and quiescence to prevent glomerulosclerosis. At the same time, both RARα and RARγ protect renal tubular epithelial cells from oxidative stress and epithelial-to-mesenchymal transition (EMT) in hypoxia-induced renal interstitial fibrosis (X. Chen et al., 2017; Y. Dai et al., 2017; L. Jiang et al., 2017; Gong et al., 2018). Recent studies pinpointed a unique function of RARα in differentiated neurons, where it

maintains synapse strength and controls long-term potentiation to preserve learning and memory function (Hou et al., 2015; Zhong et al., 2018). This aligns with the observation that vitamin A deficiency causes cognitive dysfunction (Misner et al., 2001; Cocco et al., 2002). Neonatal maternal separation, an early stressor, reduced neurologic development in rats. In these animals, the *Rara* promoter is subject to repressive methylation, which impaired neuronal differentiation in adult life (Boku et al., 2015). Finally, a microRNA, miRNA-138, is upregulated in Alzheimer's disease (AD) and stimulates tau phosphorylation by reducing RARα protein content. The resultant increase in tau phosphorylation promotes neurodegeneration. Interestingly. *RARA* (retinoic acid receptor alpha) overexpression normalized tau phosphorylation, suggesting that stimulation of RARα signaling may prevent the development and/or slow the progression of AD. (X. Wang et al., 2015).

4. RARα Modulates Dendritic Cell-Mediated T Cell Polarization. RAR signaling plays a significant role in the adaptive immunity of the gut mucosa, where immune responses must be delicately controlled to simultaneously tolerate commensal gut microbes while combating pathogenic microbes. RA skews monocyte-derived dendritic cells (moDCs) toward a $CD103^+$ lineage, which, upon antigen presentation, drives naıve T cells differentiation into regulatory T cells (Tregs), a cell subtype that inhibits proinflammatory T helper 1 and 17 (T_H1 a T_H17, respectively) cells involved in autoimmune diseases like multiple sclerosis (MS) (Larange and Cheroutre, 2016). Additionally, $CD103^+$ moDCs promote $\alpha4\beta7$ and CCR9 expression, two receptors targeting the gut mucosa. In vitro, the differentiation of murine monocytes into moDCs is potentiated by nanomolar concentrations of ATRA. RAR agonism during this differentiation assay also produced $CD1a^-/CD103^+/IRF4^-$ moDCs, a specialized cell type that blocks effector T cell responses (Bene et al., 2017). However, co-administration of ATRA and BMS19561, a RARα-selective antagonist, during moDC differentiation inhibits $CD1a^-/CD103^+/IRF4^-$ moDCs formation. In primary human moDCs, ATRA directly upregulates CD103 protein expression. However, the remainder of $CD103^-$ moDCs were equally capable of inducing Treg cells, which suggests CD103 is instead a nonfunctional marker of ATRA-induced intrinsic cell changes (Roe et al., 2017). $CD103^+$ moDCs also express RALDH1/2, the dehydrogenase enzymes responsible for ATRA biosynthesis and secretion (Coombes et al., 2007). $CD103^+$ moDC-released ATRA directly affects both naıve and stimulated T cells, which may augment the ability of moDCs to induce Treg development. For example, the *FOXP3* gene, the master TF of Treg cells, is induced when Treg cells are treated with the RARα agonist RAR568 but not when co-cultured with $CD103^+$ moDCs in the absence of ATRA (Roe et al., 2017; Goldberg et al., 2019). RARα also suppresses inflammation by inhibiting effector T cell expansion. In T_H1 and T_H17 cells, RARα directly binds to and stimulates *P2X7* receptor gene transcription to reduce their numbers, which could be highly relevant to autoimmune diseases (Hashimoto-Hill et al., 2017). Earlier studies had found that ATRA significantly reduced in vivo T_H17 development and function and reduced the clinical severity of experimental autoimmune encephalomyelitis (EAE), a murine model of MS. RAR mediated these anti-inflammatory properties by interfering with transforming growth factor beta (TGF-β) and interleukin (IL)-6/IL-21/IL-23 signaling pathways. Cell culture experiments in this study indicated that RAR may also promote Treg cell development, although ATRA treatment in EAE mice did not increase their frequency (S. Xiao et al., 2008). The anti-inflammatory benefits of RAR extend to other immune-medicated conditions. ATRA treatment suppressed the development of T helper 9 (T_H9) cells, another pathogenic T subset implicated in allergy, asthma, and even early-stage MS. A potential explanation for this is the suppression of *Il9* gene transcription, the signature cytokine of T_H9. Indeed, high-throughput sequencing of DNA occupancy (ChIP-seq) and chromatin accessibility (assay for transposase-accessible chromatin with sequencing) revealed that ATRA treatment induced RARα recruitment to the *Il9* promoter, which reduced its transcription via the ligand-dependent RARα corepressor NRIP1 (Schwartz et al., 2019). These results were corroborated in an experimental model of T_H9-induced allergic lung inflammation, where ATRA treatment ameliorated disease markers.

5. RARβ Protects Against Metabolic Disease. RAR signaling suppresses obesity by inhibiting PPARγ, the master regulator of adipogenesis (Schwarz et al., 1997; McIlroy et al., 2016). However, in further differentiated adipocytes, RAR signaling may be pathogenic. Indeed, in mature adipocytes, RARα and RARγ agonists inhibited adiponectin secretion, an adipose tissue-derived factor that protects against insulin resistance and inflammation (Landrier et al., 2017). These opposite effects can be explained by the contribution of RARβ. In fact, RARβ induces consistent cardiometabolic benefits. The RARβ-selective agonist AC261066 normalized the phenotype of several models of metabolic syndrome. To achieve this, RARβ reduces lipogenic and increases oxidative metabolism gene expression in the liver, pancreas, and kidney tissues (Trasino et al., 2016). RARβ-specific activation also prevents hepatic steatosis and fibrosis (Trasino et al., 2016). Another study indicated that this anti-steatotic effect is mediated by inhibiting hepatic stellate cell activation (Ohata et al., 1997). Finally, long-term studies showed promise for the use of RARβ-selective agonists to prevent severe sequelae of high-fat diet (HFD-induced diabetes, including reduced glomerulosclerosis, podocyte effacement, and the associated decrease in renal function, and even reduced oxidative stress in a mouse model of myocardial infarction (Marino et al., 2018; Trasino et al., 2018). Thus, RARβ appears to mediate systemic, anti-inflammatory

effects of great therapeutic interest for cardiometabolic diseases.

6. RARs in Hematologic and Solid Tumor Malignancies. The RARs are frequently implicated as either oncogenes or tumor suppressors, given their pleiotropic roles in cell stemness, proliferation, and differentiation. RAR signaling has a unique role in cancers of the hematopoietic system, especially myeloid malignancies, given that ATRA promotes the differentiation of immature myeloid cells. In acute myeloid leukemia (AML), *RARA* can inactivate chromosomal translocations or deletions, the most well-known example being promyelocytic leukemia protein (PML)-RARA (Trosclair et al., 2014), which is responsible for the clinically distinct acute promyelocytic leukemia (APL). Advances in whole genome sequencing showed a high prevalence of *RARB*-targeting translocations in APL that do not involve *RARA* (Osumi et al., 2018). APL is highly sensitive to combined ATRA and arsenic trioxide therapy, which cooperatively promotes the degradation of the PML-RARA fusion protein. Interestingly, ATRA also reduces wild-type RARα via a negative retrofeedback loop that requires functional RAR/RXR dimers and DNA binding (J. Zhu et al., 1999; Gianni et al., 2002). In differentiation programs requiring sustained RAR transcription, the presence of RAR isoforms helps offset the proteasomal degradation, which is an important consideration for the use of ATRA in non-APL forms of AML (de The et al., 2017). For example, inhibition of the methyltransferase lysine-specific demethylase 1 promotes *RARA* transcription and significantly sensitizes AML cell lines to promote their differentiation and inhibit self-renewal (Schenk et al., 2012). Similarly, a novel method for directly inhibiting RARα proteasomal degradation, which involved 2-bromopalmitate covalent binding to Cys105 and Cys174 of RARα, also sensitized non-APL AML cells to ATRA, leading to their differentiation (Y. Lu et al., 2019). AML cells may also up- or down-regulate a variety of RARα-interacting coregulatory proteins, including PRAME and UTX, respectively, to suppress RAR transcriptional activity (Bullinger et al., 2013; Rocha-Viegas et al., 2014).

RARβ is almost universally considered a solid tumor suppressor and is epigenetically inactivated by promoter methylation in a wide variety of carcinomas, including bladder, lung, ovarian, breast, prostate, esophageal, gastric, and vulvar squamous cell (Berrada et al., 2012; Dumache et al., 2012; T. Gao et al., 2013; Bhagat et al., 2014; C. Fang et al., 2015; Ju et al., 2015; Muniz-Hernandez et al., 2016; R. N. Li et al., 2014; Rotondo et al., 2018). Given its role in suppressing HCS activation, RARβ plays a unique, preventative role in hepatic cell carcinoma (HCC). RARβ also represses fibrotic marker *MLC-2* (Cortes et al., 2019). The roles of RARα and RARγ in solid cancers are not clearly defined and may rely on their nongenomic functions rather than RARβ. For example, it was recently shown that RARγ inhibits p53 transcription. This effect was entirely mediated through RARγ activation of the p85a subunit of PI3K and subsequent activation of the AKT pathway. Still, it could be blocked by a flavonoid compound that prevents RARγ:p85a interaction (W. Zeng et al., 2017). In colorectal cancer, RARγ promotes drug resistance via *MDR1* expression in a β-catenin-dependent manner (G. L. Huang et al., 2017). Given that AKT inhibits β-catenin degradation (Anderson and Wong, 2010), RARγ may similarly act via the PI3K/AKT pathway in colorectal cancer. The most recent information regarding RARss and their ligands can be accessed on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=85).

C. Retinoic Acid Receptor Related Orphan Receptors (RORα-NR1F1, RORβ-NR1F2, RORγ-NR1F3)

The retinoic acid-related orphan receptors alpha, beta, and gamma (RORα, RORβ, RORγ, or NR1F1-3) were named based on their high sequence homology to RAR (Jetten, 2009; Solt and Burris, 2012; Jetten et al., 2013). RORs have prominent roles in regulating the circadian rhythm, immune function, and neuronal development. Given their central role in pathogenic T_H17 cell development and function, as well as encouraging data on preclinical testing of ligands, the RORs have emerged as drug target candidates for the treatment of various autoimmune diseases, including MS, rheumatoid arthritis, and psoriasis. This section highlights isoform-specific roles in health and diseases, transcriptional regulation, ligand development, and challenges associated with clinical testing of novel immunotherapies.

1. ROR Tissue Distribution and Transcriptional Activity. The RORs are constitutive activators of transcription as they continuously bind coactivators. Each isoform has a differential expression pattern that confers nonredundant roles. While RORα is broadly distributed, its highest tissue expression abundance is found in the central nervous system (CNS), especially in the cerebellum and hypothalamus (Ino, 2004; Feng et al., 2015). RORβ expression was initially considered restricted to the CNS (Carlberg et al., 1994). However, it has been detected at low levels in the periphery (Z. Wen et al., 2017, 2021; Aquino-Martinez et al., 2019). Although RORγ1 and RORγ2 (RORγt) differ only by their N-terminal sequence, their expression patterns are distinct. Unlike the widely expressed RORγ1 isoform, RORγ2 is confined to immune tissues (N. Sun et al., 2021). RORs regulate target genes through DBD-dependent and DBD-independent mechanisms. In DBD-dependent regulation, RORs bind as monomers to ROR REs (ROREs), which consist of AGGTCA proceeded by a short 5′ A/T rich sequence. For example, RORα and RORγt have been proposed to bind to ROREs within the conserved noncoding region 2 to induce *Il17* gene transcription in T_H17 cells (X. O. Yang et al., 2008). Additionally, RORs can regulate target gene

transcription in a DBD-dependent fashion when it binds as a homodimer to RevDR2 sequences (two ROREs separated by two nucleic acids (Moraitis and Giguère, 1999). In DBD-independent regulation, the RORs modulate target genes by tethering to other TFs. For example, RORα regulates the transcription of *Cyp2e1* by tethering to ERRγ in hepatocytes (Y. H. Han et al., 2016). The concept of tethered-NR transcriptional regulation will be further examined in *Subgroup III*. While the DBD is highly conserved between ROR isotypes, the LBD is more variable, providing the ability to design receptor subtype-specific ligands (Kojetin and Burris, 2014).

2. RORγ Functions in the Immune System. RORγt$^+$ is expressed in LTi cells, a subset of lymphoid cells (ILC3) that play instrumental roles in lymphoid tissue development. (Kurebayashi et al., 2000; Z. Sun et al., 2000; Kiss and Diefenbach, 2012). RA regulates LTi cell maturation by directly activating RAR bound to the promoter region of the gene encoding RORγt (van de Pavert et al., 2014). RORγt regulates other ILC3 subsets in the gut required for mucosal immunity (Hoorweg et al., 2012; Serafini et al., 2014). RORγt is also the master TF of T_H17 cells. These proinflammatory T cells play a critical role in the immune response to pathogens; however, systemic elevation of T_H17 promotes autoimmunity (Ivanov et al., 2006; Nurieva et al., 2007; C. Dong, 2008; X. O. Yang et al., 2008; Jetten, 2011; S. Xiao et al., 2014). RORγt drives T_H17 cell differentiation and proliferation and increases the expression of crucial T_H17 proinflammatory cytokines, including *Ilf17a*, *Il17f*, and *Irf4* (X. O. Yang et al., 2008; F. Zhang et al., 2008; Huh and Littman, 2012; Yosef et al., 2013). RORγt deficient-mice display reduced T_H17 signature cytokine and are less susceptible to experimental autoimmune diseases and allergy-induced lung inflammation (Ivanov et al., 2006; S. L. Tilley et al., 2007; X. O. Yang et al., 2008). Inversely, RORγt overexpressing in mice developed steroid-resistant neutrophilic inflammation (Ano et al., 2013). RORγ also regulates T cell receptor signaling via direct modulation of L-phenylalanine oxidase *IL41* gene (Santarlasci et al., 2012).

3. RORα/β Function in the Brain and Retina. RORα deficiency in Purkinje cells causes cerebellar degeneration, resulting in a staggerer phenotype (B. A. Hamilton et al., 1996; Steinmayr et al., 1998). It has been hypothesized that RORα contributes to several neuropsychiatric disorders (Nguyen et al., 2010; Amstadter et al., 2013; Logue et al., 2013; Miller et al., 2013; Devanna and Vernes, 2014; Etain et al., 2014). For instance, individuals with autism spectrum disorder have reduced expression of RORα target genes (Sarachana et al., 2011).

RORβ expression is mainly restricted to areas of the CNS, particularly in the brain, retina, and pineal gland. With such tissue distribution, RORβ primarily affects motor and visual functions (Schaeren-Wiemers et al., 1997; Jetten et al., 2013). A genome-wide association study provided a correlation between RORβ expression and verbal intelligence (Ersland et al., 2012). The RORβ1 variant is required for amacrine and horizontal interneurons differentiation from retinal progenitor cells (H. Liu et al., 2013). This process involves RORβ binding to the *Ptf1a* gene. Both RORβ1 and RORβ2 also induce neural retina leucine zipper factor (NRL), a TF driving rod formation (Y. Fu et al., 2014). In turn, NRL upregulates to Nr1f2 gene expression driving an expansion of the RORβ2 pool in the retina. By forming two positive feedback loops, NRL and RORβ synergistically reinforce rod cell lineage commitment.

4. ROR Function in Metabolism and the Circadian Rhythm. RORα and RORγ both play roles in regulation of bioenergetics (Kang et al., 2007; Raichur et al., 2007, 2010; Lau et al., 2008, 2011; Y. Wang, Solt et al., 2010; Fitzsimmons et al., 2012; Jetten et al., 2013; Y. Takeda, Kang, Freudenberg et al., 2014; Y. Takeda, Kang, Lih et al., 2014). RORα is considered an exacerbator of obesity and metabolic syndrome. This is supported by studies showing that RORα-deficient mice are less prone to developing metabolic syndrome than wild-type littermates as indicated by their lean phenotype, improved inflammation profile, reduced ectopic lipid deposition, and higher insulin sensitivity (Kang et al., 2011; Lau et al., 2011). RORα impairs glucose clearance by repressing the expression of the solute carrier family 2 (facilitated glucose transporter) 4 (*SLC2A4*; GLUT4) gene in skeletal muscle (Lau et al., 2011; Fitzsimmons et al., 2012). In the liver, RORα modulates the expression of several genes involved in inflammation as well as lipid, glucose, and cholesterol metabolism (Kang et al., 2007, 2011; Wada et al., 2008; Y. Wang, Solt et al., 2010; Z. Ou et al., 2013; Pathak et al., 2013; Tuong et al., 2013). ChIP-seq, along with promoter analysis, identified arrays of genes in these metabolic pathways as direct RORα targets. Furthermore, RORα single nucleotide polymorphisms were associated with higher susceptibility to type 2 diabetes (T2D) (Gamboa-Melendez et al., 2012).

Like RORα, RORγ increases the transcription of genes that have deleterious metabolic actions (Kang et al., 2007; Raichur et al., 2007; Wada et al., 2008; Meissburger et al., 2011; Tinahones et al., 2012; Z. Ou et al., 2013; Y. Takeda and Jetten, 2013; Y. Takeda, Kang, Freudenberg et al., 2014; Y. Takeda, Kang, Lih et al., 2014). Integrative cistromic profiling identified critical regulatory genes of glycolysis and gluconeogenesis, and lipid metabolism as direct RORγ target genes (Y. Takeda, Kang, Freudenberg et al., 2014). The disturbing effects of RORγ in glucose homeostasis were corroborated in other genetic studies demonstrating a positive correlation between *RORγ* expression and insulin resistance (Meissburger et al., 2011; Tinahones et al., 2012).

5. Natural ROR Ligands. Numerous physiologic ligands for RORs that act as either endogenous agonists or inverse agonists have been identified. When the X-ray structure of RORα LBD was solved, cholesterol was discovered in the LBP (J. A. Kallen et al., 2002). Although cholesterol has been suggested to be an agonist, as well as cholesterol sulfate, definitive studies with cholesterol and cholesterol sulfate are challenging given their low affinity, including RORα agonist (cholesterol sulfate), RORγ agonists (desmosterol, zymosterol, 25-hydroxycholesterol), RORα/γ inverse agonists (7α-hydoxycholesterol, cerebrosterol), and RORγ inverse agonist (24*R*-hyroxycholesterol) (Ladurner et al., 2021). The ubiquitous presence of cholesterol and its derivatives in cellular media may be responsible for the observed endogenous activity of apo-RORα/γ in cell-based assays (J. A. Kallen et al., 2002), but this has not been compellingly demonstrated. Although the structure of RORβ LBD was solved with stearate in LBP, this lipid has no functional effect (Stehlin et al., 2001). ATRA, a RAR agonist, is an identified ligand of RORβ that acts as an inverse agonist in neuronal cells but not in other cell types (Stehlin-Gaon et al., 2003). Given that RORs carry all typical NR domains, ligand binding can result in the recruitment of both coactivators or corepressors, thus resulting in either the up- or downregulation of gene transcription. When ROR binds to an agonist, the LBD recruits a coactivator by interacting with an NR box (LXXLL motif) on the coactivator surface (L. Jin et al., 2010). When RORs bind to an inverse agonist, the LBD recruits a corepressor by interacting with a CoRNR box (LXXI/HIXXXI/L motif) on the corepressor surface (X. Hu and Lazar, 1999).

6. Synthetic ROR Ligands. Some of the earliest synthetic compounds discovered targeting ROR are promiscuous compounds intended for other targets. For example, the cardiac glycoside digoxin modulates RORγ, and studies showed both inverse agonist and agonist effects (Huh et al., 2011; Karaś et al., 2019). Tularik, acquired by Amgen, developed the compound T091317 as an LXR agonist, but this compound was later discovered to display agonist activity for both FXR and pregnane X receptor and inverse agonist activity for RORα and RORγ (Schultz et al., 2000; Houck et al., 2004; Mitro et al., 2007; N. Kumar et al., 2010). Burris and collaborators at the Scripps Research Institute performed a structure-activity relationship (SAR) analysis on the T0901317 compound to develop the first ROR-specific synthetic ligands. The group developed SR1078, a specific RORα and RORγ agonist (Y. Wang, Kumar et al., 2010). Further modification of the T0901317 and SR1078 scaffold yielded SR3335, a RORα specific inverse agonist with reasonably favorable potency and pharmacokinetic properties. When injected intraperitoneally, this compound attenuated glucose levels in diet-induced obese mice (N. Kumar et al., 2011). From the T0901317 scaffold, the group also identified SR1001, an inverse agonist specific to RORα and RORγ. T_H17 cells are essential to the pathophysiology of autoimmune disease, and both ROR isotypes contribute to their differentiation. SR1001 administration delayed the onset and reduced the severity of EAE (Solt et al., 2011).

Despite the efficacy of SR1001 in blocking T_H17 differentiation and reducing autoimmune disease symptoms, side effects are possible. Generating a compound capable of achieving the same results while targeting only one ROR isotype might reduce potential adverse reactions. Relative to RORγ, RORα plays a unique role in cerebellar development and has a more prominent role in circadian modulation (Ino, 2004). Additionally, RORα has a mixed role in regulating inflammation, acting as an anti-inflammatory regulator in macrophages while promoting the differentiation of pathogenic T_H17 cells (X. O. Yang et al., 2008; S. Han et al., 2019). Thus, the need for a RORγ specific inverse agonist was recognized. Two RORγ-specific inverse agonists, SR2211 and its analog, SR1555, were derived from the SR1001 structure (N. Kumar et al., 2012; Solt, Kumar et al., 2012). Both compounds successfully suppressed T_H17 differentiation. Surprisingly, although less potent, SR1555 promoted the differentiation of Treg cells, thus providing a second mechanism underlying the anti-inflammatory properties of ROR inverse agonism (Solt, Kumar et al., 2012; M. R. Chang et al., 2014). These data suggest different downstream effects from distinct compounds sharing the same NR target are possible.

Structural studies of the RORγ LBD in complex with synthetic ligands have allowed researchers to pinpoint mechanisms providing a high degree of affinity and selectivity. When an agonist binds to RORγ, an "agonist lock" stabilizes, consisting of strong hydrogen bonding and π–π stacking interactions between residues His479, Tyr502, and Phe506 within the LBD (N. Sun et al., 2021). This agonist lock places helix 12 in tight contact with helix 11 to stabilize AF2 on helix 12. In this conformation, a charge clamp pocket, formed mainly by Lys336 (H3) and Glu504 (H12), recruits coactivators via their LXXLL NR box motif (L. Jin et al., 2010). All RORγ inverse agonists disrupt the stability of the coactivator binding surface either via direct or indirect interactions with helix 12. Inverse agonists that physically contact helix 12 can bind to the orthosteric binding pocket or an allosteric site closer to the helix (Scheepstra et al., 2015). Large compounds binding to the orthosteric binding pocket protrude and sterically clash with helix 12. Other compounds employ a push-pull mechanism, pushing Trp317 and pulling His479 away from hydrogen bonding with Tyr502, destabilizing the agonist lock (L. Jin et al., 2010; T. Wang et al., 2015). Other ligands bind to the allosteric pocket, forming hydrogen bonds with helix 12 amino acids to inhibit coactivator recruitment (Ouvry et al., 2016). Some inverse agonists can

produce their effects through a "water trapping" mechanism without touching helix 12. In such instances, the compound traps a water molecule near helix 12 that forms a hydrogen bond with Tyr502. The water molecule is easily released into the solvent, moving Tyr502 and destabilizing helix 12 (J. Kallen et al., 2017).

RORγ inverse agonists effectively suppress autoimmunity in vivo. Like SR1001, both SR2211 and, to a lesser degree, SR1555 effectively decreased the clinical severity of rheumatoid arthritis in a mouse model. These compounds decreased infiltrating immune cells into the affected joint and reduced the number of double-positive ($CD4^+CD8^+$) and single-positive ($CD4^+CD8^-$ or $CD4^-CD8^+$) T cells. More importantly, drug-treated animals displayed a significantly reduced frequency of pathogenic IL-17–secreting T cells (M. R. Chang et al., 2014). GSK805, a RORγ inverse agonist with oral bioavailability, strongly inhibited T_H17 cell responses and reduced EAE severity (Xiao et al., 2014). This compound was then tested in transgenic mice that spontaneously develop colitis, which is characterized by the accumulation of T_H17 cells in the colon. In this model, GSK805 ameliorated the clinical severity of the colitis measured by both an endoscopic and histologic scoring system (López-Posadas et al., 2019). Thus, RORγ inverse agonists have the potential to treat a variety of autoimmune conditions.

Since the first generation of RORγ inverse agonists was developed at the Scripps Research Institute by the Burris and Griffin laboratories, numerous companies produced compounds that progressed to Phase 2 clinical trials. Therapeutic candidates include AUR-101 (Aurigene), ESR-114 (Escalier), JTE-451 (Japan Tobacco/Akros), VTP-43732 (Allergen/Vitae Pharmaceuticals), and BI-730357 (Boehringer Ingelheim) (N. Sun et al., 2021). These clinical trials evaluate the efficacy and safety of orally/topically administered RORγ inverse agonists in treating plaque psoriasis. The Japan Tobacco/Akros study monitored the percentage of subjects achieving at least a 50% improvement from baseline based on the Psoriasis Area and Sensitivity Index (PASI-50). Patients achieving this benchmark include 17.6% of the 50 patients given a placebo twice daily, 33.3% of the 51 patients given a low dose of JTE-451 (200 mg twice daily), and 42.0% of the 50 patients given a high dose of JTE-451 (400 mg twice daily) (https://clinicaltrials.gov/ct2/show/results/NCT03832738). While no other phase 2 clinical trial data has been released, one study was terminated early (N. Sun et al., 2021).

Some have cautioned against the long-term use of RORγ inverse agonists in humans, given the susceptibility of RORγ-null mice to develop thymic lymphomas (Ueda et al., 2002). This concern grew further when Liljevald et al. demonstrated that the RORγ-null mouse phenotype was not solely a developmental abnormality observed in knockout mice. Using a conditional knockout mouse, these researchers found that deleting the RORγ gene in healthy adult mice results in lymphoblastic lymphomas (Liljevald et al., 2016). Progressive thymic alterations, similar to those seen in RORγ-null mice, were also visualized in mice treated with some, but not all, RORγ inverse agonists. Preneoplastic thymic alterations were apparent when the compound was administered at 10-fold the minimal efficacious dose for 13 weeks (Guntermann et al., 2017). Whether humans are prone to these adverse effects and over what length of time/dose these compounds may be safe in humans has yet to be evaluated. The most recent information on RORs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=85).

D. Peroxisome Proliferator-Activated Receptors (PPARα-NR1C1, PPARδ-NR1C2, PPARγ-NR1C3)

The PPARα, PPARδ, and PPARγ have attracted pharmacological interest owing to their prominent roles in glucose and lipid metabolism and their large ligand binding pockets (LBPs), which can accommodate a variety of synthetic ligands (Forman et al., 1997; Liberato et al., 2012; J. Shang et al., 2018). PPARα and PPARδ are primarily associated with lipid catabolism, while PPARγ is associated with lipid anabolism and adipogenesis. (Ahmadian et al., 2013; Mansour, 2014; Pan et al., 2017). PPAR ligands are employed to target specific manifestations of metabolic syndrome. Despite the high number of Food and Drug Administration–approved PPAR ligands, their mechanisms of action are not fully elucidated and remain a highly active field of research. This section presents recent advancements and challenges in PPAR pharmacology, such as optimizing currently approved PPAR modulators to reduce their side effects. We discuss drug specificity with examples of isoform-selective or non-isoform-selective (dual and pan) and introduce the concept of biased NR modulation and signaling.

1. Clinically Used PPAR Ligands. While PPARs share many structural features, each isoform has distinct expression patterns and physiologic roles. Consequently, drugs have been developed to target individual PPARs, although later efforts were focused on designing drugs that target two PPARs simultaneously. The most employed pharmacological agents are the thiazolidinediones (TZDs; PPARγ agonists) and fibrates (PPARα agonists). These two families of compounds provide distinct therapeutic effects. TZDs are insulin sensitizers used in T2D patients, while fibrates are used to treat hypertriglyceridemia (Jun et al., 2010). No clinically approved drugs are known to bind to and activate PPARδ; however, recent experimental therapies show promise as a treatment of metabolic disorders.

Insulin sensitization is one of the most effective approaches to prevent or reverse chronic hyperglycemia. Only two antidiabetic classes of drugs increase insulin

sensitivity, TZDs and metformin (Schernthaner et al., 2013). Interestingly, TZDs (rosiglitazone and pioglitazone) are more efficient at normalizing glycemia than metformin. Pioglitazone delays the progression from prediabetes to overt diabetes (DeFronzo et al., 2011). Some clinical trials showed that pioglitazone significantly reduces atherosclerotic plaque volume (Christoph et al., 2015). However, in other clinical studies, important side effects surfaced with the long-term use of TZDs, making these therapeutics much less attractive for treating T2D. For instance, a multicenter study found that rosiglitazone-treated T2D patients were more susceptible to cardiovascular events, bone fractures, and weight gain than those treated with a combination of metformin and a sulfonylurea. As a result, drug administration agencies then mandated that pharmaceutical companies disclose these initially undocumented health risks (Home et al., 2009). The warning led to a significant decrease in rosiglitazone prescriptions in the United States and an outright ban in Europe (European Medicines Agency, 2010). However, adverse cardiovascular effects have been questioned by more recent post-marketing evaluations (Soccio et al., 2014; S. I. Taylor and Leslie, 2018), in which pioglitazone was found to decrease cardiovascular events (Dormandy et al., 2005). Given that pioglitazone appeared safer than rosiglitazone, the number of prescriptions increased somewhat, but total TZD use fell in the United States (Ahuja et al., 2015).

The underlying basis for the differential clinical outcomes between pioglitazone and rosiglitazone may be explained by relative isoform potencies and activities. Both TZDs bind to and activate PPARα with similar affinity and potency; however, pioglitazone induces superior clinical benefits (i.e., has higher efficacy) than rosiglitazone. In addition, rosiglitazone binds and activates PPARγ at a ~200-fold lower concentration than PPARα while the difference in potency for pioglitazone between γ and α is ~20 fold (Sakamoto et al., 2000; N. J. Kim et al., 2007; B. K. He et al., 2012). This has led to the suggestion that pioglitazone, but not rosiglitazone induces PPARα-mediated responses (Soccio et al., 2014). Although TZDs are currently only recommended for treatment of T2D and prediabetes in certain patients as a second-tier therapy (Schernthaner et al., 2013; Davies et al., 2018), the unique beneficial effects of PPARγ agonists could reach more patients if new PPARγ-targeted drugs did not cause the adverse events observed with current TZDs (weight gain, increased risk of heart failure, and osteopenia) (Soccio et al., 2014).

The PPARα agonists gemfibrozil, fenofibrate, fenofibric acid, bezafibrate, and ciprofibrate are routinely prescribed fibrates to lower plasma triglyceride levels and are well tolerated (D. Wang et al., 2015). A meta-analysis of clinical trials between 1950 and 2010 indicated that fibrates prevent major cardiovascular events, particularly in patients with dyslipidemia (Jun et al., 2010). These drugs display distinct PPAR subtype selectivity, potency, and efficacy. Bezafibrate targets all three PPARs to some degree (Willson et al., 2000) and will be discussed in the next paragraph as a pan-PPAR agonist. Gemfibrozil binds to and activates PPARα and PPARγ with equal potency but has higher PPARα efficacy (N. J. Kim et al., 2007), while fenofibric acid is more selective for PPARα than PPARγ (P. J. Brown et al., 1999; R. Mukherjee et al., 2008). Ciprofibrate and fenofibrate potency for PPARα is 20 to 30 μM and 300 μM for PPARγ (Guerre-Millo et al., 2000; Willson et al., 2000). Ciprofibrate has minimal efficacy at PPARγ and PPARδ activation (Forman et al., 1997). These reports indicate that ciprofibrate, fenofibrate, and fenofibric acid produce most of their therapeutic effects through PPARα activation, while bezafibrate and gemfibrozil might be considered pan or dual agonists.

PPARδ pharmacology and drug development are less advanced than the other PPARs. Although no PPARδ-selective ligands have been approved, there are unique properties of PPARδ agonists that suggest potential clinical utility. For example, overexpression of constitutively active PPARδ or administration of the PPARδ agonist GW501516 increases exercise endurance in sedentary mice and induces a fuel utilization shift from glucose to fatty acids (Y. X. Wang et al., 2004; W. Fan et al., 2017). These drugs are classified as "exercise mimetics" since they provide exercise-like health benefits. In mice, PPARδ agonists prevented HFD-induced obesity and increased energy expenditure, fatty acid oxidation, and insulin sensitivity (W. Fan et al., 2017). Unfortunately, evidence that PPARδ agonists may serve as ergogenic aids has led to substance abuse in the Tour de France in 2019 (Long, 2019). Enthusiasm for further development of PPARδ agonists has been tempered by the observation of increased cancer risk with chronic PPARδ activation (Gupta et al., 2004; Duran et al., 2016; Y. Liu et al., 2018). However, the development of PPARδ agonists has not been completely abandoned. Seladelpar (MBX-8025) is perhaps the most promising PPARδ-specific (Haczeyni et al., 2017) drug currently under development. Although a phase 2 clinical trial of seladelpar for primary biliary cholangitis showed some adverse liver effects (Jones et al., 2017), preliminary results from another phase 2 clinical trial using lower doses are encouraging (Mayo, 2019). A phase III trial (ENHANCE) for primary biliary cholangitis using the lower dosing showed positive results (Hirschfield et al., 2023).

Recent drug development efforts for improved PPAR binding drugs with less undesired effects or increased desired effects have focused on two areas: the development of dual or pan agonists (i.e., drugs that activate two or three members PPAR sub-family simultaneously) and the development of selective PPAR modulators (SPPARMs).

2. Dual and Pan PPAR Agonists. Dual and pan agonists (drugs that bind and activate two or three PPAR isoforms) have been developed and tested in clinical trials. We focus here on drugs used in clinical trials reported in the past several years. Dual and pan PPAR agonists were developed with the hope that targeting multiple PPARs would provide the clinical benefits of each PPAR isoform-specific agonism while eliminating some of their adverse effects (Henry et al., 2015).

Several drugs that bind to and activate both PPARα and PPARγ, including muraglitazar and aleglitazar, failed to provide a better safety profile than single agonists (Nissen et al., 2005; Lincoff et al., 2014), leading to termination of development (Mansour, 2014; Balakumar et al., 2019). Currently, a few drugs of this class are still under development, including saroglitazar, which is clinically approved in India (Chatterjee et al., 2015; Kaul et al., 2019). As previously stated, gemfibrozil and possibly pioglitazone could be considered currently prescribed α/γ dual agonists. Given the number of promising drugs in this class that did not reach the market, it is not surprising that the development of dual α/γ PPAR agonists lost popularity.

On the other hand, the dual PPARα/δ agonist elafibranor showed promise for treating nonalcoholic steatohepatitis (NASH) in a report of a phase II clinical trial (Ratziu et al., 2016). While elafibranor did not meet its primary endpoint of reversal of NASH without worsening fibrosis, the results were encouraging enough that further testing for NASH treatment, but this compound did not show favorable results (https://clinicaltrials.gov/ct2/show/NCT02704403).

Bezafibrate, a currently prescribed fibrate, has similar potency for all three PPARs (Willson et al., 2000), although it appears to have higher PPARα efficacy (Inoue et al., 2002). In a recently reported phase III trial, bezafibrate combined with ursodeoxycholic acid was superior to placebo and urodeoxycolic acid for the treatment of primary biliary cholangitis (Corpechot et al., 2018). A conference abstract reported that another pan PPAR agonist, chiglitazar (B. K. He et al., 2012), may hold promise as an antidiabetic agent (J. Li et al., 2019). Interestingly, chiglitazar and pioglitazone appear to have similar potency and efficacy for all three PPARs, although chiglitazar has slightly higher potency for all three PPARs and higher efficacy for PPARδ (B. K. He et al., 2012).

Overall, many dual and pan PPAR agonists have failed to move on to the clinic due to safety concerns; however, a few have shown efficacy for treating liver disease and T2D. In addition, some PPAR-targeted drugs currently in use that were thought to act primarily through one specific receptor may produce some effects through multiple PPAR receptors (e.g., bezafibrate and pioglitazone). These examples suggest that dual or pan agonists can succeed clinically.

3. Biased PPAR Modulation and Signaling. While SPPARMs refer to drugs that bind to and modulate the activity of just one of the three PPAR isoforms but display unique mixed context-dependent agonist/antagonist profiles, this is not how we use the term here. Instead, we discuss SPPARMs in the sense of biased agonism. The idea of selective NR modulation in the sense of biased agonism has been around for several decades, with the ER antagonist tamoxifen as one of the first examples (C. L. Smith and O'Malley, 2004). The basic concept of biased agonism is that distinct drugs can produce different outcomes in the same cell, in different tissues, or in the whole organism through binding and activating the same receptor. The physical mechanisms that lead to distinct signaling through a single receptor can be divided into three types: *system bias*, *receptor bias*, and *drug/ligand bias* (J. S. Smith et al., 2018). System bias refers to signal transducers that transmit the signal from the receptor onward to clinical outcomes that vary between cells and/or tissues. In the case of NRs, variation in the recruitment of coregulators or variation in their expression levels between cells could produce system bias (a notion extensively developed with the ERs in the *Subgroup III* section) (Martinkovich et al., 2014). Receptor bias can originate from receptor mutation (as discussed in the *Subgroup I* section). Drug bias is encoded by each drug. Drug bias is different from partial or inverse agonism. Partial and inverse agonists are expected to produce less or opposite signal intensity compared to agonists. In contrast, a drug/ligand bias arises from differential conformational changes upon ligand binding, downstream signaling, and co-modulator recruitment from a reference drug (Fruchart, 2013, 2017). Recent structure studies provided solid evidence for NR ligand bias where the use of distinct PPARγ-selective inverse agonists triggered different conformational changes (Heidari et al., 2019).

The structural mechanism for discrimination between the coactivator and corepressor classes of coregulators is understood for PPAR and depends on the positioning of the c-terminal helix (helix 12) (Weikum et al., 2018). Rheostat-like modulation of helix 12 positioning can explain PPAR partial and inverse agonism and antagonism. The proposed mechanism for drug bias in NR pharmacology is that biased drugs induce different coactivator and/or corepressor recruitment profiles (Fruchart, 2013, 2017). These ideas fit well with a recently published structural model of drug bias in NRs, which includes the idea that reduced stabilization of helix 12 by partial agonists causes preferred recruitment of only one of two classes of transcriptional coactivators (Nemetchek et al., 2022). The proposed mechanism for drug bias in NR pharmacology is that biased drugs induce different coactivator and/or corepressor recruitment profiles (Fruchart, 2013, 2017). Recent work demonstrates a structural mechanism for biased agonism in NRs, especially PPARγ (Nemetchek et al., 2022). Many reports

show that experimental selective PPARγ modulators induce different coregulator recruitment profiles, different signaling, and different outcomes compared to reference drugs, often rosiglitazone or pioglitazone (Camp et al., 2000; Rocchi et al., 2001; T. Fujimura et al., 2005; Schupp et al., 2005; Burgermeister et al., 2006; K. R. Kim et al., 2006; Motani et al., 2009; Soccio et al., 2014; C. Liu et al., 2015; Frkic et al., 2017; Lavecchia and Cerchia, 2018). The physical mechanisms by which biased drugs accomplish this are ill-defined.

One mechanism underlying drug bias may be associated with PPAR PTMs (Ahmadian et al., 2013). One widely reported PTM is the phosphorylation of PPARγ at serine 273 (S273) (S245 in PPARγ1 numbering) by CDK5 kinase, which has been correlated with insulin resistance. Several classes of PPAR modulators, including agonists, partial agonists, and nonagonists/antagonists block PPARγ phosphorylation. These observations raised the possibility that insulin sensitization can be achieved by various PPAR-targeting drugs, even with the use of nonagonists that do induce all genes being modulated by full-agonists like with rosiglitazone (Choi et al., 2010, 2011, 2014; Bostrom et al., 2012; Banks et al., 2015; Prokoph et al., 2016; Ribeiro Filho et al., 2018). The structural mechanism of S273 phosphorylation is poorly defined and appears to be dependent upon corepressor affinity modulation (i.e., the corepressor NCoR) (P. Li et al., 2011), complicating the structural understanding of this mechanism. To examine structural mechanisms underlying S273 phosphorylation, a computational docking model of the kinase-PPAR interaction was created. With this technology, PPARγ anchor residues responsible for S273 phosphorylation were identified. However, PPARγ ligands that inhibit S245 phosphorylation do not interact with these residues (Ribeiro Filho et al., 2019).

Pemafibrate (K-877) could be an example of the first selective PPAR modulator (biased agonist) that succeeded clinically (Fruchart, 2013, 2017). Pemafibrate-induced outcomes are expected to be almost entirely through PPARα activation because it binds to and activates PPARα with 1,000-fold higher potency than PPARγ or PPARδ. Pemafibrate is much more potent in PPARα activation than fenofibrate (Fruchart, 2013; Toshiaki et al., 2013). The PPARα selectivity has been confirmed in a genetic model in which PPARα-deficient hepatocytes showed no molecular response to pemafibrate treatment (Raza-Iqbal et al., 2015). Recent phase II and phase III clinical trials and a meta-analysis of seven randomized controlled trials suggest that pemafibrate may be a safer but clinically equivalent to fenofibrate (Ishibashi et al., 2016, 2018; Ida et al., 2019). In fact, pemefibrate induced less kidney damage than fenofibrate, most likely due to their routes of excretion. Fenobifrate is mainly eliminated via urine, whereas pemafibrate is eliminated through bile secretion (Ida et al., 2019). Pemefibrate was also found to induce less liver damage and more desired outcomes that have been attributable to either higher selectivity for PPARα over other PPARs or the fact that it induces biased signaling compared to fenofibrate (i.e., it is a biased PPARα agonist). Fenofibrate potency is only 10-fold higher for PPARα than for PPARγ (Willson et al., 2000), while pemafibrate has a 1,000-fold higher potency for PPARα than PPARγ. Some but not all transcriptomic effects of fenofibrate are abrogated in human liver cells by PPARα knockdown using small interfering RNA, suggesting that some, if not all, the clinical differences are attributable to the lack of PPARγ/δ or other receptor activation by the highly potent pemafibrate.

4. Advances in PPAR Structure Function. Drug bias originates from the drug-receptor structural state (J. S. Smith et al., 2018). Because bias is encoded in this structural state, analysis of receptor structure can define the mechanism of drug bias and guide drug development platforms. As previously stated, our current understanding of how drugs affect the structure of PPARs is limited to understanding graded agonism (e.g., partial vs. full agonism) (Weikum et al., 2018). Crystal structures showed that the conformation of helix 12 is different when bound to a corepressor (SMRT) (H. E. Xu et al., 2002) versus a coactivator (e.g., SRC1) (Nolte et al., 1998). Surprisingly, crystal structures of PPARγ bound to full agonists, antagonists, and inverse agonists are remarkably similar (Kaupang et al., 2017). In contrast, solution state methods, including protein and fluorine nuclear magnetic resonance (NMR), simulation, hydrogen-deuterium exchange mass spectrometry (HDX-MS), and fluorescence anisotropy demonstrate that ligands have dramatic and varied effects on the structural state of PPAR (Chalmers et al., 2006; Hamuro et al., 2006; J. B. Bruning et al., 2007; Choi et al., 2010, 2011; Hughes et al., 2012, 2014; Marciano et al., 2015; Brust et al., 2018; Chrisman et al., 2018; Frkic et al., 2018; J. Shang et al., 2018; Zheng et al., 2018). Discrepancies between crystal and solution structures may be due to the ensemble nature of protein structure and/or the constraints of crystallization. Solution methods show that PPAR adopts different conformations depending upon which type of ligands is bound. Effective agonists and inverse agonists favor a primary structure, while partial agonists and ligand-free exchange between many different structures (Brust et al., 2018; Chrisman et al., 2018; B. A. Johnson et al., 2000). In general, crystallization apparently favors a low-energy structure that is common between the structural ensembles of all liganded states and apo form of PPAR, leading to uniform crystallized structures.

Almost all PPAR drugs that induce biased coregulator recruitment or functional outputs have been discovered without selecting specifically for bias. More solution-state atomic-level structural information comparing structures

of liganded PPARs would provide physical mechanisms underlying drug bias. Such information would guide structure-activity relationship-based biased drug development. While solution studies showed that drugs induce a wide variety of PPAR conformational ensembles, they have not revealed discernable atomic level detail to capture drug-induced conformational dynamics. NMR structures of PPAR are challenging to obtain due to the potential effects of intermediate exchange. Although providing high-resolution 3D receptor architecture, crystal structures are snapshots of structural ensembles with or without ligands that do not inform on ligand-induced conformational shifts and protein function predictions.

While high-resolution structure determination demonstrating the exact dynamics upon ligand binding is not feasible, computer-aided methods can provide atomic resolution detail of hypothetical NR conformation upon ligand binding. These models predict how NRs adopt diverse confirmations from a reference structure (e.g., apo-PPARγ crystal structure) under various physiologic conditions and ligand binding and their impact on receptor function. Software and technological advances have made biologically meaningful structural sampling at atomic level resolution in explicit solvent (where the solvent is modeled as individual water molecules and ions) for relatively large proteins such as PPAR feasible (Pierce et al., 2012; Miao et al., 2015). Simulations have provided insight into the molecular mechanism explaining G protein-coupled receptor–mediated arrestin activation (Latorraca et al., 2018) and have offered structural information consistent with PPAR solution state and crystal structure data (Batista and Martinez, 2015; Fratev et al., 2015; Fratev, 2017; Brust et al., 2018; Chrisman et al., 2018). Computer-aided methods provide critical information to understand, develop, and refine strategies for biased drug development.

The most recent information on PPARs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=86) .

E. REV-ERBs (REV-ERBα-NR1D1, REV-ERBβ-NR1D2)

The REV-ERBs are unusual members of the NR superfamily, given their structural and functional divergence from other NRs and their endogenous ligand–heme (as opposed to lipids or steroid hormones). The regulatory roles of the REV-ERBs are highly complex due to robust circadian rhythmicity and cell-type and/or isoform-specific functions. Despite these challenges, REV-ERB-targeting ligands have shown strong therapeutic utility for treating a wide range of conditions, including circadian disruption, inflammation, metabolism, and cognition, which will be discussed in this section.

The REV-ERB moniker is based on the identification of REV-ERBα on the opposite strand of the TR alpha gene (*erbA*). Thus, REV-ERB is derived from its positioning as the reverse strand of *erbA* (Lazar et al., 1989; Miyajima et al., 1989). The second isotype, REV-ERBβ, was discovered by multiple laboratories in 1994, and it similarly exists in close proximity to the TRβ transcriptional unit (*erbB*) (Bonnelye et al., 1994; Dumas et al., 1994; Forman et al., 1994; Retnakaran et al., 1994). Many similarities exist between the two REV-ERB isoforms, including structure, tissue distribution, and functions. Investigations in *Nr1d1*- or *Nr1d2*-deficient mice demonstrated a significant level of functional redundancy between both isoforms, where the remaining isotype can at least partly compensate for the lost functions (H. Cho et al., 2012). The study of REV-ERBβ has been relatively limited compared to REV-ERBα due to the lack of available tools, such as transgenic mice or REV-ERBβ-specific chemical probes. The REV-ERBs lack the AF2 domain, which completely prevents coactivator recruitment. As a result, the REV-ERBs have been taxonomized as "transcriptional repressors" as they constitutively bind corepressors (L. Yin and Lazar, 2005). Despite the absence of helix 12, the tertiary structure of the REV-ERB LBD is well conserved with that of other NRs and carries the three-layered alpha-helical sandwich (H1-H11) and a hydrophobic LBP (Pardee et al., 2009; Phelan et al., 2010; Matta-Camacho et al., 2014; Mosure et al., 2021).

Like other NRs, the REV-ERBs repress transcription via DBD-dependent and DBD-independent mechanisms. However, DBD-dependent gene regulation by the REV-ERBs is unique as they compete with the RORs to bind ROREs as monomers and Rev-DR2s as homodimers (Everett and Lazar, 2014). By competing for these binding sites, the RORs and REV-ERBs mutually regulate their shared target genes. In most cases, the RORs induce genes that are constitutively repressed by the REV-ERBs. Thus, their relative abundance drives transcriptional activity and the directionality of shared target genes. A feedback loop also exists between the RORs and REV-ERBs. In fact, the *NR1D1* gene promoter contains a RevRE that permits autoregulation and regulation by RORs. In turn, *NR1F1* (RORα) gene is also modulated by REV-ERBβ.

The REV-ERBs also modulate transcription without binding through their DBD. For instance, the REV-ERBs associate with NF-Y to bind to and inhibit myogenic regulatory factor expression in proliferating myoblasts (Welch et al., 2017) and to hepatocyte nuclear factor 4a and 6 to inhibit metabolic genes in the liver (Y. Zhang et al., 2015). This noncanonical binding via tethering to other TFs allows tissue-specific gene reprogramming.

1. Natural REV-ERB Ligands. Two research groups independently discovered heme as an endogenous ligand of both REV-ERB isotypes(Raghuram et al., 2007; L. Yin et al., 2007). Heme was a prime candidate for a REV-ERB endogenous ligand since it had previously

discovered roles modulating circadian proteins, like E75, a *Drosophila* NR with high LBD sequence alignment to REV-ERB (Raghuram et al., 2007). Heme binds to the LBP of REV-ERB, where its central oxidized iron (Fe^{3+}) is coordinated by two residues, a cysteine (Cys418 in REV-ERBα; Cys384 in REV-ERBβ) and a histidine (His602 in REV-ERBα; His568 in REV-ERBβ) (Pardee et al., 2009).

Since the REV-ERBs do not recruit coactivators, REV-ERB ligands can only impact gene expression by modulating corepressor recruitment. Agonists increase corepressor recruitment to repress target gene transcription. In contrast, antagonists inhibit corepressor association with REV-ERB LBD. Heme is a REV-ERB agonist that is continually available in cell culture systems, making REV-ERB appear like a constitutive repressor of target genes. When heme binds, enhanced NCoR1 recruitment to REV-ERB LBD and enhanced NCoR1 presence at ROREs are detectable (Raghuram et al., 2007). NCoR1 complexes with HDAC3, which acts to remove acetyl groups from histone lysine residues, tightening the association of the positively charged lysine groups and negatively charged DNA. The resulting heterochromatin attenuates REV-ERB target gene expression (Papazyan et al., 2016).

2. Post-Translational Regulation of REV-ERB Activity. Post-translational modifications, including phosphorylation, sumoylation, and ubiquitination, impact the ability of REV-ERB to function. One well-known posttranslational modification of REV-ERB involves the N-terminal phosphorylation of serine residues (Ser55 and Ser59 of REV-ERBα) by glycogen synthase kinase 3β (GSK3β). This phosphorylation blocks REV-ERBα ubiquitin-dependent proteasome degradation, increasing REV-ERB target gene repression (L. Yin et al., 2006). In contrast, phosphorylation by casein kinase 1 results in cytoplasmic localization of REV-ERB, decreasing REV-ERB target gene repression (Ohba and Tei, 2018). A sequence of phosphorylation, sumoylation, ubiquitination, and proteasomal degradation of REV-ERB occurs in the presence of high concentrations of pro-inflammatory cytokines. This allows pro-inflammatory conditions to prevail instead of being counteracted by the presence of REV-ERB (Pariollaud et al., 2018).

3. REV-ERB Regulation of the Circadian Rhythm. The principal circadian clock, the suprachiasmatic nucleus (SCN), receives inputs from the retinohypothalamic tract to synchronize the circadian rhythm to light–dark cycles. The SCN projects outputs to multiple brain regions containing local circadian clocks that direct behavioral, autonomic, and neuroendocrine rhythms. Rhythmic changes in hormones, temperature, or feeding-fasting are cues to synchronize circadian gene expression in peripheral tissues with the central clock (Hastings et al., 2018).

A 24-hour circadian loop consists of positive and negative arms, each dominantly operating for 12 hours in opposing rhythmic cycles. The positive arm of the core circadian clock consists of brain and muscle arnt-like protein 1 (Bmal1), a basic helix-loop-helix protein, forming a heterodimer with other basic helix-loop-helix proteins, including circadian locomotor output cycles kaput or neuronal PAS domain protein 2. The resulting heterodimer binds to E-boxes (CACGTG) to upregulate rhythmically expressed genes, including genes encoding negative-arm proteins. Negative-arm proteins PER and CRY assemble into a complex with over 30 polypeptide subunits, which directly interacts with the BMAL1 heterodimers, repressing the expression of their target genes (Papazyan et al., 2016).

Multiple mechanisms for regulating circadian gene expression exist, including a secondary loop where ROR upregulates target genes out of phase with REV-ERB repressing target genes. ROR and REV-ERB compete for binding to the same RORE and RevDR2 REs. Rhythmic changes in the abundance of ROR and REV-ERB bound to their gene regulatory sites result in the circadian expression of their target genes (Guillaumond et al., 2005; Papazyan et al., 2016). In the positive arm of this secondary circadian loop, BMAL1 heterodimers bind to the REV-ERB promoter via E-boxes. Thus, the positive arm upregulates REV-ERB expression at the transcriptional level (Delerive et al., 2002; Raspe et al., 2002). REV-ERB protein then binds to ROREs within the *Bmal1* promoter, suppressing the transcription of this positive arm component (Guillaumond et al., 2005). Thus, the upregulation of the constitutive repressor REV-ERB is one mechanism for suppressing the positive arm and initiating the negative arm of the circadian loop.

4. REV-ERB Regulation of Immune Function. Several aspects of immune function in both mice and humans exhibit a circadian rhythm. Upon awakening (dusk for mice, dawn for humans), the expression of chemokines and adhesion proteins is at an acrophase, resulting in peak recruitment of leukocytes to peripheral tissues (Scheiermann et al., 2013). This temporally dependent increase in inflammatory capacity corresponds to intensifying inflammatory pathology at the start of the active phase. Near the beginning of the dark period, mice have the highest mortality rate to lipopolysaccharide (LPS) and tumor necrosis factor-alpha (TNFα)-induced inflammation (Scheiermann et al., 2013). Comparably, humans with allergic rhinitis, bronchial asthma, and rheumatoid arthritis have exacerbated symptoms upon awakening (Scheiermann et al., 2013). Given the rhythmic nature of immune activation, circadian regulators are attractive targets for treating these disease states. ROR and REV-ERB are circadian regulators and ligand-gated TFs; thus,

their ability to be targeted by pharmaceuticals increases interest in the immunologic roles of these proteins. Often opposing the actions of ROR, REV-ERB is an established regulator of the Toll-like receptor (TLR)-nuclear factor kappa B (NFκB)-proinflammatory cytokine pathway. TLR1-5 and TLR9 contain ROREs in their promoter, allowing them to be upregulated by RORα and downregulated by REV-ERBα, establishing the circadian expression of these receptors in intestinal epithelial cells (Mukherji et al., 2013). In smooth muscle cells, RORα indirectly inhibits NFκB activation, while REV-ERB indirectly promotes NFκB activation in this cell type (Delerive et al., 2001; Migita et al., 2004). Serum IL-6 concentrations exhibit a circadian rhythm in rheumatoid arthritis patients, and transcription of this pro-inflammatory cytokine is regulated by both ROR and REV-ERB (Journiac et al., 2009; Gibbs et al., 2012). In addition to *Il6*, REV-ERB regulates the expression of a wide variety of other inflammatory genes in macrophages, including *tlr4*, *p65*, *ccl2*, *mmp9*, and *cx3cr1* (S. Wang et al., 2020).

Like ROR, REV-ERB regulates innate immune cell differentiation and cytokine expression. REV-ERB represses the transcription of *Il17a* and *Il17f* in $\gamma\delta$-17 T cells, limiting their proinflammatory potential (S. Wang et al., 2021). Additionally, REV-ERB is a core TF that directly impacts the development of ILC3s (Q. Wang et al., 2019).

The role of REV-ERB in regulating the NLRP3 inflammasome is well established. The activation of the NLRP3 inflammasome occurs in a two-step process: (i) priming (the induction of NFκB to transcriptionally upregulate inflammasome components and pro-inflammatory cytokines) and (ii) activation (the inflammasome assembles cleaving pro-caspase-1 into its active form) (Y. He et al., 2016). The active caspase-1 then processes IL-1β and IL-18 for release. In macrophages, *Nlrp3*, *Il1b*, and *Il18* genes are all expressed in a circadian fashion via direct regulation by REV-ERB. Bone marrow-derived macrophages isolated from REV-ERBα-null mice exhibit upregulated inflammasome activation and release of pro-inflammatory cytokines (Pourcet et al., 2018). Targeting this pathway may contribute to treating NLRP3-dependent disease states, including AD, stroke, atherosclerosis, gout, silicosis, and more (Mangan et al., 2018). REV-ERBα has a dual role in T_H17 cells. An initial study demonstrated that REV-ERBα reinitiates the circadian loop's positive arm by repressing a repressor of RORγt, *Nfil3*. Thus, REV-ERBα indirectly promotes T_H 17 differentiation by initiating normal RORγt expression (S. Yu et al., 2013). A seemingly contradictory study demonstrates that REV-ERBα represses T_H17 differentiation by directly attenuating *Il17* (Amir et al., 2018). A final study concluded that at low levels, REV-ERBα upregulates RORγt expression, promoting T_H17 differentiation, while at high levels, REV-ERBα downregulates *il17*, repressing T_H17 differentiation. Thus, REV-ERBα exhibits a dual role in T_H17 differentiation in a concentration-dependent manner (Chang et al., 2019).

5. REV-ERB Regulation of Metabolism. REV-ERBα knockout mice (KO) have an obesity-prone phenotype, which can be attributed to the excess fat storage and lower energy expenditure seen in these mice (Delezie et al., 2012; Woldt et al., 2013). Putting REV-ERBα KO mice on an HFD exacerbates the difference in fat mass between the KO and wild-type mice. In the KO mice, hepatic and white adipose expression of multiple lipid metabolic genes is upregulated at ZT12, a time point when REV-ERBα expression is ordinarily high. The upregulation of lipoprotein lipase, the rate-limiting step in lipid hydrolysis, enhances the uptake of nonesterified fatty acids for storage, exacerbating fat overload (Delezie et al., 2012). Additionally, REV-ERBα KO mice demonstrate reduced energy expenditure; the skeletal muscle of these mice exhibits reduced mitochondrial number and oxidative function, limiting the exercise capacity of these mice (Woldt et al., 2013). Interestingly, this finding appears to be isotype specific. Unlike the REV-ERBα KO mice, REV-ERBβ KO mice exhibit neither increased fat mass nor repressed oxidative/mitochondrial biogenesis genes relative to wild-type (Amador et al., 2018). These results are supported by a human study identifying a REV-ERBα polymorphism (rs939347) that is associated with obesity in the Spanish population (Ruano et al., 2014).

In contrast to skeletal muscle, a great deal of functional redundancy exists between the two REV-ERB isotypes in the liver (Bugge et al., 2012; Cho et al., 2012). While REV-ERBα KO mice exhibit moderate hepatic steatosis, knocking down REV-ERBβ in these mice greatly exacerbates the disease severity. This would suggest the ability of REV-ERBβ to compensate for the loss of REV-ERBα (Bugge et al., 2012). Indeed, ChIP-seq experiments targeting hepatic REV-ERBα and REV-ERBβ demonstrated a high level of overlapping peaks localized to the regulatory regions of lipid metabolic genes (Bugge et al., 2012; Cho et al., 2012). These data are consistent with the hyperlipidemic phenotype observed in REV-ERBa-null mice (Raspe et al., 2002; Le Martelot et al., 2009). Both REV-ERB isotypes localize near cholesterol synthesis regulatory genes, including *Insig2* (Cho et al., 2012). When REV-ERB protein is elevated (ZT 8-12), it represses *Insig2* transcription, promoting the proteolytic activation and nuclear accumulation of sterol regulatory element binding proteins (SREBPs). These TFs drive the rhythmic transcription of the rate-limiting enzyme in cholesterol synthesis, *Hmgcr*. Thus, the synthesis of the endogenous ligands for ROR and cholesterol and its derivatives occurs in a circadian fashion regulated by REV-ERB (Le Martelot et al., 2009).

REV-ERB also regulates the circadian rhythm of multiple glucose metabolic pathways. REV-ERB positively

enhances the expression of exocytosis genes in pancreatic alpha and beta cells, allowing the cells to appropriately secrete either glucagon in response to low serum glucose or insulin in response to high serum glucose (Vieira et al., 2012, 2013). Putting wild-type mice on an HFD induces leptin release, which dysregulates the rhythmic expression of REV-ERB in pancreatic beta cells through a mitogen-activated protein kinase (MAPK)-dependent mechanism. This attenuates glucose-stimulated insulin secretion from pancreatic beta cells in a ZT-dependent manner (Vieira et al., 2012). Additionally, hepatic insulin sensitivity naturally peaks upon waking when REV-ERB expression is at a peak. REV-ERBα and REV-ERBβ in SCN GABAergic neurons (SCN^{GABA}) repress the firing of these neurons, which is at a trough upon waking when REV-ERB levels are high. This timing correlates with a peak in insulin-mediated suppression of hepatic glucose production. SCN^{GABA}-specific REV-ERB double KO mice show an arrhythmic SCN^{GABA} firing rate and hepatic insulin sensitivity. Losing the peak in hepatic insulin sensitivity at the start of the active period results in excessive hyperglycemia upon awakening. This hyperglycemic "dawn phenomenon" is also seen in a subset of human patients with T2D. Notably, peripheral blood macrophages isolated from these patients had abnormal REV-ERB rhythmicity (Ding et al., 2021).

6. Synthetic REV-ERB Ligands. The endogenous agonist of REV-ERB, heme, has multiple off-target binding sites, making it a poor candidate for developing synthetic ligands (Pardee et al., 2009). GlaxoSmithKline discovered the first REV-ERB synthetic ligand via a fluorescence resonance energy transfer–based NCoR recruitment assay. This compound, GSK4112 (1,1-dimethylethyl *N*-[(4-chlorophenyl)methyl]-*N*-[(5-nitro-2-thienyl) methyl]glycinate), is a REV-ERBα and REV-ERBβ dual-agonist with an unfavorable pharmacokinetic profile, which prohibited its use in vivo (Grant et al., 2010). This limitation inspired groups to undertake a structure-activity relationship analysis of the GSK4112 scaffold. From this investigation, groups at GlaxoSmithKline and the Scripps Research Institute developed compounds with improved potency, efficacy, and pharmacokinetics, allowing them to be used in vivo (Solt, Wang et al., 2012; Trump et al., 2013). While all of these compounds target both REV-ERB isotypes, two of these compounds, SR9009 and SR9011, have been screened against a panel of all 48 NRs, indicating no off-target activity. These two compounds have been attractive tools in rodent studies, but they contain a nitrothiophene group with toxic liability, which makes them unsuitable for clinical trials.

To bypass this adverse effect, several groups have proposed REV-ERB agonists without a nitrothiophene group (Noel et al., 2012; Trump et al., 2013; Westermaier et al., 2017; Murray et al., 2022). One of these scaffolds was a line of tetrahydroisoquinolines proposed by the Scripps Research Institute group following the publication of SR9009 and SR9011. These compounds were designed to limit the rotation of the scaffold around the central tertiary amine, improving the performance of these compounds (Noel et al., 2012). One of the newer tetrahydroisoquinolones is SR12418, a compound that is about 10-fold more potent than SR9009/SR9011 in a *Bmal*-luciferase assay and has good plasma exposure in mice (Amir et al., 2018). An independent group discovered a triazolopyridazine scaffold and a structurally similar scaffold for REV-ERB agonists (Westermaier et al., 2017). A completely unique REV-ERB agonist chemical scaffold was described by Murray et al. (2022) that also provides the first X-ray crystal structure of a synthetic ligand bound to the REV-ERB LBD.

Cobalt and zinc protoporphyrin are natural antagonists for the NR REV-ERB (Matta-Camacho et al., 2014). However, the first synthetic antagonist to REV-ERB was not designed with the protoporphyrin ring in mind; rather, this ligand was derived from the GSK4112 tertiary amine scaffold. The synthetic antagonist, SR8278, targets both REV-ERBα and REV-ERBβ and was discovered to increase transcription of REV-ERB target genes in an upstream activation sequence-luciferase assay (REV-ERB LBD–GAL4 DBD) as well as gene expression assays (Kojetin et al., 2011).

Following the discovery of SR8278, additional REV-ERB antagonist scaffolds were developed by Istituto Italiano di Tecnologia and GlaxoSmithKline. The Italian group used a virtual screening approach to identify ARN5187, a novel spirocyclic cyclopentane scaffold, which was confirmed to inhibit REV-ERB activity in cell-based assays (De Mei et al., 2015). More recently, GSK1362 was discovered as an inhibitor of NCoR recruitment to REV-ERB LBD in a fluorescence resonance energy transfer assay. The activity of this novel oxazole REV-ERB antagonist was confirmed in cell-based assays; however, its poor pharmacokinetic profile has restricted its use to in vitro experiments (Pariollaud et al., 2018).

Much work is left to be done in developing REV-ERB agonists. Crystal structures of physiologic ligands, heme, cobalt protoporphyrin, and zinc protoporphyrin, in complex with the REV-ERB LBD, have been published (Pardee et al., 2009; Matta-Camacho et al., 2014), but these structures do not provide any insight into the structure-function relationship of synthetic REV-ERB ligands. While a crystal structure of apo-REV-ERBα LBD in complex with NCoR was suggested to reveal an active conformation (Phelan et al., 2010), structures of REV-ERB LBD in complex with synthetic agonists/antagonists are necessary to give a clearer insight into the mechanism of synthetic ligand function.

Rodent studies have confirmed the utility of REV-ERB agonists in treating inflammatory disease states. Several studies have demonstrated that REV-ERB agonists attenuate NLRP3 inflammasome activity in vivo (H. Wang et al., 2018; Pourcet et al., 2018, Reitz et al., 2019). One of these studies demonstrated that treating mice with SR9009 in the days following myocardial ischemia/reperfusion injury reduced NLRP3 inflammasome-related gene expression and cardiac inflammation/remodeling and, ultimately, improved cardiac ejection fraction months after the treatment (Reitz et al., 2019). Additionally, REV-ERB activation suppresses the severity of dextran sodium sulfate-induced colitis by repressing the NFκB-NLRP3 axis (H. Wang et al., 2018). In another inflammatory model, treatment of collagen-induced arthritis mice with SR9009 reduced cartilage damage, bone loss, inflammatory cell infiltration, and synovial hyperplasia (Liu et al., 2020). Additionally, SR9009 crosses the blood–brain barrier, which is significant given that REV-ERB regulates the rhythmic activation of microglia and pharmacologic activation of REV-ERB reduces LPS-induced neuroinflammation (Griffin et al., 2019; Guo et al., 2019). Aberrant neuroinflammation is a hallmark of many neurodegenerative diseases, like AD and Parkinson's disease, that currently have limited treatment options (Griffin et al., 2019).

REV-ERB agonists have also succeeded in improving the metabolic profile in rodent models. Mice treated with SR9011/SR9009 have decreased obesity and increased energy expenditure relative to vehicle-treated mice despite no difference in their daily food intake. The serum cholesterol levels, triglycerides, and nonesterified fatty acids are all attenuated in REV-ERB agonist-treated mice. This result correlates with decreased expression of cholesterol synthesis genes (liver: *Hmgcr*, *Srebpf2*), triglyceride synthesis genes (liver/white adipose: *Gpat*, *Agpat1*, *Mgat*, *Dgat2*), and fatty acid synthesis genes (liver: *Scd1*, *Fasn*). Additionally, mice treated with REV-ERB agonists show increased oxygen consumption (Solt, Wang et al., 2012). A later study showed increased oxidative capacity in the skeletal muscle of agonist-treated mice that correlated with enhanced exercise endurance seen in these mice (Woldt et al., 2013).

REV-ERB agonist-treated mice also show decreased fasting plasma glucose and hemoglobin A1c levels in wild-type and diabetic mice (Yuan et al., 2019). This result correlates with studies demonstrating that REV-ERB suppresses gluconeogenesis through repressing rate-limiting enzymes (X. Li et al., 2014; Yuan et al., 2019). This result also correlates with a study suggesting that REV-ERB upregulates hepatic insulin sensitivity and suppresses hepatic glucose production by regulating the firing of GABAergic neurons in the SCN (Ding et al., 2021).

Although no REV-ERB agonists have progressed to clinical trials, SR9009 is sold on the black market under the name stenabolic (a name selected by individuals marketing this compound on the black market) as a non-Food and Drug Administration (FDA)-approved performance-enhancing drug and is often falsely advertised as a selective AR modulator (hence the marketed name stenabolic) (Van Wagoner et al., 2017). To discourage the illicit use of this compound, researchers have examined potential metabolites of SR9009, seeking to develop an assay to test for this compound in athletes (Geldof et al., 2016; Mazzarino et al., 2018). The most recent information on REV-ERBs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=87).

F. Liver X Receptors (LXRα-NR1H3, LXRβ-NR1H2)

The LXRs, LXRα (NR NR1H3), and LXRβ (NR NR1H2) are members of the NR superfamily with critical roles in lipid and cholesterol homeostasis. Separate genes encode the two LXR isotypes and display distinct biodistribution. LXRα abundance is highest in the liver and found in adipose tissues, intestines, kidneys, and macrophages, whereas LXRβ is ubiquitously expressed (Apfel et al., 1994; Willy et al., 1995). Human LXRα and LXRβ share a high degree of homogeneity in their LBD (77%) and DBD (78%) amino acid sequence (Alberti et al., 2000; Svensson et al., 2003).

Crystal structures have provided invaluable insights into LXR function (Svensson et al., 2003; Lou et al., 2014). Like RARs, LXRs heterodimerize with RXR before binding REs, primarily consisting of DR4 (Willy et al., 1995; C. Song et al., 1994). When bound to DR4, LXR-RXR can control gene transcription by either LXR or RXR ligands (Wiebel and Gustafsson, 1997). Historically, LXRs were considered transcriptional activators. In the absence of ligands or in the presence of antagonists, LXRs remain bound to LXREs and recruit corepressors, resulting in silencing or suppression of transcriptional activity of the receptor (X. Hu et al., 2003). Upon binding to agonists, LXRs undergo a conformational change in the C-terminal helix H12 of the receptor, stabilizing it into an active state, leading to the dissociation of corepressors and recruitment of coactivators, leading to transcriptional activation (Farnegardh et al., 2003; Svensson et al., 2003). Subsequent studies then defined a pathway where LXR can be post-translationally modified by adding a small ubiquitin-like modifier (SUMO) group to permit corepressor recruitment, even when bound to an agonist. More recently, an assay for transposase-accessible chromatin with sequencing and ChIP-seq experiments demonstrated that T0901317, a potent agonist for LXRα and LXRβ, represses gene expression by

closing chromatin at enhancer regions occupied by LXRs, a mechanism that does not always require corepressor recruitment (Thomas et al., 2018). A better understanding of these mechanisms could be extremely valuable to LXR drug development, given that the atheroprotective properties of agonists largely depend on LXR repressive functions, such as suppressing inflammation.

1. LXR Ligands and Modulators. LXRs were first described as orphan NRs, but oxygenated cholesterol derivatives were identified as endogenous ligands (Willy et al., 1995). Endogenous oxysterol ligands or exogenously derived oxysterol from nutrition can bind and activate LXRs at physiologic concentrations (Janowski et al., 1996; Lehmann et al., 1997). 20(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxycholesterol, and 24(S), 25-epoxycholesterol are more potent oxysterols that bind both LXR isotypes (Lehmann et al., 1997; W. Chen et al., 2007). The role of oxysterols on LXR activity was confirmed in mice lacking oxysterol biosynthetic enzymes in which a high-cholesterol diet failed to induce LXR target genes (W. Chen et al., 2007). The availability and effects of oxysterols on LXR activity appear to be cell/tissue-specific in vivo. For example, 27-hydroxycholesterol, a byproduct of excessive dietary cholesterol, induces ABCA1 and ABCG1, specifically in cholesterol-loaded macrophages (X. Fu et al., 2001). In the brain, 24(S)-hydroxycholesterol is synthesized via cholesterol 24-hydroxylase (CYP46A1) enzyme and has vital functions in brain cholesterol homeostasis (Lund et al., 1999; Abildayeva et al., 2006; M. Han et al., 2020). Pioneering studies by Janowski et al. demonstrated that alteration of stereochemistry, position, and functionality of oxygenation on the side chain of the sterol are essential determinants of LXR binding and activation (Janowski et al., 1999). With SAR studies, the group elucidated key determinants of LXR binding affinities of oxysterols and identified isotype-specific ligands. By adding a second epoxide at the 5,6 position on 24(S), 25-epoxycholesterol, they were able to convert an equipotent LXRα and LXRβ ligand structure into 5,6-24(S), 25-diepoxycholesterol ligand with LXRα selectivity and weak LXRβ activity. The discovery of these isoform-specific interactions between ligands and LXR binding pockets opened the possibility of developing LXRα as well as LXRβ-selective ligands for different therapeutic applications and fewer side effects.

In addition to oxysterol and its derivatives, the intermediates of the cholesterol biosynthesis pathway, desmosterol and zymosterol, exhibit LXR activity (C. Song et al., 2000; C. D. Yang et al., 2006). Desmosterol is converted to cholesterol by the action of 24-dehydroxycholesterol enzyme and has been shown to activate an LXR-dependent pathway while suppressing SREBP (Muse et al., 2018). With the high conformational plasticity of their LBP, both LXRs can accommodate ligands of various sizes and structures (Farnegardh et al., 2003; M. Wang et al., 2003). Pharmacological steroidal and nonsteroidal LXR ligands with higher potency than endogenous ligands have been developed. T0314407 and its analog T0901317 were the first nonsteroidal ligands to be identified, followed shortly by GW3965, a novel nonsteroidal tertiary amine ligand (Schultz et al., 2000; J. L. Collins et al., 2002). Synthetic pan-LXR agonists have been preferentially employed to characterize LXR functions due to greater potency relative to endogenous ligands. LXR activation provides both therapeutic and pathogenic effects (discussed in the *Subgroup I* section) (C. Li et al., 2019; Pontini et al., 2021). Consequently, several groups have focused on bias ligand development with the goal of developing agonist ligands that would spare the undesired effects or antagonists/inverse-agonists targeting these effects. *N,N*-dimethyl-3β-hydroxy-cholenamide (DMHCA), a sterol-based ligand, was the first reported biased LXR agonist and was used in the late 1990s to validate essential structural requirements necessary for LXR agonism (Janowski et al., 1999). Biased LXR ligand development gained attention when discovering that DMHCA induces the gene network involved in macrophage cholesterol efflux (a therapeutic arm of the LXR pathway) without activating the LXR pathogenic program (Quinet et al., 2004; Kratzer et al., 2009). The development of macrophage-targeting LXR agonists is particularly interesting as the systemic lipogenic program would be bypassed entirely (Magida and Evans, 2018). Similar to DMHCA, endogenous ligands (e.g., oxysterols and desmosterol) can drive cholesterol efflux via LXR activation yet suppress cholesterol accumulation by blocking the activation of SREBP, a master regulator of lipid synthesis (Adams et al., 2004; Muse et al., 2018). DMHCA and its analogs are thus mimicking beneficial aspects of endogenous oxysterols and desmosterol to mediate their compelling therapeutic utility.

Most recently, three groups have characterized a series of optimized cholenamide derivatives, including MePipHCA, PFM009, and PFM018 (S. Yu et al., 2016; Martínez et al., 2018; Pontini et al., 2021). These cholenamide-based LXR modulators induce obviously biased responses with distinct regulation of LXR and SREBP pathways in macrophages versus hepatocytes (Muse et al., 2018). Extensive efforts have been made to identify critical determinants for designing LXR modulators with no adverse lipogenic activity. With hydrogen-deuterium exchange experiments, Belorusova et al. pinpointed differences between atheroprotective LXR compounds with versus without lipogenic activity (Belorusova et al., 2019). For instance, ligands that engage helix 3 without impacting helix 12 promote reverse cholesterol transport without inducing lipogenic activity (Belorusova et al., 2019). Further characterization of their modulatory mechanisms is needed. These newer sterol-based modulators constitute an exciting new class of LXR modulators with broader therapeutic

applications and are safer than first-class LXR synthetic agonists.

On the other side of the spectrum, an ongoing drug discovery effort aims at generating ligands that inhibit LXR lipogenic functions. Endogenous LXR antagonists such as arachnoid acid and other fatty acids were shown to block the activation of LXR target genes in rat hepatoma cell lines (J. F. Ou et al., 2001). GSK2033, the first synthetic LXR antagonist described, is a tertiary sulfonamide that inhibits LXR target genes (Zuercher et al., 2010). However, this compound displays nonspecific activity at other NRs (Griffett and Burris, 2016). More recent compounds have been described with potent inverse agonist activity owing to their ability to actively recruit corepressors to silence LXR target genes (Flaveny et al., 2015; Griffett et al., 2013, 2015). Compound SR9238, the first synthetic liver-specific inverse agonist, was developed to avoid undesirable effects on reverse cholesterol transport in peripheral tissues (Griffett et al., 2013). This compound has shown efficacy in reducing hepatic lipid accumulation and inflammation in diet-induced obesity and nonalcoholic steatosis models. Therapeutic strategies utilizing agonists and/or inverse agonists may be tailored to different pathologic conditions, tissues, or processes and are currently being actively explored across many diseases.

2. LXRs as Integrators of Lipid Metabolism, Inflammation and Disease. LXRs function as cholesterol sensors, and their activity is induced in response to excess cellular cholesterol, which triggers various adaptive mechanisms protecting cells from cholesterol overload. Cholesterol loading of cells results in increased formation of oxysterols to activate LXRs and normalize endogenous cholesterol levels. Global LXR activation suppresses cholesterol biosynthesis and absorption but mainly works through enhancing reverse cholesterol transport. In the liver, LXR promotes cholesterol efflux by activating ATP-binding cassette transporters ABCA5 and ABCG5, two essential transporters facilitating cholesterol incorporation into bile while reducing cholesterol uptake by inducing IDOL-mediated low-density lipoprotein receptor degradation (W. Chen et al., 2007; Zelcer et al., 2009). In macrophages, LXR promotes reverse cholesterol transport by inducing the expression of ABCA1, ABCG1 transporters, and ApoE cholesterol acceptors to promote the efflux of cholesterol to high-density lipoproteins (Costet et al., 2000; Repa et al., 2000; Kennedy et al., 2001; Laffitte et al., 2001). In the gut, LXRs promote transintestinal cholesterol excretion via direct upregulation of ABCG5 and ABCG8 and reduce absorption by reducing NPC1L1 protein abundance (Lo Sasso et al., 2010). LXRs also play critical roles in the brain, the body's largest cholesterol reservoir. LXR endogenous ligand 24-hydroxycholesterol reduces cholesterol content in astrocytes through activation of LXR target genes involved in cholesterol efflux along with inhibition of SREBP (Abildayeva et al., 2006; M. Han et al., 2020). Induction of APOE expression, regulation of myelination processes, and anti-inflammatory function point toward critical physiologic roles of LXR in the brain (Lefterov et al., 2007; Terwel et al., 2011; Meffre et al., 2015).

Besides regulating cholesterol homeostasis in the periphery and the brain, genetic and pharmacological studies have demonstrated that LXRs are an essential link between lipid metabolism and inflammation. LXRs can inhibit the induction of pro-inflammatory genes via transrepression (S. B. Joseph et al., 2003; Zelcer and Tontonoz, 2006). SUMOylation LXR stabilizes the repressive nuclear complexes on NFκB and AP-1 bound to promoters of pro-inflammatory target genes and inhibits transcriptional induction of inflammatory genes such as Tnfα, Il-6, and inducible nitric oxide synthase (S. B. Joseph et al., 2003; Ghisletti et al., 2007). LXRs also influence dendritic cell (DC) maturation and migration by altering the expression of CC chemokine receptor-7 (Feig et al., 2010; Villablanca et al., 2010). The anti-inflammatory effects of LXRs are also linked to lipid regulation and membrane signaling modification. Increased expression of ABCA1 was shown to reduce inflammation by removing excess free cholesterol (Ito et al., 2015; Oishi et al., 2017).

The ability of LXRs to promote reverse cholesterol transport and mitigate inflammation stimulated great interest in the therapeutic potential of LXRs as drug targets for metabolic and inflammatory diseases, and the vast majority of effort has been directed toward developing synthetic LXR agonists with a sufficient therapeutic window for clinical use. Historically, LXRs were targeted for treating atherosclerosis, hypercholesteremia, and cardiovascular diseases (N. Levin et al., 2005). The precedent for these efforts lay in studies in mouse models of atherogenesis, where hematopoietic LXR deficiency increased atherosclerosis, and LXR agonist-mediated atherosclerosis plaque regression was shown to be impaired in mouse models deficient for LXRs (Tangirala et al., 2002; N. Levin et al., 2005). Treatment with LXR agonists leads to attenuation of atherosclerotic lesions in animal models of atherosclerosis demonstrated using synthetic LXR agonists T0901317 and GW3965 as well as endogenous ligand desmosterol (S. B. Joseph et al., 2002; N. Levin et al., 2005; X. Zhang et al., 2021).

Despite these early encouraging results, activation of LXR with these first-class synthetic agonists was found to induce fatty acid and triglyceride synthesis, leading to hypertriglyceridemia and liver steatosis (Lund et al., 1999; S. B. Joseph et al., 2002). LXR activation leads to strong activation of SREBP1c, the key regulator of hepatic de novo lipogenesis. Other key lipogenic factors such as *Fasn*, *Scd-1*, *Acc*, and *Fasn* are also direct LXR targets (S. B. Joseph et al., 2002; K. Chu et al., 2006). Despite the apparent benefits of LXR activation, the undesirable lipogenic effect has

hindered the therapeutic potential of LXR agonists, hence the ongoing bias drug discovery effort. Since hepatic lipogenesis is mainly driven by LXRα and LXRβ activity alone is sufficient to reduce atherosclerosis, agonists with LXRβ selectivity may circumvent hepatic complications while retaining the desired effects on the reverse cholesterol pathway (Lund et al., 1999; Quinet et al., 2006; Ratni et al., 2009). Several compounds were designed and reported to have some degree of LXRβ selectivity, including modest sparing of adverse effects on lipogenesis. Pharmacological activation with LXR-623, an indazole-based LXRβ-selective ligand, or BMS-852927, a partial LXRβ-selective agonist, was shown to induce reverse cholesterol transport pathway genes and attenuate disease progression in mouse models of atherosclerosis without causing hepatic lipogenesis. In human clinical trials, BMS-852927 potently induced expression of RCT genes ABCG1 and ABCA1 in the blood but significantly elevated hepatic triglycerides and plasma low-density lipoprotein levels, suggesting that the drug activated the LXR lipogenic program in the liver (Kirchgessner et al., 2016). While several synthetic nonsteroidal ligands of LXRs have been developed since the early 2000s, none meet the standards for clinical use. Lipogenesis-associated undesirable effects are still among the main LXR ligand safety concerns, hence the importance of developing novel bias strategies.

Technology advances led to a better understanding of LXR biology in tissues that initially received little attention. LXR emerged as a novel therapeutic target beyond cardiovascular and metabolic diseases, particularly cancer. It has long been known that lipid and cholesterol metabolism are dysregulated in cancer cells (Yasuda and Bloor, 1932). Data from several preclinical cancer models have demonstrated that LXR agonists inhibit tumorigenesis and metastases in various types of cancer (Lo Sasso et al., 2013; Pencheva et al., 2014; Y. B. Dai et al., 2016; Villa et al., 2016; T. Chen et al., 2020). LXR agonism inhibits tumor cell cycle machinery by regulating p27 protein to inhibit CDK activity, decreases E2F2 expression in breast cancer cells, and downregulates the proto-oncogenic MYC (Fukuchi et al., 2004; Geyeregger et al., 2009; Lo Sasso et al., 2013; Vedin et al., 2013; C. Y. Lin and Gustafsson, 2015). LXR agonism induced apoptosis in cancer cells via ABCG1 induction and lipid raft modulation (El Roz et al., 2012). In glioblastoma, LXR agonism provided antitumor effects in CDOX studies by regulating LDLR expression in EGFRvIII mutant cancer cells (D. Guo et al., 2011). In hepatocellular carcinoma, LXRα agonism-induced lipogenesis caused HCC cell death due to a toxic accumulation of saturated fatty acids in mouse xenograft models resistant to sorafenib (Rudalska et al., 2021). It was hypothesized that LXR agonists resensitize HCC to sorafenib via inducing miR-378 (an inhibitor of insulin-like growth factor1 receptor). Sorafenib-resistant HCC cells reportedly lose their capacity to express miR-378 in coordination with the development of sorafenib resistance, and re-induction of the microRNA via LXR agonist treatment synergistically killed sorafenib-resistant HCC cells in vitro and reduced tumor growth in a patient-derived xenograft (PDX) mouse tumor model (Z. J. Lin et al., 2020). APOE is an LXR target gene that plays a role in a variety of tumor mechanisms associated with tumor metastasis, angiogenesis, and TME immune surveillance (Pencheva et al., 2014; Tavazoie et al., 2018). Abequolixron (RGX-104) is an isoform-selective LXR agonist in ongoing clinical trials for APOE-dysregulated tumors. Phase 1 data showed ApoE gene expression increases in whole blood leukocytes that correlated with RGX-104 dose and exposure. Peripheral immune-cell monitoring revealed myeloid-derived suppressor cell depletion, DC stimulation, and cytotoxic lymphocyte activation in patients with refractory solid tumors, suggesting strong proof of principle in humans (Mita et al., 2018).

Additional roles of LXRs in neuronal cholesterol homeostasis, myelination, neuroprotection, and neuroinflammation are being explored for targeting neurodegenerative disorders with cholesterol dysregulation, such as AD, amyotrophic lateral sclerosis, and MS. In AD, multiple mechanisms link the expression of ABCA1 with Aβ clearance and the development of AD to loss of function APOE mutations (Lewandowski et al., 2022). Increased cholesterol efflux to APOE, via induction of ABCA1, has been shown to restore lipidation of the dysfunctional APOE variant mutation APOE4. In mice, overexpression of ABCA1 enhances lipidation and rescues aggregation of APOE (Wahrle et al., 2008; Rawat et al., 2019). APP/PS1 mice (a model for AD) treated with the LXR agonist GW3965 reduced amyloid burden in the hippocampus and whole brain in an ABCA1-dependent manner (Donkin et al., 2010). Additionally, similar to the development of foamy macrophages in atherosclerosis, microglia in aging brains can accumulate lipid droplets and associate with neurodegenerative diseases (Jaitin et al., 2019; Jung and Mook-Jung, 2020; Marschallinger et al., 2020). In multiple preclinical mouse models of AD, LXR synthetic agonists GW3965 and T0901317 have been shown to increase ABCA1 and APOE expression, reduce Aβ and inflammatory markers, and improve cognitive performance. In some studies, ABCA1 KO mice have been used to demonstrate that many of the therapeutic benefits were ABCA1 dependent (Lewandowski et al., 2022).

Despite the significant adverse effects and clinical trial failures, LXR drug discovery efforts were never abandoned. The potential of LXR ligands to treat cancer and other non-cardiometabolic diseases provides a strong rationale for pursuing this therapeutic avenue. With the constant progress in computational drug discovery, it is also only a matter of time before biased

LXR ligands get approved for the treatment of cardiometabolic diseases. The most recent information on LXRs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=89).

G. Farnesoid X Receptors (NR1H4)

In 1995, the FXR was identified as an NR activated by farnesol metabolites (Forman, Goode et al., 1995). Other than being recognized as the master regulator of BA metabolism, FXR inhibits inflammation and acts as a nutrient sensor (Massafra et al., 2018; Massafra and van Mil, 2018). Two FXR genes were identified: (i) FXRα, which is evolutionarily conserved across species, encodes four isomers (i.e., α1, α2, α3, and α4) and (ii) FXRβ, which is a pseudogene in humans and primates (Huber et al., 2002; Otte et al., 2003; Y. Zhang et al., 2003; H. Wang et al., 2018). FXR regulates systemic energy homeostasis by controlling BA synthesis and transport, hepatic lipid content, and glucose homeostasis (Neuschwander-Tetri et al., 2015; Xi and Li, 2020). FXR exhibits the typical modular structure of NRs composed of AF1, DBD, LBD, and AF2, along with the flexible hinge region (Modica et al., 2010; El-Gendy et al., 2018). Like other members of this NR subfamily, FXR can be activated by steroid hormones (Staudinger et al., 2001; Makishima et al., 2002; Goodwin et al., 2003; Vacca et al., 2011).

1. FXR Ligands. FXR agonists have been used to treat liver diseases and T2D in animal models and are also being examined in clinical trials (NCT04702490) (L. Jin et al., 2013; Mudaliar et al., 2013; Neuschwander-Tetri et al., 2015; Hui et al., 2019; Patel et al., 2020; Loomba et al., 2021). Agonists are classified based on their chemical structures into steroidal and nonsteroidal. Steroidal agonists often cause undesirable side effects (such as pruritus), while nonsteroidal synthetic agonists appear to lack these side effects, and many of these agonists are currently in clinical trials. Preclinical and clinical data have demonstrated that both FXR agonists and antagonists may also hold beneficial therapeutic utility for metabolic diseases. For instance, FXR antagonists have been used to treat diabetic nephropathy (NCT03804879) and hepatitis C virus (NCT01492998) (Chianelli et al., 2020; Y. Fang et al., 2021).

Initially, all steroidal FXR agonists were based on the BA structure, and many of the primary BAs [e.g., cholic acid, chenodeoxycholic acid (CDCA)] and secondary BAs (e.g., deoxycholic acid, lithocholic acid) were among the first identified agonists of FXR. SAR studies showed that modifications at positions 3 and 7, as well as the side chain of the BA skeleton, can lead to significant enhancement in FXR agonism. Other steroidal compounds not based on Bas, such as androsterone and etiocholanolone, were then identified as FXR agonists (Y. Fang et al., 2021).

Most synthetic FXR agonists are isoxazole-based, and the isoxazole core was preserved in most of these agonists. The isoxazole core is described as a "hammerhead" structure, and very few isosteres were identified over the years. Isoxazole cores have a common binding mode in FXR LBD where they bind in a favorable pocket and turn the His447-Trp469 activation switch on and enhance the transcriptional activity (Akwabi-Ameyaw et al., 2008). GW4064 was the first potent and selective FXR full agonist and remains the main lead compound in drug discovery. The clinical applicability of GW4064 has been largely limited due to poor bioavailability and hepatobiliary toxicity. Most of the identified clinical candidates were based on the GW4064 template. Examples of GW4064 that have better drug-like properties and have advanced to clinical trials are PX-104, GS-9674, GSK8062, and GSK2324. Fexaramine (Methyl (*E*)-3-[3-[cyclohexanecarbonyl-[[4-[4-(dimethylamino)phenyl]phenyl]-methyl]amino]phenyl]prop-2-enoate) is structurally distinct from steroidal FXR agonists and GW4064. Fexaramine is a gut-restricted compound 100-fold more potent than CDCA. Fexaramine sparked a great interest in developing other intestine-specific FXR agonists, and multiple analogs with better drug-like properties have been identified (H. Wang et al., 2017; Pathak et al., 2018; Shim et al., 2022).

Knowledge of FXR antagonists is much less advanced than agonists. Two BA conjugates, Tauro-β-muricholic and glycine-muricholic, showed FXR an antagonistic effect on CDCA and GW4064. They also showed reduced ileal *Fgf15* and *Shp* gene expression when administered to mice (Shim et al., 2022). Glycine-muricholic is gut-restricted. It improved metabolic parameters and demonstrated potential therapeutic utility for treating obesity (C. Jiang et al., 2015). Although 5β-bile alcohols, 5β-cyprino, and 5β-bufol activate FXR, their α-counterparts such as 5α-cyprino and 5α-bufol have been identified as potent FXR antagonists. Both 5α- and 5β-bile alcohols bind to FXR, but only 5β-isomers induce coactivator recruitment. This difference is likely due to the difference in orientation of the A-ring in both isomers (A/B cis in 5β-isomers but trans in 5α-isomers) (Nishimaki-Mogami et al., 2006).

Progress in developing synthetic FXR antagonists is also limited. A representative example of these antagonists is the *N*-phenylbenzamide analogs. These antagonists were potent nanomolar antagonists and reduced the expression of the FXR-regulated genes SHP and BSEP in HepG2 cells and competitively antagonized FXR activated by an agonist. These novel antagonists showed selectivity toward FXR over closely related NRs (J. Schmidt et al., 2018).

There is a growing interest in modulators that simultaneously target FXR and other biologic pathways, especially for treating multifactorial liver diseases. Recently, Helmstädter et al. (2021) designed benzamide analogs as

a dual FXR/soluble epoxide hydrolase modulator. The lead compound of this series was 4-(*tert*-butyl)-*N*-(2-chloro-4-(methylsulfonamido)benzyl)benzamide, which was a potent FXR agonist (EC_{50} = 20 nM, E_{max} = 35% versus obeticholic acid) and potent soluble epoxide hydrolase inhibitor (IC_{50} = 4.1 nM). This compound is a promising clinical candidate as it simultaneously reduces the circulating lipid profile and ameliorates all main aspects of NASH: intrahepatic lipid accumulation, inflammation, and fibrosis (Hye Khan et al., 2019).

Recently, novel and efficacious dual FXR/PPARδ agonists based on the privileged isoxazole scaffold were developed as tools to study the synergistic effect of such agonists on both receptors (Schierle et al., 2020). For example, 2-(4-((2-chloro-4-((3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl)methoxy)benzyl)amino)phenyl) acetic acid was a selective partial agonist of FXR and PPARδ. This ligand is endowed with high aqueous solubility and metabolic stability and no toxicity up to 100 μM. Interestingly, this compound upregulated the expression of the FXR-related genes *BSEP* and *SHP* and indirectly downregulated *CYP7A1* in HepG2 cells. In C2C12 cells, this compound downregulated lipoprotein lipase (*Lpl*) and phosphoenolpyruvate carboxykinase 1 (*Pck1*), two PPARδ target genes. Despite the tremendous progress in developing FXR ligands, more research is needed to develop tissue-specific and target-gene selective modulators to overcome the deleterious side effects observed with numerous FXR modulators.

2. FXR Structure. Numerous X-ray crystal structures of FXR have been solved as a monomer, a homodimer, or a heterodimer. The LBD of FXR in complex with different types of modulators (i.e., agonists, partial agonists, and antagonists) has also been reported (G. Li, Lin et al., 2012). The majority of reported ligands share a common binding where they occupy the hydrophobic pocket of the FXR LBD and interact with residues located on helices H3, H5, H7, H11, and H12 (Mi et al., 2003; Flatt et al., 2009; Di Leva et al., 2013; D'Amore et al., 2014). Hydrogen bonding or π-π stacking with Phe284 or π-π stacking with His447 and Trp469 of H12 are the most frequently observed interactions between these ligands and FXR LBD (Akwabi-Ameyaw et al., 2008; Y. Fang et al., 2021). In the active conformation of FXR, H12 adopts a conformation that facilitates coactivator binding through two charge clamp ionic interactions between the coactivator and K303 (H3) and E467 (H12) (Y. Fang et al., 2021). Apo FXR showed similar interactions and overall conformation to the active conformation when complexed with the coactivator peptide (Gaieb et al., 2018; Merk et al., 2019). Interestingly, X-rays showed a significant difference in binding between the natural agonist CDCA and synthetic ligand GW4064 when both were complexed with FXR (Merk et al., 2019). While CDCA binding was found to destabilize the loop region linking H4/5 and H6 (residue K339-P341), GW4064 binding stabilized the same loop region (Merk et al., 2019). The binding of FXR antagonists such as ivermectin induces an inactive conformation where the H11-H12 loop is disordered, and corepressor peptide binds to FXR (L. Jin et al., 2013). Interestingly, partial agonists induce a conformational state where the receptor can recruit both corepressors and coactivators (Y. Fang et al., 2021).

3. FXR and Liver Diseases. Nonalcoholic fatty liver disease (NAFLD) is characterized by the accumulation of lipids in the liver in the absence of alcohol consumption or other common causes and is estimated to affect 20% to 40% of the worldwide population (Polyzos et al., 2016, 2017; Venetsanaki et al., 2019). NASH is an advanced form of NAFLD, which is characterized by inflammation and fibrosis. NASH can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma. FXR plays a key pathophysiology role in NADFL and NASH due to its abundant expression in the liver and the enterohepatic circulation of the BAs. FXR agonists are potential therapeutics for the treatment of liver diseases by mitigating abnormalities in lipid accumulation, suppressing metabolic stress-induced p53 activation, and inhibiting the progression of fibrosis and reducing inflammation (Adorini et al., 2012; Polyzos et al., 2016; Goto et al., 2018).

NAFLD is highly linked to obesity and its related metabolic abnormalities, including T2D, dyslipidemia, and activation of de novo lipogenesis (synthesis of fatty acids from glucose and other substrates). These metabolic abnormalities are also linked to an increased risk of progressing to more damaging forms of the disease. FXR plays an essential role as a regulator of lipid and glucose homeostasis as well as amino acid metabolism (Sinal et al., 2000; K. Ma et al., 2006; Massafra et al., 2017). FXR ligands have the potential for the treatment of T2D, obesity, hepatic disease, and other diseases associated with metabolism (Gadaleta et al., 2011; Chavez-Talavera et al., 2017; Sepe et al., 2018; Masaoutis and Theocharis, 2019). Because FXR agonism can potentially improve these metabolic defects, there has been a great deal of interest in targeting this receptor to treat NAFLD/NASH. Moreover, because most people with NASH die from other complications, such as cardiovascular disease, rather than liver failure per se, taking a holistic view to improving systemic cardiometabolic health has emerged as a promising therapeutic approach.

Cilofexor, PX-104, and EDP-305 completed different phases of clinical trials for the treatment of NAFLD. Tropifexor, TERN-101, EDP-305, Cilofexor and Semaglutide, Tropifexor and Cenicriviroc, and Tropifexor and LYS006 or Licogliflozin are currently in clinical trials for the treatment of NASH. FXR modulators (i.e., agonists and antagonists) are potential therapeutics

for the treatment of primary biliary cholangitis and primary sclerosing cholangitis (Bowlus, 2016). This is attributed to the regulatory role of FXR in BA homeostasis and hormonal regulation (F. Y. Lee et al., 2006). The FDA has approved obeticholic acid for treating primary biliary cholangitis. Moreover, several FXR modulators, such as Tropifexor and EDP-305, are currently in clinical trials for the treatment of PBS, while Cilofexor and a combination of Cilofexor and Semaglutide are in clinical trials for the treatment of primary sclerosing cholangitis. The most recent information on FXRs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=89).

III. Subgroup II

Subfamily II consists of RXR, COUP-TF, and hepatocyte nuclear factor-4 receptor. Although RXR is well characterized for its ability to bind to retinoids and various synthetic ligands, the other NRs in this subgroup are less characterized for their ability to bind to ligands. Both functional and structural studies confirmed the ability of some fatty acids to bind these receptors (J-I. Park et al., 2003; Evans and Mangelsdorf, 2014); however, it remains unclear whether binding of these ligands has functional consequences. In this section, RXR and COUP-TF will take center stage, with a detailed discussion of RXR as a promiscuous heterodimeric partner of various NRs and as the only receptor from Subgroup II with a confirmed activating ligand, 9-cis retinoic acid (Mangelsdorf and Evans, 1995).

A. Retinoid X Receptors (RXRα-NR2B1, RXRβ-NR2B2, RXRγ-NR2B3)

RXRs ($\alpha/\beta/\gamma$) are encoded by three different genes (*NR2B1–3*). Similar to RARs, RXRs bind RA and related retinoid compounds. RXRs are the obligatory partners for type II receptors, such as RARs, TRs, LXRs, vitamin D receptors, and PPARs. RXR contributes to gene-specific recognition and high-affinity binding to DNA while exerting different roles in regulating ligand-dependent receptor functions as permissive or nonpermissive partners. RXRs also bind to the DR1 RE as a homodimer and thus can play a role independent of its function as a dimer partner. Here, we review developments focusing exclusively on RXR and its ligands (for comprehensive reviews, see Evans and Mangelsdorf, 2014).

1. New Insight into DNA- and Receptor-Specific Regulation of RXR Function. RXR homodimers bind to DRs separated by a 1-bp spacing (DR1). However, little is known about the role of the spacing nucleotide in the regulation of RXR conformation and function. Studies using thermodynamics, X-ray crystallography, and NMR spectroscopy (Osz et al., 2019) showed that the half-site modulates the ability of the two DBDs of RXR homodimer to bind to DNA cooperatively. Variations in the half-site sequence introduce changes that can propagate from the protein-DNA interfaces to dimerized surfaces of the DBDs. Receptor-specific permissive and nonpermissive regulation of RXR is a well-established phenomenon, but the underlying mechanisms remain unknown. Using structural information derived from NMR, X-ray crystallography, and HDX-MS assays, statistical coupling analysis (SCA) (Kojetin et al., 2015) identified an evolutionarily conserved network of amino acids. This SCA network plays a role in integrating ligand binding, coregulator recruitment, and receptor dimerization to govern permissive or nonpermissive characteristics of heterodimerized RXR, such as the permissive PPAR/RXR and the nonpermissive TR/RXR. These results showed that mutagenesis within the SCA network may alter permissive or nonpermissive characteristics of RXR heterodimers. While RXRs have been viewed as silent partners in the TR/RXR heterodimer, Fattori et al. showed that 9-cis RA binding to RXR induces dissociation of corepressors from TR/RXR (Fattori et al., 2015). However, no conformational changes or recruitment of coactivators were detected. These results suggest that the "silent" behavior of RXR in its "nonpermissive" heterodimers, such as TR/RXR, is incomplete and that RXR can still partially respond to its ligands. However, this does not functionally impact gene transcription, which should be viewed as the ultimate definition of permissive or nonpermissive regulation of RXR. Given that RXR AF2 has been shown to regulate corepressor interactions in various RXR heterodimers (J. Zhang et al., 1999), it may be relevant to determine whether corepressor dissociation would still occur in TR-RXR heterodimer carrying AF2 mutations upon 9-cis RA treatment.

2. RXR Crosstalks with Other TFs and Pathophysiologic Signals. As a member of the NR family of TFs, RXRs mediate functional crosstalk with other TFs and act as a downstream target of pathophysiologic signals. Two ChIP-seq studies revealed global interplays between RXR and other transcription regulators. In the first study, ChIP-seq performed in IL4-treated macrophages revealed an extensive overlap between RXR and signal transducer and activator of transcription (STAT) 6 cistromes. Notably, a subset of the RXR cistrome co-occupied by STAT6 was enriched with active enhancers in the human $CD14^{+}$ monocyte-derived differentiating macrophages (Czimmerer et al., 2018). These studies revealed a role for RXRs in macrophage polarization. In the second study, genome-wide ChIP-seq performed in macrophages showed that RXR binds to thousands of genomic sites. However, only a small fraction of these were of functional importance. These sites engaged long-range enhancer-promoter interactions, were occupied by the pioneer factor PU.1 and the active enhancer mark

p300, and resided in CTCF/cohesin domains (B. Daniel, Nagy, Hah et al., 2014). These results suggest that while a given TF may stochastically bind to many different sites, only a small portion of the sites are functionally relevant and are likely predetermined by pre-existing chromatin and transcription regulators in a sequence- and cell-type-specific manner. Several other studies explored parallel and hierarchical interactions between RXR and pathophysiological signaling pathways in various cell types and tissues. For instance, activation of RXRα promoted HCC differentiation, which appears to be mediated by the inhibition of Wnt signaling, a suppressor of HCC differentiation. These results indicate that RXRα antagonism could serve as a therapeutic target in progressing HCC (J. Li et al., 2015). Second, granulocyte-macrophage colony-stimulating factor (GM-CSF) and RA were found to jointly induce retinal dehydrogenase 2, an enzyme encoded by the *ADH1A2* gene (Ohoka et al., 2014). Mechanistically, dual activation of SP1 and RAR/RXR synergistically stimulated the expression of the *Aldh1a2* gene. GM-CSF did not affect *Aldh1a2* expression in several other cell types in which the *Aldh1a2* promoter was also demethylated. These results revealed functional cooperation between GM-CSF/Sp1 and RA/RAR/RXR axes through a DNA methylation-independent mechanism. Third, in the demyelinating spinal cord, certain oligodendrocyte precursor cells (OPCs) remain in the demyelinated region without differentiating into oligodendrocytes. Electroacupuncture can increase the number of OPCs as well as oligodendrocytes expressing RXRγ and retinal dehydrogenase 2 (involved in RA synthesis) and promote remyelination (X. H. Yang et al., 2017). In agreement with these findings, activation of RXRγ by exogenous 9-cis retinoic acid enhanced the differentiation of OPCs into oligodendrocytes. These results suggest that electroacupuncture may promote remyelination through activation of RXR. Finally, a genome-wide association study implicated RXR in smallpox vaccine immune responses (McKinney et al., 2016), consistent with a previous epistasis network analysis of the smallpox vaccine (Davis et al., 2013).

3. Physiologic and Pharmacological Roles of Endogenous and Synthetic RXR Ligands. Although 9-cis RA is the first identified endogenous ligand for RXR, its physiologic importance remains debatable (de Lera et al., 2016). First, a study in mice deficient of the retinol-binding protein *Rbp1* gene, a molecule providing bioavailability of RA, suggested that 9-cis-13,14-dihydroretinoic acid (9CDHRA) is a more potent endogenous physiologic ligand for RXR (Ruhl et al., 2015). Rbp1 deficient mice had reduced levels of 9CDHRA and displayed memory deficits. Second, 9CDHRA can bind and activate RXR to regulate gene transcription both in vitro and in vivo. Third, treating Rbp1 deficient mice with 9CDHRA normalized their phenotype like RXR ligands. While studies of endogenous ligands help dissect the physiologic functions of RXR, synthetic RXR ligands, also known as rexinoids, have gained attention, given their potential therapeutic uses in human diseases. An FDA-approved RXR agonist, bexarotene, is currently employed in the clinic to treat cutaneous T-cell lymphomas (Querfeld et al., 2006). Studies of bexarotene in various other tissues and disease models have revealed multifaceted beneficial and/or side effects. The use of bexarotene in an aggressive model of AD mitigated neurodegeneration and improved cognitive function (Mariani et al., 2017). Bexarotene also reduced deposits of the amyloid-beta plaques, which could further contribute to its therapeutic effects in AD. Mechanistic studies show that bexarotene directly impacts the RXR-controlled cistrome and transcriptome in the cortex of both APOE3 and APOE4 mice and that bexarotene also induces epigenetic changes associated with neuronal differentiation. These results show that the RXR-controlled gene network antagonizes the deleterious effects of amyloid-beta oligomers (Mounier et al., 2015; K. N. Nam et al., 2016). In another study, bexarotene improved synaptic integrity through neuronal LRP1 (Tachibana et al., 2016). However, this study revealed significant health risks, such as liver failure, thus raising caution about its therapeutic applications. Finally, bexarotene and tazarotene (a selective agonist of RAR) were shown to reduce femur index through different mechanisms affecting bone turnover in rats (Nowak et al., 2016).

In studies of other RXR ligands, 9-cis RA, docosahexaenoic acid, and methoprene acid were examined for their effects on platelet regulation (Unsworth et al., 2017). The results showed that RXRs may prevent thrombus formation and platelet responses to various stimuli. These results offer new insight into the cardioprotective effects of RXR ligands. The pan-RXR ligand PA024 suppressed adrenal synthase (*CYP11B2*) gene expression, aldosterone secretion, and blood pressure (Suzuki et al., 2017). With such benefits, PA024 may be proposed as a novel anti-hypertensive drug. In another study, the RXR pan-agonist HX630 inhibited *Nur77* and *Nurr1* mRNA expression in a corticotroph tumor of the pituitary gland, which underlies its inhibitory effect on tumor growth (Saito-Hakoda et al., 2015). This latter study also suggests that RXR agonists would be great therapeutic candidates to normalize cortisol production in Cushing's disease.

It was hypothesized that RXRγ activity contributes to melanoma relapse by driving the accumulation of neural crest stem cells, a cell lineage strengthening cancer cell stemness (Rambow et al., 2018). Harnessing this issue, treatment with an RXR antagonist reduced neural crest stem cells in minimal residual disease and delayed cancer recurrence. In contrast, RXR shows anti-breast cancer activities. Two RXR agonists, tributyltin isothiocyanate and triphenyltin isothiocyanate were cytotoxic in MCF7 and MDA-

MB-231 breast carcinoma (Hunakova et al., 2019). Mechanistic studies showed that RXR agonists caused DNA damage in these cells. Other RXR agonists, 9-cis-UAB30 (UAB30) and Targretin reduced the incidence of methylnitrosourea-induced mammary cancers. Src tyrosine kinase, an enzyme that regulates cell motility and invasives, was suppressed by UAB30 and Targretin. This is an off-target effect that may mediate their anticancer properties (M. S. Kim et al., 2015). Similarly, UAB30 reduced cell survival, proliferation, and motility of group 3 medulloblastoma PDX cells and diminished in vivo PDX cell invasion. This therapeutic effect was observed with RA treatment, thus justifying further investigation (Garner et al., 2018). RA has been commonly used to reduce tumor resistance to traditional therapies for neuroblastoma and has been provoking inevitable side effects. However, the benefits may outweigh the adverse reactions. In a preclinical evaluation, treating neuroblastoma cells or tumor xenografts with UAB30 induced an array of antitumor effects, including reduced cell survival, invasion, and migration, arrested cell-cycle progression, and increased cancer cell apoptosis (Waters et al., 2015). Together, these studies support the claim that RXR targeting ligands may hold oncologic therapeutic potential. The most recent information on RXRs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=92).

B. Chicken Ovalbumin Upstream Promoter Transcription Factors (COUP-TFI–NR2F1, COUP-TFII–NR2F2)

The COUP-TF subfamily comprises two members encoded by *NR2F1* and *NR2F2* genes located on different chromosomes (Miyajima et al., 1988). Isolation of a human complementary DNA clone encoding COUP-TFs and comparing these with known NR sequences revealed similarities with Subgroup II (L-H. Wang et al., 1989). COUP-TFI mutations increase the risk of hypotonia, seizure, and intellectual disability (Bosch et al., 2014); optic atrophy syndrome (Martin-Hernandez et al., 2018); and autism spectrum disorders, oromotor dysfunction, thin corpus callosum, and hearing defects (C. A. Chen et al., 2016). Mutations of COUP-TFII have been identified and associated with heart defects (Al Turki et al., 2014) and diaphragmatic hernia (High et al., 2016). Specific functions of COUP-TFs include central and peripheral neurogenesis (Y. Qiu et al., 1997; C. Zhou et al., 1999, 2001; Yamaguchi et al., 2004; Armentano et al., 2006, 2007; Faedo et al., 2008; B. J. Kim et al., 2009; S. Satoh et al., 2009; Tomassy et al., 2010; Rada-Iglesias et al., 2012; K. Tang et al., 2012) angiogenesis (Alliegro, 2007), lymphangiogenesis (F-J. Lin et al., 2010), heart development (Pereira et al., 1999), arterial-venous specification (You et al., 2005), energy metabolism (L. Li et al., 2009), adipogenesis (Z. Xu et al., 2008), and organogenesis (C. T. Lee et al., 2004; Petit et al., 2007; B. J. Kim et al., 2009; C. T. Yu et al., 2012). COUP-TFI is involved in the development of the neocortex, hippocampus, and ganglionic eminences, which may explain why haploinsufficiency leads to various cognitive disorders (Bertacchi et al., 2019). Both isoforms play roles in human forebrain development but have different expression patterns. COUP-TFI is expressed in a posterior high/anterior low gradient, while COUP-TFII is restricted to the ventro-temporal cortex (Alzu'bi et al., 2017).

1. COUP-TF Structure, Molecular Action, and Chromatin Remodeling Function. No COUP-TF ligands have been identified (Pereira et al., 2000). Parts of the COUP-TF structure closely resemble that of other NRs with nearly complete homology within the DBD (97%) and LBD (99%) (Y. Qiu et al., 1995; Alfano et al., 2014). AF1 is a less conserved region, thus suggesting that COUP-TF factors recognize similar cis-regulatory elements but bind to different co-factors that distinguish their roles from other NRs (Cooney et al., 1992; J-I. Park et al., 2003).

In contrast to other NRs, COUP-TF does not require heterodimerization for active gene repression but rather transrepresses the ligand-dependent activation of its heterodimeric partners lacking their own DBD (Leng et al., 1996). For direct repression, COUP-TF binds to oligonucleotides containing both DRs of GGTCA and palindromes and with different spacings of the GGTCA repeats. Like many other NRs, well explained in the ROR chapter, COUP-TFs repress gene transcription by binding to genomic DNA and recruiting corepressors and HDACs (S. Y. Tsai and Tsai, 1997). COUP-TF dimers adopt a confirmation that can accommodate binding to various DR sequences (Cooney et al., 1992). To stimulate gene expression COUP-TFs, bind to the same DR elements but recruit coactivators and HATs (Hall et al., 1995). Given the shared binding sites, cofactor accessibility and cellular context dictate COUP-TF transcriptional action. Novel putative COUP-TF DNA binding sites have been identified through computational and bioinformatics analyses. Hits were validated for direct regulation, identifying two conserved COUP-TFI binding sites in the *Fabp* gene promoter (Montemayor et al., 2010). These findings challenge the general consensus that COUP-TFs have the highest affinity for DR1 (Sagami et al., 1986). COUP-TFI binding sites are associated with H3K9 acetylation and enriched for coactivators, such as chromatin remodeling protein (CBP) and SRC1, creating an open chromatin environment to stimulate gene transcription (Montemayor et al., 2010). In addition to these chromatin remodelers, DNMT3a/b DNA methyltransferase may associate with COUP-TFI to activate gene expression (Gallais et al., 2007).

2. COUP-TFII as a Potential Therapeutic Target for Tumor Progression and Metastasis. COUP-TFII directly promotes tumor progression due to its essential roles in angiogenesis and lymphangiogenesis (Alliegro,

2007; F-J. Lin et al., 2010), two processes required for tumor progression, invasion, and metastasis (Pereira et al., 1999; Pralhad et al., 2003). COUP-TFII results in embryonic lethality due to atrial and vascular underdevelopment (Pereira et al., 1999; F-J. Lin et al., 2010). The angiogenic properties of COUP-TFs arise from two mechanisms, the Ang-1/Tie2 pathway (Ang-1, Angiopoietin-1) (Fukuhara et al., 2010) and the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)-2 pathway (J. Qin, Chen, Yu-Lee et al., 2010). COUP-TFII directly binds to the *Ang-1* promoter to induce its transcription, thus enhancing vessel remodeling in progressing cancers (J. Qin, Chen, Xie et al., 2010). COUP-TFII represses VEGFR-1 transcription in epithelial cells, which enhances the VEGF/VEGFR-2 signaling and promotes blood epithelial cell sprouting and proliferation (L-R. You et al., 2005; X. Chen et al., 2013). In experimental models of breast and pancreatic cancer, COUP-TFII deletion aborted lymphangiogenesis, thereby inhibiting lymph node metastasis (F-J. Lin et al., 2010; J. Qin, Chen, Yu-Lee, et al., 2010). However, COUP-TFII plays divergent roles in prostate cancer. On the one hand, COUP-TFII destroys the TGF-β-dependent growth barrier, which drives prostate tumor progression (J. Qin et al., 2012). On the other hand, COUP-TFII also inhibits androgen-dependent prostate cancer cell proliferation by corepressing the AR (C-H. Song, Lee et al., 2012).

The ligand-free 1.48 Å crystal structure of the human COUP-TFII LBD indicates that COUP-TFII contains a ligand-binding pocket whose activity can be regulated by small diffusible ligands (Kruse et al., 2008). Also, 9-cis- and ATRA induce COUP-TFII-dependent transactivation and increase the recruitment of coactivators (B. Lin et al., 2000). Therefore, COUP-TFII may be a "druggable" target for cancer treatment. Further characterization of COUP-TFII is needed for unraveling specific functions in different cancer types to select the proper kind of ligands (e.g., agonists, antagonists, etc.). IUPHAR guide to pharmacology website: https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=95.

IV. Subgroup III

This group consists of steroid receptors and ERR, which are critical regulators of reproductive, developmental, and metabolic functions (Fuller, 1991). Corticosteroids, sex hormones, and other cholesterol-derived hormones regulate these receptors via direct interaction. GRs, ARs, PRs, ERs, and ERRs belong to this group.

A. Glucocorticoid Receptor (NR3C1)

In recent years, research on GRs has advanced our understanding of the mechanisms by which glucocorticoids elicit cell-specific responses. Much of this work has been possible due to technological advances in cellular and molecular biology. The use of ChIP-seq, for example, has facilitated the identification of GR DNA-binding sites. Moreover, the growing number of genetic models has advanced our understanding of local and systemic roles played by glucocorticoids. This section focuses on the genetic regulation, structure, and signaling of GR.

1. GR-Mediated Gene Regulation. Gene activation by liganded GR occurs through GR binding to glucocorticoid-responsive elements (GREs). GR-mediated gene repression is less understood. GR is thought to inhibit transcription through transrepression, a process dependent on protein-protein interactions between liganded receptors and other DNA-bound TFs, such as NFκB and AP-1. Surjit et al. showed that GR-dependent gene repression also employs a negative GRE (nGRE), in which GR binds to DNA and recruits the corepressors SMRT and NCoR (Surjit et al., 2011). This form of regulation occurs when two GR-liganded monomers bind to the nGRE, a palindromic sequence [consensus sequence: CTCC$(n)_{0\text{-}2}$GGAGA] with a variable spacer of 0 to 2 basepairs (Hudson et al., 2013). Indeed, glucocorticoid-induced repression of GR transcription, a negative feedback process known as homologous downregulation or autorepression, occurs through a nGRE in exon 6 of the *NR3C1* gene (Ramamoorthy and Cidlowski, 2013).

The classic model for GR-mediated gene regulation, however, has been brought into question with the findings of Uhlenhaut et al., who used genome-wide profiling of GR, p65 (NFκB subunit), and c-Jun (AP-1 subunit) in LPS-stimulated macrophages. This team correlated transcriptional outcome with TF occupancy at enhancer REs (Uhlenhaut et al., 2013). Strikingly, GR binding to canonical GREs or the sequence described as nGREs was not predictive of transcriptional polarity. In fact, GR occupancy at either RE can equally activate or repress gene transcription (Uhlenhaut et al., 2013). The authors concluded that the presence of a GRE in a gene enhancer confers responsiveness to GR but does not dictate the transcriptional outcome. Rather, the effect of GR-GRE binding on transcription depends on chromatin organization and epigenetic regulation.

2. GR Splice Variants and Isoforms. Although GR is nearly ubiquitously expressed, responses to glucocorticoids are highly heterogeneous (also known as "system bias" discussed in the *Subgroup I* section). The level of sensitivity to and biologic effects of glucocorticoids depends on GR localization. The discovery of GR splice variants (GRα, -β, -γ, -A, and -P) has provided, at least in part, a molecular mechanism for this long-standing mystery. Further complicating matters is the alternative translation initiation. Translation from these alternative sites affects the length and, thus, the function of NTD, which impacts cofactors and

transcriptional machinery. Eight alternative translation initiation sites occur in exon 2 (exon 1 is not translated) and are conserved across humans, monkeys, rats, and mice. Thus, a single GR mRNA transcript can generate eight GR isoforms with progressively shorter NTDs: GR-A, GR-B, GR-C1, GR-C2, GR-C3, GR-D1, GR-D2, and GR-D3 (N. Z. Lu and Cidlowski, 2005, 2006). All eight translational isoforms have been identified for the GRα splice variant. Each of the four other splice variants contains the same alternative translation start sites, thus yielding 32 additional translational isoforms.

All GRα translational isoforms bind glucocorticoid ligands and interact with GREs (N. Z. Lu et al., 2007), given their intact DBDs and LBD. However, selective expression of individual GRα isoforms in cells has revealed isoform-specific transcriptomes and distinct capacities to mediate glucocorticoid-induced cell death (N. Z. Lu et al., 2007; I. Wu et al., 2013). In GRE-based reporter assays, the GRα-C3 isoform is the most transcriptionally active, whereas GRα-D isoform is the least active (N. Z. Lu and Cidlowski, 2005). Moreover, cells expressing GRα-C3 are most sensitive to dexamethasone, whereas those expressing the GRα-D3 isoform are relatively insensitive (N. Z. Lu et al., 2007). GRα-D does not repress NFκB activity like other GRα isoforms or repress antiapoptotic genes (Gross et al., 2011). Moreover, unliganded GRα-D isoforms are constitutively localized within the nucleus. In contrast, GRα-A, -B, and -C isoforms remain in the cytoplasm until ligand binding initiates their translocation in the nuclear compartment (N. Z. Lu et al., 2007).

GRα translational isoforms are expressed throughout the body, but the relative abundance of each isoform varies substantially across cell types. GRα-C isoforms, for example, are highly expressed in the pancreas, lung, and colon but are low in the liver (N. Z. Lu and Cidlowski, 2005; N. Z. Lu et al., 2007). GRα-D isoforms are abundant in the spleen and bladder but are relatively scarce in the heart and pancreas—GR isoform distribution changes with maturation or activation within a cell lineage. For instance, DCs predominantly carry GRα-D isoforms in the early stages and acquire GR-A at the expense of other isoforms during maturation. Changes in relative isoform abundance have a significant impact on their susceptibility to glucocorticoid-induced cell death (Y. Cao et al., 2013). Relative amounts of GR translational isoforms may be an important mechanism behind system-biased responses to GR ligands.

3. GR Signaling. Acute and high doses of steroids exert rapid immunosuppressive effects that are independent of transcriptional modulation by GRs and are thought to result from the nongenomic effects of GR signaling (Stahn and Buttgereit, 2008). Nongenomic effects of glucocorticoids do not require protein synthesis and occur within seconds to minutes of GR binding to ligand (Haller et al., 2008). In thymocytes, activated GR translocates to mitochondria and regulates apoptosis (Boldizsar et al., 2010). A membrane-bound form of GR induces nongenomic effects through crosstalk with the T cell receptor (Bartholome et al., 2004) and regulating neural progenitor cell proliferation (Samarasinghe et al., 2011). Protein kinases may contribute to these nongenomic effects (Lowenberg et al., 2005).

Cell-specific roles of GR signaling have been delineated using numerous mouse strains bearing cell-specific deletion of GR. For example, cardiac-specific deletion of GR demonstrated the role of GR signaling in cardiovascular system development and maintenance (Oakley et al., 2013; Rog-Zielinska et al., 2013). Ablation of GR in myeloid cells increased susceptibility to LPS-induced septic shock (Bhattacharyya et al., 2007). Another conditional knockout informed that immunosuppression in a mouse model of MS (Wust et al., 2008) and helminth infection (Kugler et al., 2013) achieved GR signaling in T cells. GR deletion in different cells of the CNS uncovered important roles of GR signaling in mood, depression, and anxiety (Boyle et al., 2005; M. V. Schmidt et al., 2009). Mice lacking GR in osteoblasts were protected from prednisone-induced bone loss, implicating osteoblasts as the cellular culprits behind glucocorticoid-induced osteoporosis (Rauch et al., 2010). The ongoing development and use of conditional GR transgenic animals will undoubtedly contribute to our understanding of the pleiotropic effects of corticosteroids. The latest information on GR and its ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=98).

B. Androgen Receptor (NR3C4)

The AR shows substantial structural similarity to the other steroid receptors ERα, ERβ, PR, GR, and mineralocorticoid receptor (Weikum et al., 2018; Nuclear Receptors Nomenclature Committee, 1999). The highest expression level of AR is found in male reproductive organs, which correlates with its essential role in male fertility. Still, AR is also found in a wide variety of male and female tissues, controlling a diversity of physiologic processes (Ruizeveld de Winter et al., 1991; Fujimoto et al., 1994; Sinha-Hikim et al., 2004; T. Matsumoto et al., 2013; C. Chang et al., 2014). AR KO mice showed the importance of this receptor in male phenotype, sexual development, and fertility. Male AR KO mice display female-like appearance, testicular atrophy, are infertile, and have reduced levels of circulating testosterone (Yeh et al., 2002; C. Chang et al., 2013). These characteristics are reminiscent of humans with androgen-insensitivity syndrome. Seminal vesicles and the prostate strongly rely on AR. AR in the stromal compartment drives organ development, while AR expressed in prostate luminal cells is necessary for cell survival and secretory

function (Yeh et al., 2002; Cunha, 2008; C. Chang et al., 2013). In humans, abnormal expression or function of AR is linked to different pathologies, such as androgen-insensitivity syndrome, spinal and bulbar muscular atrophy (Kennedy's disease), hypogonadism, benign prostatic hyperplasia, and prostate cancer (Shukla et al., 2016). The number of cytosine-adenine-guanine/polyglutamine (polyQ) repeats in the NTD is highly variable within the human population and influences AR folding, stability, and coactivator binding. The length of the polyQ is associated with partial loss in AR transcriptional function (M. Sasaki et al., 2003; Tan et al., 2015; Giorgetti and Lieberman, 2016). Specifically, the expansion of AR polyQ drives muscle dysfunction underlying spinal and bulbar muscular atrophy (Tan et al., 2015; Nath et al., 2018). Furthermore, associations between the number of polyQ repeats and prostate cancer development and response to therapy have been identified in mouse models (Robins, 2012; Higgins et al., 2015).

1. AR-Mediated Signaling. The AR is a ligand-activated TF that binds with the highest affinity to the testosterone metabolite dihydrotestosterone and regulates the expression of a wide range of genes in a tissue- and cell-specific manner (C. Chang et al., 2014; D. Li et al., 2019; Ozturan et al., 2022; Westaby et al., 2022).

In the absence of androgens, AR is located predominately in the cytoplasm complexed with chaperones and cochaperones that maintain the receptor in an inactive state with the appropriate structure for ligand recognition and binding (Azad et al., 2015). Ligand-binding induces receptor phosphorylation and conformational changes that promote homodimer formation, cofactor binding, and nuclear translocation (Echeverria and Picard, 2010; Heemers and Tindall, 2007; T. Matsumoto et al., 2013). Different interactions between AR monomers allow homodimer formation, including interactions between the DBD, the LBD, and N/C interactions (intra- and intermolecular). Interrupting these interactions impedes AR signaling and results in a female phenotype in male mice (Shaffer et al., 2004; Askew et al., 2012; van Royen et al., 2012; Nadal et al., 2017; Chauhan and Heemers, 2021; El Kharraz et al., 2021). While DBD and LBD interactions are involved in dimerization, N/C interactions can also occur within the same molecule. Intramolecular interactions begin in the cytoplasm after ligand binding. In contrast, intermolecular N/C interactions subsequently occur in the nucleus and are necessary to mediate optimal AR binding to androgen REs (AREs) in chromatin (van Royen et al., 2012). Analysis of the structure of the ligand-activated and DNA-bound AR using cryo-electron microscopy revealed that AR monomers are localized in parallel with dimerization interfaces formed by LBDs and DBDs. In this model, the NTDs wrap around the LBD, allowing N/C interactions. Interestingly, N/C interactions, a distinct characteristic of the AR, affect coactivator binding. N/C interactions limit the participation of the LBD and allow the NTD to mediate the binding to coactivators SRC3 and p300, a mechanism that differs from ERα (X. Yu et al., 2020).

AR translocates into the nucleus by gliding along microtubules (Bai et al., 2019; Echeverria and Picard, 2010). The AR contains several nuclear localization signals that promote binding to import receptors in the nuclear membrane, such as importin α and β (Kaku et al., 2008; Echeverria and Picard, 2010; Clinckemalie et al., 2012; Thadani-Mulero et al., 2012). Once in the nucleus, zinc finger motifs in the DBD allow AR binding to AREs in regulatory regions of target genes, which facilitates the recruitment of RNA polymerase II (RNAPII) to the transcription start site (TSS). AR binds with different affinities to the chromatin, leading to biased system responses. While consensus AREs seem to induce expression of pro-proliferative genes in prostate cancer, selective AREs, which are half-sites of the palindromic consensus element and show higher specificity for AR, control genes involved in cell differentiation (Kregel et al., 2020). Unlike other steroid hormone receptors, AR transcriptional activity is more reliant on AF1, as exemplified by the constitutive activity of AR variants (AR-V) that lack the LBD (Jenster et al., 1995; Bevan et al., 1999; B. He et al., 2006; Badders et al., 2018; X. Yu et al., 2020; Westaby et al., 2022). In fact, these AR mutants induce gene transcription in the absence of androgens (Y. Zhu and Luo, 2020). Dimerization is a prerequisite for AR and AR-V transcriptional activity, but AR-V dimerize via DBD interactions. Additionally, AR-V can heterodimerize with full-length AR in an androgen-independent manner by DBD and N/C interactions or form heterodimers with other AR-V to potentiate their actions (D. Xu et al., 2015; Y. Zhan et al., 2017).

Understanding the cessation of AR activity after androgen withdrawal has been intensively studied. New findings indicate that nuclear AR is not exported back to the cytoplasm as previously believed; instead, AR is retained in the nucleus and undergoes polyubiquitination and proteosome-mediated degradation. A nuclear degradation signal located in the DBD is critical for this nuclear AR degradation, the final step of the androgen signaling process (Lv et al., 2021).

AR activation is regulated through interactions with an array of proteins, including chaperones, coregulators, cytoskeletal, kinases, and TFs (Y. Shang, Myers, and Brown, 2002; D. K. Lee and Chang, 2003; Heemers and Tindall, 2007; Echeverria and Picard, 2010). Over 200 AR coactivators and corepressors have been identified (Heemers and Tindall, 2007; X. Yu et al., 2020). Pioneer factors such as FOXA1 and GATA2 play critical roles in regulating AR transcriptional activity by directing AR chromatin binding (N. Gao et al., 2003; Q. Wang et al., 2007; B. He, Lanz et al., 2014; J. C. Zhao et al., 2016). Comprehensive analysis of the contributions of a

panel of clinically relevant AR coactivators in phosphatidylcholine (PC) revealed intricate modes of AR-mediated gene expression, which depends on the particular AR target gene, AR coregulator, and AR binding sites (S. Liu et al., 2017).

Similar to the GR (discussed in the *Subgroup III* section), membrane-initiated AR signaling provides rapid responses through nongenomic actions (Michels and Hoppe, 2008; E. R. Levin and Hammes, 2016; Mauvais-Jarvis, Lange, and Levin, 2022). Palmitoylation of the AR allows binding to caveolin-1 and migration to the caveolae at the plasma membrane, where AR can interact with other receptors such as endothelial growth factor (EGF) receptor (Acconcia et al., 2003; Pedram et al., 2007; Sen et al., 2010). Rapid cellular response to androgens through these cell-surface receptors promotes activation of transduction pathways, leading to transcription-dependent or transcription-independent effects contributing to cellular processes including proliferation, migration, and apoptosis (Lutz et al., 2001; Hatzoglou et al., 2005; Papadopoulou et al., 2008; Migliaccio et al., 2011; Peinetti et al., 2018).

2. Regulation of the AR *Gene.* The human *NR3C4* (*AR*) gene is located on the X chromosome at the locus Xq11-Xq12 with its expression tightly controlled by multiple regulatory elements (Lubahn et al., 1988; C. J. Brown et al., 1989; Burnstein, 2005; Hunter et al., 2018). The promotor region of the *AR* gene has been mapped between −74 and +87 bp of the TSS (Takane and McPhaul, 1996). Although the promotor region lacks TATA and CAAT boxes, it consists of GC-rich regions that serve as binding sites for many TFs, including a primary driver of *AR* gene expression, SP1 (W. D. Tilley et al., 1990; Takane and McPhaul, 1996; Hunter et al., 2018). Three independent studies using samples from patients diagnosed with castration-resistant prostate cancer (CRPC) that progressed following androgen deprivation therapy identified an *AR* gene enhancer region (Quigley et al., 2018; D. Y. Takeda et al., 2018; Viswanathan et al., 2018). This enhancer, which is located 650 kilobase pairs (kbp) centromeric to the *AR* gene, is acetylated on H3K27 (epigenetic modification present in active enhancers) (Pradeepa, 2017) and amplified in metastatic CRPC tumors versus localized prostate cancer (D. Y. Takeda et al., 2018). Disruption of this enhancer results in an AR-dependent decrease in cell growth. In contrast, the addition of extra copies to androgen-dependent cells promotes higher *AR* expression and cell proliferation in low androgen conditions, as well as resistance to enzalutamide, the potent second-generation AR antagonist used in advanced prostate cancer. Due to selective pressure, the *AR* enhancer is co-amplified with the *AR* gene or is relatively more amplified than the *AR* gene in advanced disease (Viswanathan et al., 2018). Histone modifications are consistent with this enhancer being active during prostate development, silenced, and then reactivated in response to androgen deprivation therapy to promote CRPC (D. Y. Takeda et al., 2018). Patient-derived xenografts from serially obtained prostate cancer samples from a single patient showed *AR* gene and enhancer amplification after metastasis (Porter et al., 2021). The *AR* gene has an unusually long 5′UTR, which serves as a docking site for different regulatory proteins (Hunter et al., 2018). The 5′UTR can enhance *AR* gene transcription but also contains inhibitory elements, which may help maintain homeostatic AR protein abundance (L. G. Wang et al., 2004; Hay et al., 2015).

AR gene expression is regulated by many TFs, including SP1, c-Myc, NF-κB, GATA2, ROR-γ, LEF1, and E2F1 (Y. Li et al., 2009; L. Zhang et al., 2009; Sharma et al., 2010; D. Wu et al., 2014; J. Wang et al., 2016; Hunter et al., 2018; Bai, Cao et al., 2019). SP1 binds to the *AR* gene promotor region and GC boxes along the 5′UTR to increase *AR* gene expression (H. Yuan et al., 2005; Hay et al., 2015; Deng et al., 2017). Purine-rich element-binding protein alpha, a repressor of *AR* gene transcription, has overlapping binding sites with SP1 in the *AR* gene. Thus, the relative amounts of these TFs may dictate the expression of *AR* (L. G. Wang et al., 2008; Hay et al., 2015; Hunter et al., 2018). NFκB subunits also bind to AREs to regulate *AR* gene expression in prostate cancer cells. The effect of NFκB on *AR* gene transcription depends on the subunit and context (Ko et al., 2008; L. Zhang et al., 2009; Thomas-Jardin et al., 2020).

The *AR* gene is subject to numerous epigenetic regulatory mechanisms. For example, methylations H3K27me3 and H3K9me2 on the *AR* gene promotor of AR-nonexpressing small cell prostate cancer cell lines maintain the repressed state of the *AR* gene. AR transcription can be restored by inhibiting methyltransferase activity (Kleb et al., 2016). In AR-expressing prostate cancer cells, the histone methyltransferase SET and MYND domain-containing protein 3 promote H3K4 di- and trimethylation in the proximal promoter of the *AR* gene. Methylation of H3K4 leads to acetylation of H3 and promotes SP1 binding (C. Liu et al., 2013). SP1 can additionally recruit the arginine methyltransferase PRMT5 to the *AR* gene promotor and together form a complex with BRG1 to induce symmetrical demethylation of H4R3 and promote *AR* gene transcription and cell growth (Deng et al., 2017). Recently, the acetylation of H4 by the HAT1 in the *AR* gene promotor was shown to increase *AR* gene transcription. Furthermore, a correlation between HAT1 and *AR* expression was observed in prostate cancer patient samples. Interestingly, reduced *AR* (and *AR-V*) expression by knocking down HAT1 resensitizes CRPC cells to treatment with enzalutamide (Z. Hong et al., 2021). A recent study described that AT-rich interaction domain 5B can recruit KMT2A to a

region of the *AR* gene spanning from the TSS to 500 bp downstream to induce histone methylation of H3K4. This epigenetic modification leads to the recruitment of RNAPII to induce *AR* gene transcription (Yamakawa et al., 2018).

Autorepression and autoinduction of the *AR* gene have been widely described. AREs located in the 5′UTR and the second intron of the *AR* gene can serve as negative regulators of *AR* gene expression (L. G. Wang et al., 2004; Hay et al., 2014). Ligand-bound AR can recruit lysine-specific demethylase 1 to the second intron of the *AR* gene to induce demethylation of H3K4me1,2 and repress *AR* gene transcription. Interestingly, this site is mono- and dimethylated during CRPC, promoting *AR* gene transcription in low-androgen environments (Cai et al., 2011). In contrast, AREs located in the coding region (exons D and E) of the *AR* gene are responsible for androgen-mediated upregulation of *AR* gene expression in some contexts (J. L. Dai and Burnstein, 1996; Grad et al., 1999). Autoregulation of *AR* gene expression may be significant in prostate cancer treatment since, androgen deprivation therapy, the gold standard therapy for advanced cases, can disrupt these feedback loops and cause therapeutic resistance.

3. Effects of AR Phosphorylation on Receptor Function. The AR acts as a node that integrates androgens with other extracellular signaling pathways via AR PTMs, such as phosphorylation, SUMOylation, ubiquitination, methylation, and acetylation (S. Wen et al., 2020). AR is phosphorylated at 19 sites on serine, threonine, and tyrosine residues in each of the major protein domains, but the vast majority of these sites located in the NTD (Koryakina et al., 2014, 2015; S. Wen et al., 2020). AR phosphorylation regulates AR stability, nuclear localization, transcriptional activity, and DNA binding. The proximal kinases and biologic manifestations of many sites are still unknown. The highest stoichiometric phosphorylation on the AR in response to hormones is S81, and studies suggest that CDK1, CDK2, CDK5, and CDK9 can all contribute to this PTM (S. Chen et al., 2006; Gordon et al., 2010; F. N. Hsu et al., 2011; Jorda et al., 2018; X. Gao et al., 2021). AR S81 phosphorylation increases AR transcriptional activity and protein stability and is required for optimal cell growth (Gordon et al., 2010; F. N. Hsu et al., 2011; S. Chen et al., 2012; Williamson et al., 2016; Grey et al., 2017; X. Liu et al., 2017). Additionally, S81 phosphorylation is associated with progression to CRPC (Russo et al., 2018; X. Gao et al., 2021). Another target site of multiple kinases is S210/213/215, which is phosphorylated by both Akt and PIM-1 (Y. Wen et al., 2000; H. K. Lin et al., 2001; Taneja et al., 2005; Linn et al., 2012; Ha et al., 2013), Akt phosphorylation of S210 regulates AR transcriptional activity (Y. Wen et al., 2000; H. K. Lin et al., 2001, 2003; Taneja et al., 2005), whereas PIM-1 phosphorylation of S213 regulates AR protein stability and transcriptional activity (Linn et al., 2012). Recently, it was demonstrated that PIM-1 also phosphorylates the AR-coactivator 14-3-3ζ, which is necessary for their association and to recruit other coactivators to promote target gene transcription, including genes involved in migration and invasion (Ruff et al., 2021). AR phosphorylation on S650 in the hinge region by JNK and p38 inhibits AR transcriptional activity by promoting AR nuclear export (Gioeli et al., 2006). Y267 and Y363 are phosphorylated by ACK, resulting in increased AR transactivation and CRPC cell growth (Mahajan et al., 2007; Karaca et al., 2015). Y534 can be phosphorylated by SRC kinase, and there is a correlation between the levels of SRC kinase and AR tyrosine phosphorylation in prostate cancer (Z. Guo et al., 2006; Chattopadhyay et al., 2017). Cyclin D3/CDK11p58 phosphorylation of S308, which allows binding to checkpoint kinase 2, decreases AR transcriptional activity and proliferation of prostate cancer cells (Zong et al., 2007; Y. Kim et al., 2015; Ta et al., 2020). Most of these phosphorylation sites are substrates for multiple kinases. Alterations in AR function depend on the type of kinase, the location of phosphorylation, the time, and the existence of AR populations with heterogeneous phosphorylation patterns.

4. Role of AR in Prostate Cancer. Recent advancements in understanding AR action originate from studies on prostate cancer. Gold standard therapy for androgen-dependent disease consists of pharmacological inhibition of AR signaling and/or androgen biosynthesis. Unfortunately, therapeutic efficacy is transient since many patients develop CRPC. However, many CRPC tumors remain AR-dependent (Nakazawa et al., 2017). Thus, much effort has been devoted to mapping detour circuits that permit AR reactivation. Analyses of the transcriptomic and mutational landscape in CRPC tumors suggest that the androgen/AR axis is still the most frequently altered pathway (Henzler et al., 2016). AR alterations in patients who developed refractory disease primarily arise from gene amplification, mutation, and splice variants (Lorente et al., 2015; Henzler et al., 2016; Jernberg et al., 2017; K. T. Schmidt et al., 2021).

Most common AR point mutations related to prostate cancer are located within the LBD, resulting in a broader spectrum of agonist recognition, which could permit AR signaling in the absence of androgens. Several studies have shown that AR harboring an F877L mutation (codon numbering based on human reference genome Hg19) can be activated by second-generation AR antagonists enzalutamide and apalutamide (ARN509) but not by darolutamide (Balbas et al., 2013; J. D. Joseph et al., 2013; Korpal et al., 2013; Lallous et al., 2016; Prekovic et al., 2016; Sugawara

et al., 2019). The clinical relevance and frequency of this mutation in patients who develop resistance to potent AR antagonists remains to be determined. This *AR* mutation has been detected in plasma DNA from apalutamide- or enzalutamide-treated patients, while not present in a separate cohort of CRPC patients after enzalutamide treatment (J. D. Joseph et al., 2013; Azad, Volik, et al., 2015; D. Robinson et al., 2015). This resistance mechanism is reminiscent of *AR* mutations H875Y and T878A that occur in response to older AR antagonists flutamide and W742C in patients treated with bicalutamide (Veldscholte et al., 1990; Fenton et al., 1997; Yoshida et al., 2005).

Another mechanism that contributes to resistance to ADT is the expression of constitutively active AR-V (Dehm et al., 2008; Z. Guo et al., 2009; R. Hu et al., 2009; S. Sun et al., 2010; Sprenger and Plymate, 2014; Luo et al., 2018; T. Ma et al., 2021). Over 20 AR-V have been identified as a response to low androgen environments (Antonarakis et al., 2014; Y. Zhu and Luo, 2020). The most studied variant is AR-V7, which contains exons 1–3 and a short unique sequence due to alternative splicing that forms a cryptic exon (R. Hu et al., 2009). AR-V7 is currently used as a prognostic biomarker for CRPC (X. Chen et al., 2018; Luo et al., 2018; Sharp et al., 2019; Kanayama et al., 2021). Human prostate tissue microarray analyses showed that nuclear localization of AR-V7 in CRPC is nearly fivefold that of androgen-dependent prostate cancer (44% vs. 9%) (Z. Guo et al., 2009). AR-V7 has double negative impacts on tumor progression. First, AR-V7 is predominantly nuclear, where it can modulate the transcription of AR bona fide target genes as well as de novo androgen-responsive genes (R. Hu et al., 2012; Cato et al., 2019). Second, AR-V7 represses tumor-suppressor genes and upregulates cell cycle, DNA damage repair, and other tumor progression-related genes (Y. He et al., 2018; Cato et al., 2019; Roggero et al., 2021).

5. New Pharmacological Approaches to Target AR and AR-V. FDA-approved second-generation AR antagonists (enzalutamide, apalutamide, and darolutamide) showed promise in relapsing patients initially treated with ADT (Tran et al., 2009; M. R. Smith et al., 2018; Sugawara et al., 2019; Desai et al., 2021). Despite this, tumors eventually develop resistance to these drugs. Preclinical studies show that AR signaling remains throughout the transition to late-stage prostate cancer. Due to the lack of an LBD and the structural disorganization of the NTD, pharmacological targeting of AR-V has been highly challenging (Sadar, 2020). To address this, antisense nucleic-acid-based therapies, such as those targeting cryptic splicing signals within the AR pre-mRNA, were shown to decrease AR-V7-mediated cell growth. These non-pharmacological approaches may be a more efficient way to restore sensitivity to AR inhibitors (Luna Velez et al., 2019; Tietz and Dehm, 2020). EPI-001 is a small molecule that binds the AR NTD and inhibits AR transcriptional activity, leading to decreased CRPC xenograft growth (Andersen et al., 2010). A stereoisomer of EPI-001, ralaniten/EPI-002, is the first drug targeting the AR NTD to be evaluated in clinical trials. Although ralaniten was well-tolerated, these trials were discontinued due to poor pharmacokinetics (Clinical trial NCT02606123). Results from a subsequent trial using an optimized ralaniten analog, EPI-7386, restored the antitumor effect of enzalutamide in patients with metastatic CRPC (Clinical trial NCT05075577) (Hirayama et al., 2020).

Disrupting AR-coactivator interactions using peptides that mimic AR-binding regions is an efficient strategy to inhibit AR-V function (Magani et al., 2017). Vav3, a guanine nucleotide exchange factor for Rho GTPases, is a coactivator of AR and AR-V, including AR-V7 (Lyons and Burnstein, 2006; Lyons et al., 2008; Peacock et al., 2012; S. Rao et al., 2012). Additionally, Vav3 expression correlates with prostate cancer progression in vitro and in vivo, and the patient data (Lyons and Burnstein, 2006; Banach-Petrosky et al., 2007; K. T. Lin et al., 2012). The DH3 domain of VAV3 interacts with the TAU5 region in the NTD of AR. Disrupting this interaction using a peptide with the DH3 sequences hindered AR-V7 binding to coactivators and nuclear localization. Furthermore, inhibiting Vav3-AR binding by overexpression of the DH3 domain of Vav3 inhibited CRPC cell proliferation, anchorage-independent growth, and migration. At the same time, it increased apoptosis and led to morphologic changes associated with a less aggressive phenotype (Magani et al., 2017). Peptides designed from the AR coactivator SRC1 inhibited AR-binding to p160 coactivators and led to repressed AR and AR-V7 activity in prostate cancer cells (Nakka et al., 2013). The development of peptidomimetics to target the LBD of AR and disrupt AR-coregulator interactions can suppress resistance to second-generation AR inhibitors in both in vitro and in vivo models (Ravindranathan et al., 2013; Y. Wang et al., 2016).

Another strategy for inhibiting AR-V activity is targeting proteins that bind to the NTD (Foley and Mitsiades, 2016). Heat shock proteins (Hsps) such as Hsp90, Hsp70, and Hsp40 are important chaperones for correct AR-folding, ligand/DNA-binding, nuclear translocation, and stability (Heemers and Tindall, 2007; Echeverria and Picard, 2010). Hsp70 binds to the AR NTD, and Hsp70 levels correlate with AR-V7 expression in patients with high Gleason score (pathologic grade) (B. He et al., 2004; C. Liu et al., 2018). Inhibition of Hsp70 reduced AR and AR-V7 expression and transcriptional activity by enhancing STUB1 binding, leading to ubiquitination and degradation (C. Liu et al., 2018; Moses et al., 2018; J. Dong et al.,

2019). Selective Hsp70 inhibitors reduced CRPC cell colony formation, which was potentiated when combined with enzalutamide (J. Dong et al., 2019). Furthermore, in vivo experiments using enzalutamide-resistant xenografts and PDXs showed that Hsp70 inhibition decreases tumor volume and increases survival, which was further enhanced when used as an adjuvant to enzalutamide treatment (C. Liu et al., 2018). Hsp40 is another chaperone family member involved in the proteasomal degradation of misfolded proteins (Shiber et al., 2013). Results from small-molecule screening found that an Hsp40 interactor, C86, inhibits both AR and AR-V7 transcriptional activity by promoting protein degradation. Pharmacological inhibition of Hsp40 reduced tumor growth of AR-V7 expressing CRPC xenografts, and interestingly, dual treatment with an Hsp70 inhibitor produced a more significant inhibitory effect on tumor growth (Moses et al., 2018). Cochaperones that bind to the NTD (e.g., Bag-1L and others) also play an essential role in promoting AR activity (Froesch et al., 1998; F. Wu et al., 2013; Cato et al., 2017). Specific knock out of Bag-1L decreases AR chromatin binding due to alterations in the AR interdomain interactions and folding of the receptor upon ligand binding, and these processes reduce cancer cell growth. Bag-1L was shown to be a targetable protein, Thio-2 an N-ethyl-4-(6-methyl-1, 3-benzothiazol2-yl)aniline compound impedes AR-Bag1L binding and inhibits cell proliferation (Cato et al., 2017; I. I. Lee et al., 2019).

Selective modulators of AR (SARMs) are small-molecule nonsteroidal compounds that bind AR and exert tissue-specific agonist and antagonist effects. SARMs promote anabolic androgenic actions while avoiding undesirable effects such as prostate cancer growth. SARMs have potential use in osteoporosis, AD, stress urinary incontinence, cachexia, and breast cancer (Narayanan et al., 2018; Christiansen et al., 2020).

Accumulating evidence suggests that androgens induce different growth responses depending on the hormonal milieu. While lower levels of androgens promote tumor growth, high levels have the opposite effect (Teply et al., 2018). Concordantly, recent studies demonstrated that SARMs can inhibit the growth of CRPC cells both in vitro and in vivo (Nyquist et al., 2021). Additionally, while ADT is the standard treatment of advanced prostate cancer, side effects can significantly reduce the quality of life (Higano, 2003; T. Lam et al., 2020). SARMs, which have tissue-specific activity, may be useful in late-stage prostate cancer (Dalton et al., 2013; Nyquist et al., 2021; Pencina et al., 2021).

C. Progesterone Receptor (PR–NR3C3)

Progesterone plays a critical role in the adult mammary gland in controlling the dynamics and maintenance of stem and progenitor cells. Mouse mammary stem cells (MaSCs) are ER/PR negative and reside in the basal compartment nearby differentiated ER/PR-positive luminal epithelial cells. Progesterone stimulation of MaSC expansion and repopulation activity is mediated by paracrine signaling, and the PR target gene RANKL (receptor activator of NFκB ligand) is a functionally crucial paracrine factor since pharmacologic inhibitors and a neutralizing anti-RANKL antibody blocked P4-induced proliferation of MaSCs. Additional P4-regulated paracrine mediators that affect stem cells include Wnt4 during the perinatal stage of development and CXCR4, a receptor for stromal-derived factor 1. Progesterone also stimulates bipotent progenitor cells in the normal human breast by paracrine mechanisms; however, the paracrine mediators may differ from the mouse. Cancer stem cells are also expanded by progesterone in breast cancer cell lines and tumor xenograft models. Furthermore, several groups have shown the induction of basal cytokeratin 5 by progestins in breast cancer cell populations and have linked progesterone to the emergence, dedifferentiation, and stem cell-like activity of cytokeratin 5-positive breast cancer cells. Progestins also stimulate the expansion of CD44+ populations of breast cancer stem cells, and PR can be expressed in these cells. Since stem and progenitor cells are sensitive targets for carcinogenic transformation, these actions provide a potential mechanism to explain progestins as risk factors for breast cancer (Horwitz et al., 2008; Graham et al., 2009; Asselin-Labat et al., 2010; Joshi et al., 2010; Axlund et al., 2013; Hilton et al., 2014; T. Sato et al., 2014; Rajaram et al., 2015; Shiah et al., 2015).

1. PR Cistrome. ChIP-seq analysis combined with gene expression profiling has identified specific PR binding sites and the consensus hexanucleotide progesterone RE (PRE). Single PREs were more abundant than full IR PREs. The majority of regulated genes contained multiple half or full PREs. Comparison of PR cistromes between breast cancer cells (T47D), nontransformed human breast epithelial cells (MCF10A), and human leiomyoma cells revealed low overlap between genomic PR binding sites and low overlap between PR-regulated genes. PR also tethers to other TFs to indirectly modulate gene transcription. PR associates with different TFs that differ across cell lineages (e.g., predominantly with FOXA1 in breast cancer tissues, NF-1/AP-1 in MCF10A, etc.). The dominant TF works with PR to orchestrate cell-specific transcriptional responses to PR signaling. This phenomenon may contribute to the concept of system bias. Functional analyses showed that FOXA1 was required for PR modulation of gene transcription. A similar mechanism was identified from database analyses in which overlapping ERα and PR binding sites were identified in breast cancer cells (Clarke and Graham, 2012; Giulianelli et al., 2012; Rubel et al., 2012; P. Yin et al., 2012; Lain et al., 2013; Khushi et al., 2014; A. R.

Daniel et al., 2015; Mazur et al., 2015). In support of this statement, ERα and PR form the PR-B/ERα/PELP1/IGF1R complex at the CTSD promoter. PR is also required for maximal estrogen responsiveness. Another piece of evidence is that ERα association with PR at cyclin D1 and myc promoters is necessary for progestin induction. These studies suggest an interplay between these two types of female hormone receptors that affect hormone responsiveness.

2. Progesterone-RANKL Paracrine Signaling Axis. In the adult mouse mammary gland, PR is expressed heterogeneously in ∼40% of luminal cells, and P4 stimulates proliferation in a paracrine manner, whereby PR-negative cells (responders) proliferate while PR+ cells (sensors) do not. RANKL is the primary paracrine mediator of progesterone-induced proliferation. P4 induces RANKL gene expression exclusively in PR+ mammary epithelial cells, and secretion of RANKL can elicit a proliferative signal in adjacent PR-negative cells. Upon binding to its receptor, RANKL activates the downstream IKKα/IkBαNFκB-cyclin D1 proliferative signaling pathway. Ectopic expression of RANKL can normalize the phenotype of PR KO mice, which provides strong evidence that RANKL mediates P4 paracrine function to induce proliferation. RANKL is also required for P4-induced secretory cell development to induce lactation. RANKL is a direct target gene of PR in PR+ mammary epithelial cells. P4-bound PR is recruited to RANKL enhancers. The RANKL signaling axis has been implicated to play a role in the early stages of P4-sensitive breast tumorigenesis. Overexpression of RANKL in the mammary gland results in hyperplasias and pre-neoplastic lesions. In chemically induced DMBA progestin-dependent mammary tumors, RANKL inhibitors and genetic depletion of RANKL reduced the incidence and delayed the onset of tumors. However, this mechanism dissipates upon the progression of human breast cancer. In fact, very few breast carcinomas express RANKL, which suggests that this mechanism may not contribute to the progression of invasive breast cancer (Beleut et al., 2010; Gonzalez-Suarez et al., 2010; A. Mukherjee et al., 2010; Schramek et al., 2010; H. J. Lee et al., 2013; Obr et al., 2013; Tanos et al., 2013).

3. Structure-Function Analysis of the Amino-Terminal Domain of PR. The NTD of PR remains poorly characterized as the AF1 contains intrinsically disordered proteins (IDP); thus, it is not amenable to crystallography and high-resolution structure. Solution-phase biophysical methods indicated that the PR NTD undergoes transitions from a disordered to an ordered structure upon binding TATA-binding protein (TBP), resulting in increased helical content and tertiary folding. TBP-induced folding facilitated the SRC1 and enhanced SRC1-dependent AF1-mediated transcriptional activity, indicating that TBP acts as a PR coregulatory protein by reorganizing structures in the NTD to permit recognition and assembly of coactivator complexes. TBP interaction has similar effects on the NTD of GR, suggesting a common mechanism of action of NTD/AF1 through coupled binding and folding of IDP. HDX-MS is a powerful technique to map conformation dynamics in specific sequence regions of intact proteins. HDX analysis confirmed the highly dynamic conformation of the NTD, characteristic of IDP, in the context of full-length purified PR versus stable conformation of the LBDs and DBDs. Additionally, HDX revealed allosteric interactions between NTD and LBD in response to binding TBP and hormonal ligands. These studies highlight the importance of structural flexibility and allosteric coupling between receptor domains for the full spectrum of steroid receptor signaling (Khan et al., 2011; R. Kumar et al., 2013; Goswami et al., 2014; Simons et al., 2014).

4. Post-Translational Modifications of PR. Like most other NRs, PR is subject to numerous PTM. There are at least 14 phosphorylation sites (serine/threonine) that all reside in the NTD except for one site (SER 676) in the hinge. Specific kinases that phosphorylate PR include CDK2, MAPK, PKA, and casein kinase II. Phosphorylation of particular sites, or groups of sites, enables diverse PR functions, including nuclear translocation, dimerization, DNA binding, protein stability, hormone sensitivity, coregulatory protein interactions, and transcriptional activity. A dual-specificity phosphatase (DUSP6) was shown to interact with a common docking domain in the NTD of PR-B to facilitate ck2-mediated phosphorylation of S81. In cooperation with STAT5a, this DUSP6-dependent site directs a subset of genes regulated by the PR-B isoform. A physiologic role for PR phosphorylation was reported in mice carrying a serine to alanine point mutation (S191A) that displayed mild yet detectable phenotype (subfertility, altered length of estrus cycle, and impaired P4 regulation of selected target genes in the mammary gland). PR is SUMOylated in a hormone-dependent manner at lysine 388 in the NTD, and this has a suppressive effect on transcriptional activity. There may be an interplay between different PTMs. For example, phosphorylation of S294 suppresses SUMOlyation, which enhances S294-induced PR activation, although these interactions have not consistently reproduced between systems. Nonetheless, a comparison of gene expression profiling of SUMOylated versus deSUMOylated PR uncovered a set of genes regulated by hyperactive deSUMOylated PR as a result of selective recruitment of CBP (MLL2). This signature gene reprogramming is associated with poor prognostic in breast cancer. PR is acetylated at a conserved KXKK motif in the hinge region and at K183 in the NTD. This site is hormone inducible and regulates PR nuclear uptake kinetics and DNA binding. The coactivator p300 acetylates K138 and potentiates PR activity by accelerating its binding to a direct target. Monomethylation of PR at K464 in the NTD has been reported to repress AF1-

mediated transcriptional activity and to increase hormonal ligand sensitivity (Knutson et al., 2012; Hagan et al., 2013; Abdel-Hafiz and Horwitz, 2014; H. H. Chung, Sze, Tay et al., 2014; H. H. Chung, Sze, Woo, et al., 2014; Grimm et al., 2014). The latest information on PR and its ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=98).

D. Estrogen Receptors (Erα–NR3A1, Erβ–NR3A2)

Estrogens are multifunctional endogenous steroid hormones synthesized from cholesterol and uniquely defined by a phenolic A-ring. These hormones participate in the global regulatory system, affecting the growth and differentiation of multiple organ systems, including sexual development, reproduction, cardiovascular and neuronal activity, and liver, fat, and bone metabolism.

Dysregulation of estrogen signaling can lead to various human diseases, such as breast/uterine cancers, osteoporosis, cardiovascular and neurodegenerative diseases, and insulin resistance. The mechanisms by which estrogen hormones exert their physiologic actions are primarily through direct control of DNA transcription and protein synthesis of target genes (Heldring et al., 2007).

1. Estrogens. Estrogens are lipophilic hormones diffusing freely into cells, where they initiate genomic signaling events that ultimately promote global changes in nuclear gene expression (Deroo and Korach, 2006). The most abundant and potent estrogen produced in the body is 17β-estradiol. The two other physiologic estrogens, estrone, and estriol, are much weaker ligands. In premenopausal women, estrogens are primarily synthesized in the ovaries by the granulosa cells of the ovarian follicles and corpora lutea (Bondesson et al., 2015). The synthesis and secretion of estrogens from the ovaries are under the control of the gonadotropic hormones follicle-stimulating hormone and luteinizing hormone from the anterior pituitary, which is regulated by gonadotropin-releasing hormone from the hypothalamus. Like several other endocrine axes, secretion of estrogens is achieved through a negative feedback loop involving follicle-stimulating hormone, luteinizing hormone, and gonadotropin-releasing hormone release. Although the ovaries are the primary source of systemic estrogens in premenopausal women, they can be produced ectopically through androgen aromatization. This alternative mechanism is critical for estrogen synthesis and actions in men and postmenopausal women (Bondesson et al., 2015).

2. Estrogen Receptor Subtypes. Mammals express two nuclear forms of ERs, ERα, and ERβ, which exhibit distinct tissue distribution and biologic roles. ERα and ERβ are encoded by two distinct genes (*NR3A1; ESR1*) and (*NR3A2; ESR2*), which share significant homology. ERα and ERβ comprise eight exons separated by seven intronic regions. Some organs express these two isoforms at equivalent ratios, whereas preferentially express one isoform. ERα expression levels are high in the uterus, mammary gland, and ovarian theca cells but much lower levels in bone, vascular endothelium, liver, prostate, pituitary gland, and certain regions of the brain. ERβ is found in many of these tissues but generally at much lower levels than ERα. ERβ is the predominant or the exclusive subtype in certain other regions of the brain and lung, colon, and ovarian granulosa cells (A. H. Taylor and Al-Azzawi, 2000). To understand the connection between the physiologic and molecular functions of ERs, the field requires an in-depth understanding of the spectrum of genes regulated in each tissue and cell type. This review will focus on the current state of knowledge about the mechanism by which ERs regulate the expression of target genes, from estrogen synthesis and secretion through protein regulation in target tissues linked to physiologic responses (Dahlman-Wright et al., 2006).

3. Physiologic Roles of Estrogen: ER Gene-Targeted Models. Our understanding of the physiology of estrogen action was significantly advanced following the generation of mutant mice devoid of *Esr1* and *Esr2* genes (Hewitt et al., 2005; Murphy and Korach, 2006; K. J. Hamilton et al., 2014). The ERα knockout mice exhibit severe reproductive phenotypes, as expected from abrogation of a major regulator of this system. Both females and males are infertile. In females, the uterus is hypoplastic and nonresponsive to estrogens, and the mammary gland shows only rudimentary prepubertal development. Males have abnormal sperm production due to fluid accumulation in the testes. Their neuroendocrine feedback control system is impaired, and these mice develop osteoporosis, obesity, and metabolic abnormalities. Several ERβ knock-out mice were generated, although they exhibited inconsistent phenotypes (Dupont et al., 2000; C. Zhao et al., 2008). The use of different gene deletion strategies and constructs may have resulted in alternative transcripts being produced. Phenotyping of the first generation of ERβ mutant mice reported ovarian pathologies with inefficient folliculogenesis and subfertility in females, while males were primarily unaffected (Harris, 2007). However, subsequently produced ERβ-knockout mice using Cre/LoxP technology caused sterility in both males and females, with few or no apparent effects (Antal et al., 2008). Loss of both *Esr1* and *Esr2* (α/βERKO) recapitulates the αERKO phenotype in all tissues except ovaries. In fact, female α/βERKO mice lost the ability to differentiate granulosa cells, which resulted in transdifferentiation to Sertoli cells (Couse et al., 1999). More advanced technologies allowed tissue-specific deletion at any time after birth. These models have been monumental in deciphering cell- and tissue-specific functions of ERs (Wintermantel et al., 2006; Gieske et al., 2008;

S. Lee et al., 2009; Winuthayanon et al., 2010; Jayes et al., 2014).

Phenotyping of humans harboring ER genomic null mutations has confirmed many clinical traits observed in the ER knockout mice. A homozygous nonsense mutation in the *ESR1* gene was identified in a 28-year-old man whose attributes included tall stature with evidence of continued slow linear growth, markedly delayed skeletal maturation, osteopenia, obesity, insulin resistance, compromised spermatogenesis, and premature arteriosclerosis (E. P. Smith et al., 1994). More recently, a homozygous amorphic mutation in *ESR1* was identified in an 18-year-old woman, leading to profound estrogen insensitivity resulting in primary amenorrhea, continued linear growth into adulthood, delayed bone age, osteopenia, absent breast development, enlarged bilateral multicystic ovaries, hypoplastic uterus, and markedly high serum estrogens (Quaynor et al., 2013). This severe phenotype requires *ESR1* mutation on both alleles as heterozygous are primarily unaffected (E. P. Smith et al., 2008).

Acquired resistance to drug treatment is a significant challenge in ER-mediated cancer therapy. Studies utilizing next-generation sequencing revealed that recurrent *ESR1* mutations are more frequent than previously affirmed and may play critical roles in acquired endocrine therapy resistance. Several ER mutations within the LBD have been identified in patients with ER-positive metastatic breast cancer after treatment with an antiestrogen. These mutations result in constitutive ligand-independent transcriptional activity, mimicking that of AR-V (discussed in the *Subgroup III* section) or estrogen-bound wild-type ER (Merenbakh-Lamin et al., 2013; D. R. Robinson et al., 2013; J. M. Dixon, 2014; Jeselsohn et al., 2014; Segal and Dowsett, 2014). Although mutated ERs are only present in a small fraction of the tumor cells, their constitutive activity contributes to treatment resistance. Short-term reduction or elimination of the selection pressure to eliminate these resistant cell populations has shown great promise in treating tumors that have acquired resistance to endocrine treatment (P. Fan and Craig Jordan, 2014).

4. ER Structure. The ER LBD is composed of 12 α helices that form the characteristic three-tiered, antiparallel α-helical sandwich, with each layer of helices being approximately perpendicular to the adjacent layers (R. Kumar et al., 2011). Approximately 75% of the LBP inner lining consists of hydrophobic residues. Most of the polar residues within the LBP make a hydrogen bond to estrogen. Estrogen entry into the LBD is mainly governed by hydrophobic interactions. Ligand binding to the receptor causes the LBD to undergo conformational changes and become compact and protease-resistant, thereby maximizing the hydrophobic contacts and contributing to the selectivity of ligand binding. These conformational changes result in exposure of the AF2 hydrophobic activation grove on the LBD, a property that makes the ER structure inductive for recruitment of coregulator proteins (Bolander, 2006).

The hydrophobic portion of the ER LBD must be exposed for ligand accessibility, but exposing this surface predisposes the receptor to aggregation. When unbound, ER transcriptional activity is inert due to their interaction with heat shock proteins, which are essential for efficient protein folding and stability of the receptor. Upon binding estrogen, ER dissociates from these heat shock proteins and changes tertiary structure, resulting in LBD dimerization. The new confirmation allows ERs to bind to estrogen REs (EREs), which consist of two AGGTCA half-sites. The structure of a biologically active full-length ERα on an ERE has revealed complex domain-domain interconnections, providing new insights into how signals transduce across domains in an allosteric fashion. Cryo-electron microscopy has uncovered that the A/B domain is located in proximity to the E domain, near the AF2 hydrophobic transactivation groove, when ER is bound by estrogen. Such a structural organization allows for intercommunication between the two distinct transactivation functions, which are located in distinct domains of the protein (Yi et al., 2015). There is a small group of nonnuclear ERs situated at the cell membrane surface (GRP30) (Pedram et al., 2006). Like the membrane-bound form of GR, GRP30 triggers a signaling cascade that results in nongenomic activity (e.g., PTMs) (E. R. Levin, 2015). In recent years, several genetically modified mouse models have examined GRP30-mediated estrogen effects (Otto et al., 2008; Pedram et al., 2013, 2014; Adlanmerini et al., 2014; Burns et al., 2014). To date, these models show minimal change in gene expression across several tissues, demonstrating the necessity of nuclear ER for function and target gene activity. This is consistent with the ER-null phenotype (loss of all estradiol-mediated gene inductive and repression) observed in ER DNA-binding deficient mouse models (Ahlbory-Dieker et al., 2009; Hewitt et al., 2014; Wall et al., 2014).

5. ER Transcriptional Regulation. The signaling and transcriptional effects of ERs underlie the physiologic and pathologic effects of ER signaling pathways. The study of transcriptional regulation is fundamental to understanding how gene expression and phenotypes are regulated. The emergence and application of high-throughput, large-scale genomic technologies have further revealed the genome-wide identification of genes induced or repressed by ERs.

Unlike previously discussed NRs, the vast majority of ER binding events do not occur within the promoter region of target genes (Theodorou and Carroll, 2010). ERs predominantly bind to introns and distal intergenic regions, commonly referred to as enhancers, often located at more than 10 kbp upstream to the nearest TSS (Carroll et al., 2006; C. Y. Lin et al., 2007; Hewitt et al., 2012). The juxtaposition of the ER binding

sites relevant to TSSs does not correlate with binding solidity or evolutionary conservation (C. Y. Lin et al., 2007; Parisi et al., 2009; Q. Tang et al., 2011). In addition, the majority of ER binding sites are adjacent to genes that are unresponsive to estrogens. These observations suggest that the canonical mode of ER function is involved in long-range control of gene regulation (Carroll et al., 2005, 2006; C. Y. Lin et al., 2007; Welboren et al., 2009; Hah et al., 2011; M. Ding et al., 2012; Kittler et al., 2013; Ikeda et al., 2015). Notably, ChIP-on-ChIP experiments showed that nearly half of Erα-bound loci do not present the cognate ERE motif, questioning the notion that ERs only bind to paired half-sites with specific orientations (Everett and Lazar, 2013). The high ratio of noncanonical binding sites most likely reflects the diversity of mechanisms facilitating ER binding that do not rely on a strong sequence specificity. Like the PR, ER can tether to other TFs (e.g., AP-1, Sp1, and NFκB) to indirectly influence gene expression (R. Duan et al., 1998; Petz et al., 2002; Chadwick et al., 2005). To distinguish the effects of direct ER-DNA binding from tethered responses, a mouse model (knock-in/KO lacking DBD functions but with preserved non-DBD responses was generated. Interestingly, the knock-in/KO phenotype nearly recapitulated that of ERα KO mouse, thus demonstrating that ER tethering plays little biologic role but may complement the direct DNA binding activity to regulate transcription and biologic response (Ahlbory-Dieker et al., 2009; Hewitt et al., 2009, 2014; Stender et al., 2010; Wall et al., 2014). The extensive number of degenerative binding sites likely contributes to the overall transcriptional efficiency. The attraction between the ERs and the transcriptional machinery is disproportionally weaker if a single ER binding site is occupied versus several bound ERs. These degenerate binding locations cluster around ER-bound cognate EREs, indicating that accessibility to chromatin and auxiliary factors can stabilize ER binding to these degenerative REs (Todeschini et al., 2014). In agreement, less potent exogenous estrogens (e.g., estrone) induce fewer ER binding events and only affect a subset of estrogen-regulated genes (Gertz et al., 2012). Thus, the number of adjacent ER binding sites may represent a powerful criterion for identifying ER targets through genome-wide binding profiling (Parisi et al., 2009; Everett and Lazar, 2013).

The genes regulated by estrogen are evenly distributed between both strands of DNA, with a proportional number of genes being induced as repressed (Hah et al., 2011; Hervouet et al., 2013; Osmanbeyoglu et al., 2013; Hah and Kraus, 2014). These genes are distributed in nonrandom clusters down the chromosomes, with long stretches of regulated genes that include both induced and repressed genes. Comparisons between ER binding profiles and corresponding gene expression have revealed exponentially more ER binding sites than estrogen-regulated target genes in a given tissue (Vaisanen et al., 2011; Ballester et al., 2014). The higher concentration of receptor facilitates cognate DNA sites, in contrast to low-copy TFs that remain permanently bound to their target sites, independent of their activity (Etain et al., 2014; B. Wang et al., 2015). In most estrogen-regulated genes, the closest ER binding site is located within the enhancer. ER-bound enhancers can physically associate with the proximal promoter by chromatin looping, which may create separate regulatory sites that will likely bring the ER-bound RE closer to the target TSS. As a result, DNA looping favors ER binding site enrichment near target promoters. Agonist or antagonist-bound ER binding distribution does not significantly differ between estrogen-induced and estrogen-repressed genes (Cusanovich et al., 2014). These findings indicate that the number and the location of ER binding locations do not impact transcription modulation direction (Welboren et al., 2009).

The intricate relationship between chromatin structure and ER transcriptional processes is gradually revealing itself. Each chromosome occupies a different territory in the nucleus, minimizing potential interchromosomal contacts upon ER signaling (Cremer and Cremer, 2001; Theodorou and Carroll, 2010; Harmston and Lenhard, 2013). Within each chromosome, long-range chromatin looping partitions the chromosomal region into ~2000 topologically associating domains (TADs; 500–900 kbp) (J. R. Dixon et al., 2012). These topological domains are conserved across cell types and between mouse and human, indicating that these chromatin structures may constitute the foundation of mammalian genome organization (J. R. Dixon et al., 2012, 2015; Jabaudon et al., 2012; Smallwood and Ren, 2013; Plank and Dean, 2014; S. S. Rao et al., 2014). Unlike the stable long-range TADs, short-range links between enhancers and promoters within TADs are highly cell-specific (<100 kbp) (Fullwood et al., 2009). Enhancers (where ERs bind the DNA) are remote transcriptional regulators not influenced by their directionality and distance to a promoter. Generally, distal enhancers and the proximal TSS do not associate, which indicates that linear juxtaposition is not the guiding principle driving enhancer-promoter selection (Ong and Corces, 2011; Sanyal et al., 2012; Smallwood and Ren, 2013). Enhancers can be located up- or downstream of interacting promoters, as well as within introns of gene bodies. The enhancer may connect with promoters during cellular tissue differentiation, which sets the stage for stimulus-specific transcriptional reprogramming.

Estrogen treatment does not alter the genomic patterns of these enhancer-promoter interactions, suggesting that preexisting interactions are not meant to respond to a particular signaling event but rather to accelerate cellular response (F. Jin et al., 2013). ER stimulation does, however, alter the interaction frequency (cross-linking strength) of preexisting enhancer-promoter interactions, which may differ from cell to cell (P. Y. Hsu et al., 2010;

G. Li, X. Ruan, et al., 2012; Ghavi-Helm et al., 2014; Quintin et al., 2014). This suggests that enhancer-promoter links allow signal-dependent TF to modulate the expression of a set of genes in specific tissues, thus representing another mechanism underlying system bias. Genome-wide analysis has revealed that enhancers can interact with multiple promoters, and vice versa (van Arensbergen et al., 2014). Deletion of enhancers located in TAD enhancers leads to a graded reduction of target gene expression interacting genes, suggesting enhancers work in an additive manner (Zaret and Carroll, 2011; Heinz et al., 2015). Scalable approaches in which functional enhancer-promoter units are perturbed in a targeted manner are now within reach and will help firmly establish casual functional relationships. Genome editing methods, particularly the CRISPR/Cas9 technology, provide an opportunity to systematically delete or inactivate enhancer regions and thus functionally identify their target promoters in a native context.

Enhancers are activated by sequential binding of TFs at different developmental stages. A group of nucleosome-binding "pioneering" TFs, such as forkhead box A and GATA binding protein, initiate this sequential binding to condensed chromatin to prime a future enhancer (Zaret and Carroll, 2011; Jozwik and Carroll, 2012). Pioneer TFs not only bind condensed nucleosomal DNA, but they also stick to their site through mitosis, providing epigenetic memory (A. Rada-Iglesias, 2013; Iwafuchi-Doi and Zaret, 2014). These TFs open the conformation of the chromatin and initiate the process of enhancer selection within specific tissue to drive lineage-specific transcriptional programs. Collaboration of multiple pioneer factors is essential to compete with nucleosomes for binding to DNA; thus, pioneer factors act in concert to eject nucleosomes and create enhancers. Thus, the selection of a large portion of cell type-specific enhancers is driven by simple combinations of lineage-determining pioneering TFs. As a result, TFs play systemic roles in determining the ER binding pattern in each cell type and thus may be at the center of system bias responses.

Gene induction increases and gene repression decreases RNAPII occupancy at estrogen-sensitive genes. ER signaling facilitates RNAPII transcription at estrogen-induced genes by increasing nucleosome turnover in the gene body and dislodging RNAPII at estrogen-repressed genes. This allows nucleosomes to reassemble and reduces their turnover, thereby disrupting the initially transcription-competent chromatin structures (Shivaswamy et al., 2008). In classic signal-dependent transcription modes, ligand activation promotes TF-binding to specific REs and the recruitment of RNAPII to the TSS to initiate gene transcription (M. J. Tsai and O'Malley, 1994). However, when ER is unbound, RNAPII is already widely distributed at the TSSs of a large number of estrogen-induced as well as estrogen-repressed genes (Kininis et al., 2009; Lupien et al., 2009; Adelman and Lis, 2012). This important observation signifies that ER signaling does not orchestrate initial RNAPII recruitment but instead regulates the post-recruitment of RNAPII (Adelman and Lis, 2012). This also indicates that in the absence of ER ligands, RNAPII occupancy at estrogen-sensitive genes is not indicative of transcriptional responses of either estrogen-induced or estrogen-repressed genes.

The presence of preloaded RNAPII across the genome counteracts DNA-influenced nucleosome organization within the promoter, resulting in TSSs being poised for activation by physiologic or developmental signals (Gilchrist et al., 2010). RNAPII binding patterns at TSSs, where chromatin is accessible, are preestablished and maintained throughout cell differentiation and well conserved across lineages (L. Song et al., 2011; Gaertner et al., 2012; Natarajan et al., 2012). These regions form areas of low-salt soluble chromatin with high nucleosome turnover and are often flanked by H2A.Z-containing nucleosomes (Ku et al., 2012). RNAPII occupancy on promoters of both estrogen-induced and estrogen-repressed genes results in the continuous production of unproductive short sense and antisense transcripts, indicating that transcription is actively initiated at TSSs of these genes (Seila et al., 2008). However, estrogen-repressed genes have higher RNAPII occupancy in their body and thus have higher nascent transcription signals prior to stimulation. Consequently, this leads to low-level production of full-length transcripts and higher basal activity (Osmanbeyoglu et al., 2013; Jangal et al., 2014). Following estrogen treatment, RNAPII propels a wave of transcription along the estrogen-responsive gene body. In estrogen-induced genes, the leading edge of the RNAPII wave travels into the estrogen-induced gene body, whereas in estrogen-repressed genes, the lagging edge of the RNAPII wave is seen as RNAPII falls off the TSS and the gene body (Hah et al., 2011; Ovaska et al., 2013; Hah and Kraus, 2014; wa Maina et al., 2014). In estrogen-induced genes, ER signaling causes the release of RNAPII complexes to allow their movement toward the gene body, while in estrogen-repressed genes, it decouples transcription-efficient RNAPII complexes from both the promoter and the gene body. In estrogen-induced genes, nucleosomes (including H2A.Z containing nucleosomes flanking the TSS) are disrupted to facilitate elongation and are reassembled in the wake of RNAPII to prevent cryptic initiation from intragenic sequences (Dalvai, Bellucci, et al., 2013; Dalvai, Fleury et al., 2013). In estrogen-repressed genes, transcription-efficient RNAPII complexes are disrupted by nucleosome reassembly within the promoter region and gene body. This reduces nucleosome solubility and turnover, thus resulting in chromatin condensation (Teves and Henikoff, 2011, 2014; Osmanbeyoglu et al., 2013; Elfving et al., 2014;

Mourad et al., 2014). RNAPII transcription rates can vary as much as fourfold at different genomic loci in response to estrogens, a significant determinant in the timing of gene expression (Danko et al., 2013; Henriques and Adelman, 2013).

RNAPII is not only pre-assembled on genes but also in enhancer regions (De Santa et al., 2010). The discovery of bidirectional short transcripts (<200 nucleotides) produced from enhancer RNAs (eRNAs) indicates that RNAPII plays an active role at enhancer elements. Transcription of eRNA is not initiated until the enhancer fuses with its cognate promoter (Harmston and Lenhard, 2013). Upon ER activation, transcription of eRNAs at ER-bound enhancers increases or decreases depending on cross-linking frequency between ER-bound enhancers and promoters (P. Y. Hsu et al., 2010; Quintin et al., 2014). These events are determining factors of transcription output since eRNA knockdown reduces enhancer-promoter interactions and expression of the corresponding gene (W. Li et al., 2013; B. Daniel, Nagy, and Nagy, 2014). Taken together, this indicates that receptor signaling alters the adhesion of promoter-enhancer pairs to promote or suppress eRNA synthesis (W. Li et al., 2013). eRNAs within a single enhancer are uniformly induced or repressed, suggesting that enhancers function as a single regulatory unit (Hah et al., 2015). Protein composition and coregulator accumulation in enhancers can shape the regulatory properties of eRNA (induction and repression) (Guertin et al., 2014).

The association between ER-bound enhancers and promoters formed by DNA looping allows RNAPII at enhancers to flow toward the promoter. eRNA knockdown decreased further RNAPII recruitment to the promoter and gene body (but not at the core enhancer itself), as well as a reduction in chromatin accessibility at the promoter (T. K. Kim et al., 2010; M. T. Lam et al., 2014; Plank and Dean, 2014). This indicates that eRNAs facilitate RNAPII recruitment to the promoter of the target gene and that the change in RNAPII occupancy at eRNA-assigned genes is the consequence, rather than the cause, of corresponding eRNA expression (Mousavi et al., 2013). Thus, eRNAs facilitate molecular events culminating in higher RNPAII occupancy and engagement at protein-coding genes. Together, this suggests that ER-induced eRNAs are functional transcription inducers.

Despite the tremendous amount of ER-specific binding sites, very few are genuinely accessible to activated ERs (V. B. Vega et al., 2006; George et al., 2011). The vast majority, if not all, ER-binding sites are located in openly accessible chromatin domains (H. H. He et al., 2012; J. Wang et al., 2012; Gertz et al., 2013; Handel et al., 2013; T. B. Miranda et al., 2013). These domains are low-salt soluble with high histone turnover and reduced nucleosome occupancy, thereby accelerating ER binding site recognition (Mito et al., 2007). The location of chromatin accessibility is highly variable across cell types (Hager et al., 2009; Natarajan et al., 2012). Thus, diverse enhancer-promoter combos are possible depending on individual availability in each cell type (B. He, Chen et al., 2014). Chromatin accessibility landscape shaped by pioneering TFs during cell development is another determinant for system bias. In contrast, cell types with similar chromatin accessibility will likely share similar functions and responses (Thurman et al., 2012).

Because of the dramatic dependence of ER binding on preexisting chromatin architecture, substantial variations in the baseline pattern of chromatin accessibility between different cells will expose distinct genomic locations of ER binding sites. Cistrome reprogramming events are a fundamental aspect of normal biology and cancer. Numerous biologic situations are linked to cistrome changes, including endogenous/exogenous signals and physiologic/pathologic states (Garcia-Bassets and Wang, 2012). Therefore, changes in chromatin accessibility are an integral determinant of ER action, dependent on cell type and context.

ER, binding profiles, and regulatory programs undergo dramatic changes during disease progression, which have profound therapeutic implications. Like CRPC (see the *Subgroup III* section), endocrine therapy-resistant ER-positive breast tumors show constitutive receptor activity, even when treated with antiestrogens. Therapy-resistant and long-term estrogen-deprived cell lines revealed sets of nascent ER binding sites that often surround genes associated with poor prognosis (Ross-Innes et al., 2012; Magnani et al., 2013; J. M. Dixon, 2014; Tokunaga et al., 2014). Without an agonist, ERα can be indirectly activated by growth factors, such as EGF and insulin-like growth factor-1. Growth factors are soluble-secreted signaling polypeptides, whose actions are transmitted by membrane receptors coupled to tyrosine kinases (RTKs). RTK signaling leads to ERα phosphorylation, which can ligand-independently activate ERα. Given their short half-lives and slow diffusion rate, RTKs are secreted locally (K. Lee et al., 2011). In normal tissues, the availability of growth factors is stringently regulated to precisely meet their needs (T. Sasaki et al., 2013). However, in cancer cells, EGF and insulin-like growth factor-1 are excessively secreted, thus causing ERα "overstimulation" and activation of prooncogenic genes via the nascent binding sites. This alternate activation pathway is one of the resistance mechanisms allowing breast cancer to bypass standard drug treatments (Hewitt, Kissling et al., 2010; Hewitt, Li et al., 2010; Arao et al., 2011).

6. ER Coregulator Recruitment. ER interaction with RNAPII at target gene promoters depends upon and is modified by coregulators (M. J. Tsai and Lee, 1994; Lonard and O'Malley, 2012). There is now a

consensus that most, if not all, coregulators operate in the form of higher-order complexes that synergistically contribute to ER regulation (Malovannaya et al., 2011). Antiestrogen treatment disrupts virtually all coregulator complexes associated with ER, thus preventing their recruitment to ER-bound enhancers (Mohammed et al., 2013; Z. Liu et al., 2014). This is consistent with the finding that antiestrogens block estrogen-induced gene transcription and prevent estrogen-repressed gene transcription.

Coregulators are IDPs that become structured upon interaction with other proteins. This results in a relatively low binding affinity while preserving specificity and versatility between coregulators and their TF partners. This also allows a single coregulator to harbor many TF binding motifs within disordered regions of the protein (Millard et al., 2013). For example, ERα binds the ERE as a dimer and recruits two SRC3 proteins, securing one molecule of p300 to the complex through multiple contacts with the SRC3s (Yi et al., 2015). Historically, coregulators and coregulator complexes have been classified as either coactivator or corepressor. However, more recent data warrant taxonomy revision of coregulators (Millard et al., 2013). For instance, RIP140, an ER coregulator, has both coactivator and corepressor properties, depending on the cellular context (Nautiyal et al., 2013). These coregulators can be recruited to estrogen-induced genes just as much as they can be recruited to estrogen-repressed genes within the same cell (Malik et al., 2010; Nwachukwu et al., 2014). Therefore, occupancy of these bifunctional coregulators at an ER-bound enhancer does not determine transcriptional modulation directionality.

It was previously thought that ER mediates transcription using a common cohort of coregulators at the majority of target genes and that recruitment is based solely on ER conformation. However, this belief was superseded by data revealing that most ER-regulated genes do not recruit coregulators. When recruited, the amount and type of coregulator for a given gene may differ from cell to cell. (Won Jeong et al., 2012; DeVilbiss et al., 2013; Foulds et al., 2013). Depletion studies showed that coregulators are simply auxiliary assistants and not determinants of ER-regulated gene expression. It has been shown that ER coregulator complexes at ER-induced enhancers but not ER-induced enhancers contain a variety of other TFs (including RARα/γ and Gata3) along with coregulators Med1 and p300 (Z. Liu et al., 2014). Knockdown of Gata3 resulted in a decrease of eRNA expression at the enhancers and mRNA expression at the interacting promoters, as well as decreased recruitment of Med1 and p300 to the ER-induced enhancers.

These findings emphasize that nuclear organization and the timing of ER association with coregulators play an essential role in controlling ER-regulated gene transcription. Obtaining a blueprint of the individual components within each coregulator complex at ER-induced enhancers versus ER-repressed enhancers will be crucial for understanding the precise molecular mechanisms of ER-regulated gene expression. The latest information on ERs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=96).

E. Estrogen Receptor-Related Receptors (ERRα–NR3B1, ERRβ–NR3B2, ERRγ–NR3B3)

The ERRs form a family of three constitutively active orphans, ERRα (*NR3B1*), ERRβ (*NR3B2*), and ERRγ (*NR3B3*), that display ligand-independent as well as ligand-dependent transcriptional activity (Tremblay and Giguere, 2007; Giguere, 2008). The ERRs were named after the ERs, given their high degree of sequence homology to these receptors (Evans, 1988; Giguere et al., 1988). In the literature, ERRs are referred to as either estrogen receptor-related receptors or estrogen-related receptors. The first publication describing ERRs did not specify the full name (Giguere et al., 1988), but a subsequent review by the same laboratory then used the term *estrogen receptor-related receptors* (Evans, 1988); thus, we will use this term. Much of the knowledge about the physiologic functions of the ERRs arises from genetic loss- and gain-of-function models. These models provided valuable information on isoform-specific roles in regulating energy metabolism, the cardiovascular system, and cognitive dysfunction. However, the scarcity of high-quality isoform-specific chemical tools has largely limited their characterization. This gap justifies the current drug discovery effort, which will be the focus of this section. We will present some of the ligands that have been developed and their therapeutic potential.

1. Structural Characterizations and Transcriptional Domain of ERRs. While the three ERRs share a high degree of homology within their DBD (91%), their LBDs and hinge regions are less conserved (∼55%–65%). The most variable region resides within their A/B domain, where merely 25% of their sequences overlap. The ERRs bind to their own DNA RE, which is distinct from that of the ERs (Giguere, 2008). Like most other NRs, ERR transcriptional activity is governed by the interaction with the coactivators or corepressors (H. Hong et al., 1999; Xie et al., 1999), peroxisome proliferator-activated receptor γ coactivator-1 α and β (PGC-1α and PGC-1β) (Huss et al., 2002; Schreiber et al., 2003), and proline-rich NR coregulatory protein 2, which can function as protein "ligands" when their LBD is unbound by small molecules (D. Zhou and Chen, 2001; Hentschke and

Borgmeyer, 2003). Recently, several studies have identified either new cofactors or new transactivation mechanisms for ERR-controlled gene expression. There is evidence that the ERRs can function independently of some coregulators. Fan et al. demonstrated that ERRγ can reprogram a gene network in the absence of PGC1α, which was thought to be an essential coactivator of ERR regulation of this pathway (W. Fan et al., 2018). In the heart, PERM1 (PGC ERR-induced regulator muscle 1) forms a transcriptional complex by interacting directly with ERRα and PGC1α through an LXXLL-type motif in cardiomyocytes (Oka et al., 2022). Recently Nakadai et al. demonstrated two distinct ERR cofactor recruitment pathways. The authors suggested that depending on the cell context, ERR can recruit specific cofactors to regulate gene expression (Nakadai et al., 2023). In cells expressing PGC1α, such as mouse embryonic fibroblasts, the AF2 region of ERR recruits PGC1α through a classic LXXLL motif and leads to the recruitment of p300 and MED1-mediator complex. However, in cells lacking PGC1α, such as ESCs, another cofactor, such as NCOA3, can replace PGC1α and bind to ERR, leading to recruitment of the Mediator complex and probably p300. Interestingly, it has also been shown that within a single cell type, ERR can recruit different cofactors to activate various pathways. In cardiomyocytes, ERRγ interacts with the cardiogenic factor GATA4 to activate genes involved in cardiomyocyte-specific functions such as contraction, but metabolic gene regulation by ERRγ is independent of GATA4 (Sakamoto et al., 2022).

It is well demonstrated that ERRs are subject to PTMs, which could induce cell-specific transcriptional responses (A. M. Tremblay et al., 2008). For example, in neurons, ubiquitination of ERRα by Parkin leads to decreased expression of monoamine oxidases and neuroprotection (Xia et al., 2018). In the liver, mammalian target of rapamycin controls ERRα ubiquitination and degradation, thus leading to the regulation of the trichloroacetic acid cycle and lipid biogenesis (Chaveroux et al., 2013). O-GlcNacylaction of ERRγ has been shown to stabilize ERR protein levels by decreasing its ubiquitination in the liver (Misra et al., 2016). Several reports show that ERRα can be phosphorylated by PKA or EGF/PKA or EGF/MEK pathways in either lung or colon cancer cells, respectively (Liu et al., 2009; Byerly et al., 2013). A thorough characterization of post-transcriptional regulation of the ERRs would help further understand their systemic and local roles.

2. Biologic Function of ERRs. While ERRα is ubiquitously expressed (Giguere, 2008; Huss et al., 2015), ERRγ is concentrated in highly metabolically active and vascular tissues (Eudy et al., 1998; Misra et al., 2017), and ERRβ is primarily expressed in the eye, inner ear, and liver (Luo, 1997; J. Chen and Nathans, 2007; Onisha et al., 2010). ERRβ expression is subdued during the cancer progression, indicating a possible role in tumor suppression (Sengupta et al., 2014; Divekar et al., 2016).

ERRβ function impacts energy balance by modulating resting energy expenditure, spontaneous physical activity, and satiety. Conditional ERRβ deletion in mice significantly reduced body and fat mass, increased voluntary wheel running distance, and increased oxygen consumption. ERRβ also plays a role in corticosterone secretion in response to stress (Byerly et al., 2013). Cardiac-specific ERRβ KO mice exhibit dilated cardiomyopathy with impairment of calcium handling (Rowe et al., 2017).

All three ERR isoforms have been detected in various types of cancer, including breast, prostate, colon, lung, adrenocortical, uterine endometrium, and ovarian cancers (J. D. Eudy et al., 1998; Ariazi et al., 2002; A. Watanabe et al., 2006; T. Fujimura et al., 2007; J. Wang et al., 2010; S. S. Lam et al., 2014; Casaburi et al., 2015; Huang et al., 2018). The ERRs, especially ERRα have been demonstrated to be critical regulators of oxidative metabolism and energy balance via PGC-1α recruitment, a potent inducer of mitochondrial biogenesis and function (Puigserver and Spiegelman, 2003). While PGC-1α has ERR-independent functions, its ability to induce mitochondrial biogenesis is significantly reduced when not interacting with ERRα (S. N. Schreiber et al., 2004). In contrast, without PGC-1α (or any activation signal), ERRα does not affect mitochondrial biogenesis, thus indicating a strong interdependence between ERRα and PGC-1α. The roles of ERRα in modulating PGC-1α, oxidative phosphorylation, and several other rate-limiting molecules of lipid metabolism (Sladek et al., 1997; R. B. Vega and Kelly, 1997) have prompted significant interest in designing ERRα modulators for the treatment of cardiometabolic disorders (Larsen et al., 2007). ERRα and ERRγ are expressed in highly metabolically active tissue such as muscle and have been shown to regulate energy production pathways (trichloroacetic acid cycle, fatty acid oxidation, mitochondria biogenesis, and oxidative phosphorylation) (Audet-Walsh and Giguere, 2015; Fan and Evans, 2015).

Several studies using genetic deletion of ERRα demonstrate a crucial role of ERRα in heart and skeletal muscle. ERRα KO mice are more susceptible to stress-induced heart failure (Huss et al., 2007). Moreover, skeletal muscle-specific ERRα KO mice display reduced mitochondrial biogenesis and impaired muscle repair (LaBarge et al., 2014). Full-body ERRα KO leads to decreased muscle mass, exercise intolerance, and impaired skeletal muscle metabolism (Perry et al., 2014). Genetic gain of function of ERRγ in the muscle leads to increased exercise endurance capacity, mitochondrial biogenesis, and oxidative muscle fiber content (Rangwala et al., 2010; Narkar et al., 2011). Unfortunately, whole-body ERRγ KO mice display 100%

lethality within 48hrs after birth due to cardiac dysfunction (Alaynick et al., 2007). Both ERRα and ERRγ play a role in cardiac metabolism and contractile functions. Mice lacking both cardiac ERRα and ERRγ develop lethal cardiomyopathy associated with cardiac metabolic and contractile dysfunctions (Wang et al., 2015).

Like the ERs, the ERRs have been involved in regulating bone mineral density (BMD) (Bonnelye et al., 1997; Bonnelye and Aubin, 2005). ERRα and ERRγ are expressed in the bone, but their impact on BMD is not clear, with literature suggesting that the various ERRs have either positive or negative effects on BMD. ERRα has been shown to promote the differentiation of osteoblasts, bone cells that synthesize bone matrix and promote bone mineralization (Rajalin et al., 2010; Cai et al., 2013; T. Huang et al., 2017). High expression of ERRα during late stages of osteogenic differentiation of human periodontal ligament tissue-derived mesenchymal stem cells is required to induce osteogenic genes (e.g., osteocalcin; *OCT*) and ERRα gene silencing significantly reduced mineralization capacity (Cai et al., 2013). ERR REs were found in the *OCT* gene, and ERR binding at these sites increases its activity to facilitate osteogenesis (H. Wang and Wang, 2013). On the other hand, several studies proposed ERRα as an inhibitor of bone mineralization (Gallet and Vanacker, 2010). The roles of ERRγ on BMD are ambiguous. For example, Kim et al. showed that activation of ERRγ inhibits the development of osteoclasts, bone-resorbing cells (H. J. Kim et al., 2019). In this study, using an ERRγ-specific synthetic agonist suppressed osteoclast differentiation and protected against inflammatory bone loss via the inhibition of RANKL, a key factor for osteoclast differentiation and activation. Paradoxically, other experiments indicated that ERRγ blocks osteoblast differentiation by suppressing Runt-related TF 2 (*RUNX2*) gene expression, the master regulator of osteoblast development (Jeong et al., 2009). Because of this effect, ERRγ has been proposed as an inducer of osteoarthritis (H. Zhao, Liu et al., 2019). Given these uncertainties, establishing the role(s) of ERRs on BMD warrants further investigation.

3. Small Molecule Modulators of ERRs. A limited number of crystal structures of ERR LBDs have been described. There are currently four ligand-bound and two unbound ERRα crystal structures. One of the structures shows ERRα forming a complex with a peptide fragment from its coactivator PGC-1α (PDB ID 1XB7) (Kallen et al., 2004), while another shows ERRα interacting with the PGC1α box 3 peptide (ID 3D24) (Greschik et al., 2008). In two structures, ERRα is bound with the synthetic inverse agonist ligand 2PJL (Kallen et al., 2007) and 3K6P (Patch et al., 2011). These structures contain 12 α helices and 2 small β- sheets similar to other NRs.

Several ERRα agonists and inverse agonists have been reported in the literature. Ding et al. developed a series of quinazolines and pyrimidines as ERRα agonists, of which the phenylquinazoline derivative DK3 and the pyridopyrimidinone derivative DK45 potently induced glucose and fatty acid uptake (K. Ding, 2010, 2014; L. Peng et al., 2011). The ER ligand 4,4',4"-(4-propyl-1H-pyrazole-1,3,5-triyl)triphenol potentiated the effects of ERRα on the cardiomyocyte metabolism target gene (R. M. Evans et al., 2016). More recently, 7-methoxy-3-methyl-2-phenyl quinazolin-4(3H)-one compound (JND003) was discovered with in vivo efficiency after oral administration, improving fatty liver disease in a mouse model as well as improving insulin sensitivity in obese mice (Mao et al., 2022).

A substituted thiadiazolyl acrylamide, XCT-790, was the first reported potent ERRα inverse agonist (B. Busch et al., 2005; B. B. Busch et al., 2004). It has been the most employed compound, with an IC_{50} of 0.37 μM in the Gal4 transfection assay (B. B. Busch et al., 2004). This ligand, however, produces many off-target effects, which has limited its utility as a specific chemical tool. Patch et al. used the selective inverse agonist 5FB to generate a crystal structure of an inactive ERRα (Patch et al., 2011). Jansen Pharmaceuticals developed a series of potent aminothiazolono indazoles ERRα inverse agonists. More than 50 compounds reported in the literature exhibited activity at single-digit nM, among which very few displayed clinical efficacy. However, (4-chloro-2-(trifluoromethyl)benzyl) azetidine-3-carboxylic acid derivative (IC_{50} of 8nM) and 2,4-bis(trifluoromethyl)benzyl-3-aminopiperidinyl derivative (IC_{50} of 4.5nM) increased insulin sensitivity (Bignan et al., 2012). Takeda Pharmaceuticals discovered that an ERRα inverse agonists with substituted 2,4-bis(trifluoromethyl)benzyl)piperidinyl methylene thiazolono markedly reduced tumor progression in breast cancer model (S. Matsumoto et al., 2013). Zhang et al. found that HSP1604, a potent and selective ERRα inverse agonist, decreased target genes' mRNA levels and suppressed the proliferation of different cancer cell lines (L. Zhang et al., 2016). Others reported a new class of 1-(2,5-diethoxybenzyl)-3-phenyl-urea analogs as ERRα inverse agonists (Du et al., 2017). A compound in this series with *N*-(4-methoxybenzyl)benzamide substitution dose-dependently inhibited the transcriptional activity of ERRα in the MDA-MB-231 cell line (Du et al., 2017). A novel ERRα inverse agonist LingH2-10 reduced the growth of the triple-negative breast cancer cell lines by 42% (Ning et al., 2017). A proteolysis targeting chimera was shown to cause >80% degradation of the ERRα protein at 30 nM. This compound is currently the most potent and selective ERRα degrader available (Peng et al., 2019). Most recently, a novel ERRα inverse agonist has been identified by virtual screening and biologic evaluation. In this study, (*E*)-4-chloro-*N*-(4-oxo-3-(*m*-tolylamino)naphthalen-1(4*H*)-ylidene)benzenesulfonamide significantly inhibited ERRα-induced genes and showed moderate anti-proliferative

activity against both the ER-positive and ER-negative breast cancer lines (H. Zhao, Lin et al., 2019).

There are currently no published ERRβ-ligand-bound X-ray structures. There is only one solution structure of the ERRβ attached to DNA (Gearhart et al., 2003). ERRβ has the highest sequence homology with ERRγ. An ERRβ homology model has been developed by using the ligand-bound crystal structures of ERRγ, which may constitute a valuable tool for designing selective β modulators (Di Micco et al., 2014). Some dual β/γ agonists (e.g., GSK 4716 and GSK 9089) were developed and reported in the literature (Zuercher et al., 2005). Older generation selective estrogen receptor modulators, such as 4-hydroxy tamoxifen (4-OHT) (Coward et al., 2001) and diethylstilbestrol (DES) (G. B. Tremblay et al., 2001), display inverse agonist activities on both ERRβ and ERRγ (Greschik et al., 2004). Yu et al. reported two very selective and potent ERRβ inverse agonists, DY181 (IC_{50} of 0.05 μM) and a related analog with IC_{50} of 0.35 μM (D. D. Yu and Forman, 2018; D. D. Yu et al., 2017).

ERRγ is the most characterized isoform because many ligand-bound crystal structures have been solved [PDB IDs: 2EWP (with GSK5182) (Chao et al., 2006); 5YSO (with DN200434) (Singh et al., 2019); 6A6K (DN201000) (J. Kim et al., 2019); 2GPP (with GSK4716) (L. Wang et al., 2006); 2GPU (4-OHT) (L. Wang et al., 2006); 2P7Z (with 4-OHT) (Abad et al., 2008); 1S9P (with DES) (H. Greschik et al., 2004); and 1S9Q (with 4-OHT) (H. Greschik et al., 2004)]. Small molecule modulators 4-OHT (Coward et al., 2001) and DES (K. Nam et al., 2003) have been identified as nonselective ERRγ inverse agonists. On the other hand, the 4-hydroxybenzohydrazide derivatives GSK 4716 and GSK 9089 (Zuercher et al., 2005) have been reported as selective dual ERRβ/γ agonists. The (Z)-4-(1-(4-(2-(dimethylamino)ethoxy)phenyl)-5-hydroxy-2-phenylpent-1-en-1-yl) phenol (GSK 5182) (Chao et al., 2006) was reported as an ERRγ selective inverse agonist. An in silico docking study helped design a library of compounds targeting selective ERRγ agonists. In their microwave-based combinatorial structure-activity relationship SAR approach, the group identified 6-amino-*N*'-((*E*)-4-((*E*)-phenyldiazenyl) benzylidene) nicotinohydrazide as the best compound. The reported compound showed a higher ERRγ to ERRβ isoform selectivity ratio compared to the reference compound GSK 4716 (Y. Kim et al., 2009). Structure-based SAR studies using the ERRγ inverse agonist, 4-(1-(4-(2-(dimethylamino) ethoxy)phenyl)-2,2-di(pyrimidin-5-yl) vinyl)phenol have shown a 27-fold selectivity ratio for γ over the β. However, this compound had poor potency compared to the reference compound used in this study (Koh and Park, 2011). Another structure-based ligand discovery approach has identified a natural product Eryvarin-H, and its bis-demethoxylated derivative, with increased selectivity between the isoforms but reduced activity than GSK 5182 (Koo et al., 2013). A 1,2,3 triazole compound has been reported that shows potent ERRγ agonist activity and direct binding to the ERR γ-LBD (S. Xu et al., 2015). In this study, the 1,2,3 triazole template has been used as a replacement core for the hydrazides. Among the compounds reported in this series, 4-(1-(4-isopropylbenzyl)-1*H*-1,2,3-triazol-4-yl)benzene-1,2-diol showed potential for increasing energy expenditure via adipocyte browning; thus, it may represent a novel therapeutic candidate for obesity-related diseases (S. Xu et al., 2015). In a separate SAR study, Kim et al. identified (*Z*)-4-(1-(4-(2-(dimethylamino)ethoxy)phenyl)-5-hydroxy-2-(imidazo[1,2-a]pyridin-6-yl)pent-1-en-1-yl)phenol, a compound with comparable activity and selectivity but better metabolic stability than GSK 5182 (J. Kim et al., 2016). Additional ERRγ selective agonists were developed using GSK4716 as a starting point with the acyl hydrazine core of the GSK 4716 replaced with amide moiety to generate a selective and potent ERRγ agonist (SR19881) with EC_{50} of 0.21μM and a partial agonist (SR20041) with improved metabolic stability (H. Lin et al., 2018). In a separate study, some organophosphate esters showed disruption of ERRγ activity (L-Y. Cao et al., 2018). In this study, tri-*m*-cresyl phosphate has been identified as the most potent ERRγ inverse agonist (L.-Y. Cao et al., 2018). Using tamoxifen-like scaffolds, a series of tetra-substituted olefin analogs showed improved ERRγ inverse-agonist potency, selectivity, in vitro absorption, distribution, metabolism, elimination, and toxicity profiles relative to the reference compound GSK 5182 (J. Kim et al., 2019). In this study, the highly potent compound with the phenolic -OH group at 3-position showed an IC_{50} of 0.035μM for ERRγ with 1,000-fold selectivity over the other isoforms (J. Kim et al., 2019). In a subsequent study, a positional isomer DN200434, where the phenolic –OH group was at the 4-position, generated the most potent orally active (functional assay IC_{50} = 0.006 μM) ERRγ inverse agonist available to date and with enhanced sodium iodide symporter of anaplastic thyroid cancer (Singh et al., 2019). Very recently, Burris et al. reported a series of 2,5-disubstituted thiophenes containing boronic acids as ERRγ agonists. One of their compounds, (3-(5-((2-fluorophenyl) carbamoyl)thiophen-2-yl)phenyl)boronic acid, was identified as a pan-ERR with an ERRγ EC_{50} of 0.378 μM, and this compound has shown better stability in microsomal assay relative to GSK 4716 (Burris et al., 2019).

No ERRα selective ligand has been developed yet, but conversion of the GSK4716 chemical scaffold leads to increased ERRα selectivity, providing pan-ERR agonists (Shahien et al., 2020). Recently, several ligands targeting all the ERRs have been published with in vitro and in vivo efficacy in different models. An ERRα/γ inverse agonist SLU-PP-1072 has been shown to inhibit prostate cancer cell metabolism and induce apoptosis in cultured cells (Schoepke et al., 2020). More recently, optimization of GSK4716, converting the isopropyl phenyl group to a

more hydrophobic moiety, led to the development of SLU-PP-332, with a 50-fold increase in potency toward ERRα compared to GSK4716. SLU-PP-332 has been shown to have bioavailability, induce an acute exercise pathway in skeletal muscle, and increase running capacity (Billon et al., 2023). A new compound, SLU-PP-915, was designed based on ERRγ/GSK4617 structure (PDB:2GPP). Replacing the central hydrazide moiety, 5-membered heterocycles led to a novel di-substituted thiophenes of GSK4716 that displays equal agonist activity toward 3 ERRs ($\alpha/\beta/\gamma$). This compound has been shown to improve heart failure in a transaortic constriction mouse model (W. Xu et al., preprint, https://doi.org/10.1101/2022.02.14.480431).

There are no ERR-targeting drugs in clinical development at this point. However, promising pre-clinical data has opened a window of opportunity to develop better ligands, and it is only a matter of time before one of them reaches clinical trials.

The latest information on ERRs and their ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=97).

V. Subgroup IV

The NR4A orphan NRs, NGFI-B, NURR1, and NOR-1 are closely related members of the NR4A subfamily play essential roles in the development, differentiation, and survival, and apoptosis of various cell types, including immature T cells, neurons, and cancer (Volakakis et al., 2010; Boldingh Debernard et al., 2012). These receptors are broadly expressed in the CNS (Q. Xiao et al., 1996; Zetterstrom et al., 1996). Their DBD sequences are almost identical, whereas their LBDs and NTDs share 58% to 65% and 26% to 28% similarity, respectively.

A. Nerve Growth Factor I-B (NGFI-B/Nur77/TR3–NR4A1)

The *NR4A1* gene is located on chromosome 12 in humans, which encodes for a 598-residue protein (Hazel et al., 1988). It is hypothesized that the NTD permits NRFI-B translocation from the nucleus to the cytoplasm (Rehman et al., 2017). The DBD recognizes specific NGFI-B REs (\ AAAGGTCA) as a monomer and binds Nur REs (NurRE; TGATATTTN$_6$AAATGCCA; N is any nucleotide) as a homodimer or heterodimer with either NURR1 or NOR-1. It has been shown that these heterodimers more potently stimulate the transcription of the pro-opiomelanocortin gene (*POMC*) than do homodimers, demonstrating the interdependence between NR4A family members (Maira et al., 1999). Like the TRs, RAR, or receptor, it also heterodimerizes with RXRs to recognize DR5 sequences (AGGTCA-N$_5$-AGGTCA; N is any nucleotide) (Perlmann and Jansson, 1995). The NGFI-B LBD has an LBP filled with hydrophobic side chains and a relatively flexible helix 12 (Flaig et al., 2005; Lanig et al., 2015).

Given its potential role in apoptosis, NGFI-B gained interest in oncology research. For instance, malignant glioma cells treated with n-butylidenephthalide derivative (PCH4) showed increased expression of NGFI-B and protein export from the nucleus to the cytoplasm, which may inhibit the growth and/or promote apoptosis of these cells (L. F. Chang et al., 2011). Another report demonstrated the role of NGFI-B in the migration of TGF-β-induced breast cancer cells (F. Zhou et al., 2014; Hedrick and Safe, 2017). NGFI-B is predominantly expressed in the nucleus of skeletal muscle, trachea, and ovaries. However, ovarian cell lines also carry NGF1-B in their cytoplasm. Patients with high-grade serous ovarian cancer have increased expression of *NGFI-B*, suggesting its role in cancer aggressiveness (Delgado et al., 2016).

In this section, we will highlight the role of NGFI-B in steroid hormone synthesis, hormone signaling, cell survival, proliferation, and apoptosis. We will then focus on several small molecule compounds that modulate the NGFI-B function.

1. NGFI-B Regulation of Steroid Hormone Synthesis and Endocrine Signaling. NGFI-B is expressed in endocrine tissues and organs responsible for steroid hormone production, including the adrenal and pituitary glands and testes. The first NurRE was identified in the promoter region of the POMC gene of pituitary gland-derived cells (Philips, Lesage, et al., 1997). In the promoter of the *POMC* gene, there is a unique NRFI-B binding site that overlaps with STAT1-3 (NurRE-STAT element composite). STAT1-3 RE and NRFI-B can bind to NurRE-STAT composite site even though STAT does not bind alone. An intermediary protein, cyclic-AMP RE binding protein (CREB), was found to bind both STAT 1–3 and NGFI-B to potentiate *POMC* transcription from the composite site (Mynard et al., 2004).

NGFI-B also contributes to testosterone synthesis in Leydig cells. NGFI-B binds near the steroidogenic acute regulatory protein (StAR)—a protein required in the transport of cholesterol through the mitochondrial membrane to initiate the synthesis of steroid hormones. Upon cAMP stimulation, NGFI-B and c-Jun synergistically increase StAR gene expression, likely due to their interaction (Martin and Tremblay, 2008). NGFI-B binding to the StAR promoter is inhibited by dexamethasone, a GR synthetic agonist (Martin and Tremblay, 2008). This GR ligand also stimulates DAX1 expression, which may play a role in GR-mediated transrepression of *NGFI-B* (Philips, Maira, et al., 1997).

NGFI-B also plays a role in the negative feedback loop of female and male sex hormone regulation. Upon ligand binding, the AR inhibits NGFI-B activity via interactions between NGFI-B NTD and AR DBD, which releases the coactivator SRC1 (C. H. Song, Gong, Park, and Lee, 2012). Moreover, the ERα hinge

region binds to NGFI-B DBD-LBD to block DNA binding and activity. Finally, TNFα inhibits steroidogenic enzyme expression via NGFI-B transcriptional activity suppression (C. Y. Hong et al., 2004).

2. NGFI-B in Cell Survival, Proliferation, and Apoptosis. NGFI-B has been implicated in regulating cellular survival, proliferation, and apoptosis in various tissues and cell types. In cultured hepatocytes, SHP interacts with either NGFI-B or CBP/p300. SHP binding to CBP/p300 blocks coactivator binding to NGFI-B, resulting in decreased receptor activity. Aside from this interaction, SHP modulates NGFI-B-mediated apoptosis in hepatocytes (Yeo et al., 2005). In pancreatic cancer cells, NGFI-B binds to SP1 and SP4, two TFs that are recruited to the promoter sites of the p21 gene (*CDKN1A*), a cyclin-dependent kinase inhibitor. Although the p21 expression is recognized as a cell proliferation inhibitor (S. O. Lee et al., 2009), another study found that the NGFI-B-SP1 complex induces the expression of the Survivin gene (*BIRC5*), an apoptosis inhibitor involved in cell survival and proliferation (S. O. Lee et al., 2010). NGFI-B DBD also blocks PML DNA binding, a tumor suppressor involved in apoptosis and cell cycle regulation. (W. S. Wu et al., 2002). In the human osteosarcoma U2OS cell line, PML enhances apoptosis in an NGFI-B-dependent mechanism.

The roles of NGFI-B are highly divergent depending on subcellular localization. For instance, when located in the mitochondria, NGFI-B becomes pro-apoptotic. Nuclear localization, however, promotes cell growth and proliferation. Interestingly, 9-cis retinoic acid causes NGFI-B-heterodimerization with RXRα and nuclear retention of the newly formed complex to prevent the activation of the pro-apoptotic gene programming. In contrast, apoptotic stimuli or treatment with the NGF trigger NGFI-B-RXRα heterodimer export from the nucleus to promote apoptosis. (X. Cao et al., 2004). In PC12 cells, NGF-induced NGFI-B translocation requires NES in its LBD (Katagiri et al., 2000). In prostate cancer cells, nuclear export of NGFI-B in response to pro-apoptotic signal requires NES and dimerization with RXRα (X. Cao et al., 2004). Cytoplasmic NGFI-B-RXRα is subsequently shuttled to the mitochondria, where NGFI-B interacts with *Bcl-2* to trigger apoptosis. A further complicating matter is that NGFI-B interacts with COUP-TFs to increase the expression of RAR-responsive genes. This simultaneously inhibits NGFI-B-RXRα heterodimerization, which suppresses their transcriptional activity (Q. Wu et al., 1997). COUP-TFs bind and repress RAR activity through competition for DNA binding. In sum, NGFI-B mediates its apoptotic and proliferative actions through interactions with other TFs. The downstream effects of these interactions on both NGFI-B activity and cellular behavior depend on cellular environmental as well as localization.

3. Small Molecule Compounds That Modulate NGFI-B Function. NGFI-B has been suggested to be a potential oncology target (To et al., 2012; Y. Zeng et al., 2017). Aside from cancer, NGFI-B may have clinical potential for treating metabolic disorders and inflammation as well. Many small molecules have been shown to regulate NGFI-B activity. A molecule isolated from the fungus *Dothiorella sp. HTF3*, octaketide cytosporone B (Csn-B), is a natural agonist of NGFI-B (EC_{50} = 278 pM) (Brady et al., 2000; Y. Zhan et al., 2008) from which Liu et al. developed synthetic analogs (J. J. Liu et al., 2010). CsnB stimulated NFGI-B nuclear export, suppressed tumor growth, and included cancer cell apoptosis in xenograft models. CsnB stimulates hepatic gluconeogenesis in an NFGI-B-dependent manner, thus holding potential as a treatment for nondiabetic hypoglycemia. There is also evidence that NFGI-B participates in nonapoptotic cell death. Wang et al. showed that a Csn-B derivative, THPN, induced melanoma cell death even when cocultured with apoptosis inhibitors. In this experiment, the authors found that THPN induced autophagy, and this process involved NFGI-B (W. J. Wang et al., 2014). This represents another mechanism through which NFGI-B could treat cancer. Another potent NGFI-B agonist, TMPA, showed promise for the treatment of metabolic disorders. In a mouse model of T2D, NGFI-B activation led to AMPKα phosphorylation, an enzyme that stimulates fatty acid oxidation and muscle glucose uptake. TMPA normalized blood glucose and reduced insulin resistance but not in NGFI-B deficient mice (Y. Y. Zhan et al., 2012). Aside from polyketides, bisindole methane (DIM) compounds and their derivatives can bind to NR4A receptors to regulate their activity. For instance, the 1, 1-Bis (3-indolyl)-1-(p-substituted phenyl) methane (C-DIM) analogs, namely DIM-C-pPhOCH_3 (C-DIM-5) and DIM-C-pPhOH (C-DIM-8) were reported to activate and inhibit NGFI-B, respectively. Despite their opposite effects on NGFI-B activity, both molecules have similar oncology therapeutic applications. For instance, chronic C-DIM-5 or C-DIM-8 aerosol therapy led to the significant tumor regression of lung tumors in a mouse model of metastatic cancer. To exert their therapeutic effects, C-DIM-5 inhibits the G0/G1 to S phase of the cell cycle, while C-DIM-8 induces A549 human adenocarcinoma cell apoptosis (S. O. Lee et al., 2010; Yoon et al., 2011; Andey et al., 2013). The anticancer properties of these compounds are not restricted to lung cancer. C-DIM-5 and C-DIM-8 suppressed the growth and promoted apoptosis of bladder cancer and pancreatic cancer cells, respectively (S. D. Cho et al., 2010; S. O. Lee et al., 2010). A follow-up study showed that treatment of rhabdomyosarcoma cells and renal cell lines, 786-O and ACHN, with C-DIM-8 and another associated analog DIM-C-pPhCO_2Me inhibited tumor growth and induced apoptosis (Hedrick et al., 2015; Lacey et al., 2016). Induction of

apoptosis has long been established as an anticancer therapeutic strategy, and evidence suggests that NGFI-B may be targeted for this purpose (Y. H. Duan et al., 2010). For example, inducing NGFI-B with CCE9, a xanthone compound, promoted apoptosis by activating the p38α MAPK pathway and NGFI-B/Bcl-2 complex formation (J. Liu et al., 2017). Z-ligustilide, a natural ingredient of widely employed Chinese herbal medicines, suppresses tumor growth by inducing NGFI-B (Kan, Cho, Rudd, and Lin, 2008; Qi et al., 2017). In fact, Z-ligustilide restored tamoxifen-induced cell death in tamoxifen-resistant MCF7 breast cancer cells, and this effect depended on NGFI-B (Qi et al., 2017). Aside from the previosuly mentioned therapeutic applications, NGFI-B has also been investigated for the treatment of inflammatory disease therapeutics. PDNPA (n-pentyl 2-[3,5-dihydroxy-2-(1-nonanoyl)-phenyl]acetate) displays high affinity for the NGFI-B LBD that can inhibit the pro-inflammatory TF NFκB by impeding the interaction between NGFI-B and p38α (L. Li et al., 2015). Interestingly, PDNPA alleviated LPS-induced inflammation (L. Li et al., 2015). Another NGFI-B targeting anti-inflammatory molecule is celastrol. This compound was shown to inhibit inflammation and promote autophagy in an NGFI-B-dependent manner. Celastrol promotes mitochondrial translocation of NGFI-B and subsequent ubiquitination by tumor necrosis factor receptor-associated factor 2 and E3 ubiquitin ligase, which are crucial players in inflammatory signaling. The protein, p62/sequestosome 1, binds to ubiquitin-linked NGFI-B, resulting in autophagy during inflammation.

Given the evidence on the therapeutic potential of NGFI-B modulation, extensive efforts are being made to develop potent and specific ligands. An endogenous, physiologically relevant ligand for NGFI-B has yet to be identified. Still, various compounds with diverse molecular scaffolds were shown to activate or inhibit NGFI-B and promote its export from the nucleus. The mechanisms mediating NGFI-B modulation are still poorly understood, and further studies are needed to investigate compounds that affect NGFI-B function to warrant subsequent clinical trials that will evaluate therapeutic use while minimizing detrimental side effects. NGFI-B remains an attractive therapeutic target for various diseases, and future research should focus on further understanding the expression, function, structure, and localization of NGFI-B, which will guide the identification of more compounds that modulate its activity. The latest information on NGFI-B and its ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=99).

B. Nurr-Related Factor 1 (NURR1–NR4A2)

NURR1 (NR4A2) plays a crucial role in the differentiation, maintenance, and survival of midbrain dopaminergic neurons by regulating specific genes involved in dopamine metabolism, mitochondrial function, axonal growth, cell survival, and neurotransmission (Eells et al., 2006; Heng et al., 2012; Kadkhodaei et al., 2013). NURR1 is possibly expressed prior to disparate phenotypic markers of dopaminergic neurons, including vesicular monoamine transporter, tyrosine hydroxylase, aromatic amino acid carboxylase, and dopamine transporter (Zetterstrom et al., 1997; Jankovic et al., 2005). The loss of NURR1 function is closely associated with neurodegenerative diseases. In support of this claim, PD patients display a substantial decrease in NURR1 expression in the substantia nigra of the brain (Y. Chu et al., 2006; Le et al., 2008). Additionally, *Nurr1* knockout mice showed an absence of dopaminergic neurons in the substantia nigra and ventral tegmentum, leading to premature death of the newborn mice. The crucial role of NURR1 in midbrain dopaminergic neuron function and development is supported by numerous other preclinical studies (Zetterstrom et al., 1997; Le et al., 1999; C. Jiang et al., 2005; Kadkhodaei et al., 2013).

NURR1 and NGFI-B share >92% DBD sequence homology and bind to similar DNA REs (Law et al., 1992). ChIP-on-chip and genome-wide transcription studies have identified many NURR1-regulated target genes. However, the physiologic effects of NURR1 activation are essentially cell-type-dependent. For instance, activation of NURR1 in dopaminergic neurons promotes their growth and maturation (Park et al., 2012; Kadkhodaei et al., 2013). In contrast, activation of NURR1 in cancer cells induces apoptosis (Inamoto et al., 2008; X. Li et al., 2012). In macrophages, NURR1 inhibits inflammatory responses (Glass et al., 2010). This section will highlight NURR1's interaction with other TFs and coregulatory proteins and the receptor's role in neurologic functions. We will discuss the development of agonists and modulators for NURR1 as potential therapies for PD.

1. Interaction of NURR1 with Other Proteins. NURR1 is an active TF in both its monomeric and dimeric states and as a heterodimer with RXR or NGFI-B. The interaction of NURR1 with RXR is abrogated by a single P560A or L562A mutation or a triple K554A, L555A, and L556A substitution (Forman et al., 1995). NURR1 transcriptional activity is suppressed when heterodimerized with RXR (Perlmann and Jansson, 1995). Moreover, NURR1 interacts with the GR, where the complex formation was shown to enhance NURR1 activity in PC12 cells in a dexamethasone-dependent manner and inhibit GR transcriptional activity in AtT20 cells (Martens et al., 2005; Carpentier et al., 2008). MAP kinases ERK2 and ERK5 both bind NURR1 and increase its transcriptional activity in a phosphorylation-dependent manner (Sacchetti et al., 2006). Several proteins, such as LIM kinase 1 and cyclin-dependent kinase inhibitor 1C, bind to the NTD of NURR1 to suppress its activity (B. Joseph et al.,

2003; Sacchetti et al., 2006). The peptidyl-prolyl isomerase Pin1 also binds to the same domain of NURR1, as well as the DBD, to enhance its transcriptional activity (van Tiel et al., 2012). Direct interaction of NURR1 and *Runx1* stabilizes *Foxp3* expression in $CD4^+$ T cells, thus playing a determining role in Treg development (Sekiya et al., 2011). NURR1 inhibits inflammation by directly binding to NFκB p65 when phosphorylated at S468. This binding results in the recruitment of CoREST corepressor complex to NURR1 and inhibition of NFκB p65 activity (Saijo et al., 2009). In addition, PIASγ, a SUMO-E3 ligase, inhibits NURR1 transcriptional activity via SUMOylation of K91 in the latter. The repression may be E3-ligase-independent and result from the NURR1/PIASγ complex formation (Galleguillos et al., 2004; Arredondo et al., 2013). X-ray crystal structures and NMR analyses showed physical interaction between the NURR1 LBD and NCoR-1 as well as SMRT (Codina et al., 2004; Sacchetti et al., 2006). However, the presence of Pitx3 prevents the NURR1/SMRT complex formation without directly interacting with NURR1, suggesting an intermediary corepressor—possibly PSF as it binds to both NURR1 and Pitx3 (Jacobs et al., 2009).

2. NURR1 in Neurologic Function. NURR1 has pleiotropic effects on gene expression in the brain, which is highly dependent on cell type, stress stimulus, or extracellular signal. Transcriptomic data acquired from human neural SK-N-AS cells showed that some genes were induced while others were suppressed as a function of NURR1 concentration (M. M. Johnson et al., 2011). Genes induced by NURR1 include *Tubb2a*, *Kif1a,* and *Crmp1*, all linked to neurodevelopment. The opposite effect was observed in NFκB and TNF-related transcripts, as well as PPARγ (M. M. Johnson et al., 2011).

NURR1 is widely distributed in the brain and is rapidly induced after a stress stimulus or traumatic injury in the CNS. Upon exposure to kainic acid, a glutamate receptor agonist, NURR1 protein levels were rapidly increased in the CA1 and CA3 layers of the hippocampus, which harbor pyramidal neurons. NURR1 is also transiently induced in the dentate gyrus, a region more resistant to kainic acid-induced neuronal injury (Crispino et al., 1998). CREB interaction with NURR1 is vital for memory and learning. This is demonstrated in experiments where the knockdown of NURR1 in the hippocampus resulted in impaired long-term memory and reversal learning (Colon-Cesario et al., 2006).

NURR1 is crucial for both the development and homeostasis of dopaminergic neurons, particularly in the substantia nigra and the ventral tegmental area (Zetterstrom et al., 1997). NURR1 is required for the maintenance and maturation of midbrain dopaminergic neurons (Kadkhodaei et al., 2009) as well as for dopamine synthesis and metabolism (Sacchetti et al., 2001; J. Satoh and Kuroda, 2002). Relative to wild-type, PD model heterozygous NURR1 knockout mice showed a progressive decline in the number of dopaminergic neurons in the substantia nigra with age (L. Zhang et al., 2012). NURR1 expression level in PD model mice correlates with their neurologic functions, which could be attributed to the decreased resistance of mesencephalic dopamine neurons to MPTP-induced injury (Le et al., 1999). A human study analyzing blood samples from healthy subjects, PD, and non-PD neurologic disorder patients revealed that PD patients expressed significantly less NURR1 than healthy and ill control subjects. This indicates that NURR1 expression may be used as a noninvasive biomarker of PD activity (Le et al., 2008). The importance of NURR1 in PD was the focus of studies that demonstrated the protection of dopaminergic neurons from MPTP-induced injury when NURR1 is activated using 1,1,-bis(3′-indolyl)-1-(p-chlorophenyl)methane (De Miranda et al., 2015). Furthermore, this TF has an important protective function against inflammatory and oxidative stress within the context of PD and other neurodegenerative disorders.

3. NURR1 Agonists. In recent years, there has been an active effort to identify novel agonists of NURR1. Activation of NURR1 function was shown to have neurogenic, anti-inflammatory, or neuroprotective effects. An antileukemia drug, 6-mercaptopurine, was the first agonist identified for NURR1 and NOR1 (Ordentlich et al., 2003). The compound was shown to directly bind to the AF1 domain at the N-terminus (Wansa et al., 2003). A group of compounds with a benzimidazole scaffold were also found to activate NURR1 with an EC_{50} of 8–70 nM (Dubois et al., 2006). These compounds were shown to alter NURR1 functions but were not explored for PD treatments. In the *Subgroup IV* section, we mentioned that C-DIM analogs bind to NR4A receptors. Therefore, it is not surprising that these compounds show anti-parkinsonian properties. One of the analogs, C-DIM12, has a higher affinity for NURR1 than NGFI-B and demonstrated the most potent neuroprotective and anti-inflammatory effects in a PD rat model (De Miranda et al., 2015).

Another novel agonist, SA0025, displayed anti-inflammatory activity, modulated several dopamine target genes, and conferred partial neuroprotection in PD models (G. A. Smith et al., 2015). The compound isoxazolo-pyridinone 7e also reduced neuroinflammation and neurodegeneration by hampering NFκB-dependent pathways (Montarolo et al., 2014). This compound has high brain absorption and distribution and good oral bioavailability, but isoxazolo-pyridinone 7e was not tested in PD models (Hintermann et al., 2007). However, its analog, SH1, was demonstrated to enhance the behavioral performance in a lactacystin-induced PD mouse model, which may be attributed to reduced neuroinflammation and enhanced dopamine-related effects (Z. Zhang et al., 2012).

None of the aforementioned NURR1 agonists are demonstrated to activate NURR1 via direct physical

binding to the LBD. Recently, the antimalarial drugs amodiaquine (AQ) and chloroquine (CQ) and the nonsteroidal anti-inflammatory drug glafenine were identified as NURR1 agonists, where AQ and CQ were shown to directly bind the putative NURR1 LBP via NMR and other biophysical methods, including fluorescence quenching, surface plasmon resonance and radioligand binding assay that employ tritium-labeled CQ (C. H. Kim et al., 2015). The anti-PD effects of AQ/CQ involve the inhibition of microglia-mediated inflammation and enhanced dopamine-dependent gene expression.

4. Other NURR1 Modulators. For decades, the neuroprotection conferred by dopamine agonists has been a controversial topic (Blandini and Armentero, 2014). Molecular analyses of blood mononuclear cells corroborated previous studies showing that dopamine agonists confer neuroprotection by activating *NURR1* expression (L. M. Zhang et al., 2015). Meanwhile, an N-methyl-D-aspartate receptor antagonist, memantine, restored PC12 cell survival from neurotoxicity induced by 6-OHDA via NURR1 upregulation and NGFI-B suppression (Wei et al., 2016).

Aside from synthetic small molecule compounds, several natural products were identified as NURR1 modulators with anti-parkinsonian effects, including radicicol, Bushen Huoxue decoction, moracenin D, and EGb 761. Dong et al. showed that radicicol confers neuroprotection from rotenone-mediated apoptosis by inducing NURR1 and inhibiting P53 (J. Dong et al., 2016). Bushen Huoxue decoction was identified as a NURR1 agonist and has demonstrated anti-PD effects in clinical trials (M. Li et al., 2015). Moracenin D from Mori Cortex radices was also shown to activate NURR1 while simultaneously inhibiting α-synuclein expression (Ham et al., 2012). Finally, EGb 761 from Ginkgo biloba extracts induced a 1.5-fold increase in NURR1 expression in substantia nigra and prevented neurodegeneration in MPTP-lesioned PD mice (Rojas et al., 2012).

5. Identification of Potential NURR1 Endogenous Metabolites Ligands. As an orphan NR, NURR1 has no previously known natural ligand. De Vera et al. mapped the putative LBP of unsaturated fatty acids (UFAs), such as docosahexaenoic acid and arachidonic acid in the NURR1 LBD, using solution NMR spectroscopy, whose binding affinities (K_d) of 30 μM and 58 μM, respectively, based on a tryptophan fluorescence assay (de Vera et al., 2016). Docosahexaenoic acid titration decreased NURR1 transactivation in HEK293t and MN9D dopaminergic cells in a luciferase reporter assay. The collapsed pocket of NURR1 filled with hydrophobic residue side chains was shown to be dynamic via solution NMR and HDX-MS. It can conformationally adapt based on molecular dynamics simulations to accommodate the binding of UFAs (de Vera et al., 2019). Moreover, the canonical LBP for UFAs and the synthetic agonist, AQ, were similar, although the latter does not affect the conformation of helix 12 to the same degree as the UFAs.

Another study has shown that a dopamine metabolite, 5,6-dihydroxyindole (DHI), modulates receptor function through direct binding to a noncanonical NURR1 LBP. The X-ray crystal structure revealed a covalent adduct of DHI with C566. The same study showed that DHI induced the transcription of the dopamine transporters vesicular monoamine transporter (*vmat*) and dopamine active transporter (*slc6a3*) and the rate-limiting biosynthetic enzyme tyrosine hydroxylase (*th*) in a zebrafish model of PD (J. M. Bruning et al., 2019).

6. NURR1 as a Therapeutic Target for Parkinson's Disease. Given its unequivocal roles on dopaminergic neuron homeostasis, NURR1 has aroused great enthusiasm in the field of PD drug development. While endogenous regulation of this NR is not clear, several metabolites were shown to modulate NURR1 signaling, including fatty acids, calcium, stress, inflammatory cytokines, calcium, membrane depolarization, and growth factors. There is also a consensus that *NURR1* expression declines throughout life, which may contribute to age-related cognitive decline and susceptibility to PD. Therefore, PD therapeutic development has largely focused on restoring NURR1 activity. NURR1 function can be increased with specific ligands or indirect targets shown to increase NURR1 activity, such as RXR, CREB, Wnt/β-catenin pathway, and neurotrophic factors can be activated to enhance. Three additional synthetic ligands, LG100268, XCT139508, and bexarotene, were shown to bind to NURR1/RXR heterodimers and protect dopaminergic neurons (Friling et al., 2009; McFarland et al., 2013). Other proposed targets to increase NURR1 activity include brain molecules that suppress its activity (e.g., α-synuclein and microRNA-132 (Devine, 2012; D. Yang et al., 2012). Clinical application(s) of NURR1 modulation has been significantly delayed by the lack of specific ligands. As reported in this section, most NURR1 ligands used in preclinical studies cross-react with other TFs or are indirect modulators that do not bind to the receptor. However, the recent elucidation of both the canonical and alternative NURR1 binding pockets from solution NMR and X-ray crystallography studies will likely propel novel ligand development with higher affinity and specificity.

Finally, NURR1 is expressed not only in the CNS. Thus, NURR1 may have additional therapeutic applications to be explored with novel ligands. The latest information on NURR1 and its ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=99).

C. Neuron-Derived Orphan Receptor 1 (NOR-1–NR4A3)

NOR-1 is the least studied member of the NR4A subfamily. Unlike NGFB-I and NURR1, NOR-1 does

not heterodimerize with RXR (Perlmann and Jansson, 1995; Zetterstrom et al., 1996). Initial studies showed a high degree of newborn or embryonic lethality in mice lacking *Nor1* (DeYoung et al., 2003); however, further investigations revealed that these mice could survive but exhibit defective hippocampal and semicircular canal development (Ponnio et al., 2002; Ponnio and Conneely, 2004). After its initial identification in the brain, tissue distribution studies found NOR-1 broadly expressed in the organism (Ohkura et al., 1996). In this section, we will highlight some of the physiologic roles of NOR-1 with an emphasis on its interactions with other TFs.

1. Interaction of NOR-1 with Other Proteins. NOR-1 recruits the TIF1β (also known as KAP1) coregulator to increase its activity (Rambaud et al., 2009). Protein kinase C (PKC) and RSK1/2 were shown to promote NOR-1 translocation to the mitochondria (Wingate et al., 2006; Thompson et al., 2010). The peptidyl-prolyl isomerase Pin1 binds the NOR-1 DBD to enhance its transcriptional activity, similar to NURR1 (van Tiel et al., 2012). FHL2 binds to the NTD to inhibit NOR-1-driven transcription (Kurakula et al., 2011). Hydrophobic analysis and molecular modeling of the NOR-1 LBD show no canonical LBP. Consequently, the coregulators SRC1/2/3, TRAP220/DRIP50, PCAF, and p300 are recruited via the NTD domain (Wansa et al., 2003). Of note, the chemotherapy drug mercaptopurine increases the activity of NR4A receptors without directly binding to their LBD and promotes TRAP220 recruitment to the NOR-1 NTD.

NOR-1 is a key player in the apoptosis of developing T cells (Cheng et al., 1997). T cell receptor stimulation induces PKC and NOR-1. Like NGFI-B, NOR-1 is a PKC substrate that, upon phosphorylation, translocates to the mitochondria to form a complex with the apoptosis regulator Bcl-2 (see the *Subgroup IV* section). This new interaction forces Bcl-2 to adopt a new confirmation that exposes its pro-apoptotic domain BH3 to trigger cell death (Thompson and Winoto, 2008; Thompson et al., 2010).

Six3 is a regulator of NOR-1 through interaction with its DBD (Ohkura et al., 2001; Laflamme et al., 2003). The expression of Six3 overlaps with that of NOR-1 in the fetal rat forebrain on embryonic day 18 (Ohkura et al., 2001). In most physiologic circumstances, Six3 enhances the activity of all three NR4A members. However, Six3 can also inhibit NOR-1 when fused with EWS (Laflamme et al., 2003).

2. NOR-1 in Neurologic Function. The role of NOR-1 on cognitive function has been highlighted by examination of its role in HDAC inhibitor-induced memory enhancement (Hawk et al., 2012). Similar to NURR1, induction of NOR-1 induces dopamine neurotransmission-related genes such as *Th*, and *Slc6a3*, suggesting NOR-1 may be a potential therapeutic target for PD (Eells et al., 2012; Xiang et al., 2012). However, other evidence indicates that NOR-1 activation may disrupt brain circuitries controlling mood and addiction. For instance, *Nor1* overexpression in the brain of WKY rats, a genetic model of depression, exacerbated their phenotype, while *Nor1* gene silencing eliminated the depression phenotype (Schaffer et al., 2010). Additionally, *NOR1* gene polymorphisms were linked to nicotine addiction in a cohort of patients with psychiatric disorders (Novak et al., 2010).

3. NOR-1 in Inflammation and Immune Responses. Like the other two NR4A members, NOR-1 is induced by stress and inflammation. Experiments in dual and triple CD4+ T cell-specific *Nr4a* KO mice demonstrated that NOR-1 and NGFI-B are key regulators of FoxP3$^+$ Treg cell development, thus playing a role in preventing autoimmunity (Sekiya et al., 2013). In another study, global deletion of both NGFI-B and NOR-1 severely disrupted HSC homeostasis in mice. The results from this study indicated that NGFI-B and NOR-1 restrict HSC proliferation by activating C/EBPα-driven antiproliferative gene network and suppressing several NFκB-induced cytokines (Freire and Conneely, 2018). In DCs, NOR-1 expression is markedly upregulated TLR signaling. In addition, NOR-1 knockdown blunts LPS-mediated induction of CD80, CD86, IL-10, IL-6, and IL-12 (Nagaoka et al., 2017). Collectively, these results show that NOR-1 meditates both pro and anti-inflammatory functions through roles on distinct cell populations involved in adaptive and innate immunity.

4. NOR-1 in Cardiometabolic Diseases. NOR-1 plays various roles in energy metabolism and the cardiovascular system, but receptor activation has both therapeutic and pathogenic effects depending on the tissue. In skeletal muscles, increasing NOR-1 signaling induces exercise training-like effects that may help combat cardiometabolic diseases. Interestingly, Pearen et al. generated a mouse overexpressing *Nr4a3* in skeletal muscle that displayed a massive increase in oxidative myofibers with nearly double the mitochondria volume of wild-type muscles. Not surprisingly, these mice were phenomenally fit and ran over twice the distance of wild-type counterparts in a maximum cardiovascular capacity test (Pearen et al., 2012). In agreement with the role of NOR-1 on mitochondrial function, NOR-1 knockdown in cultured myocytes resulted in a shift from oxidative to glycolytic metabolism, as demonstrated by functional assays and gene expression profiles (Pearen et al., 2008). While the previously mentioned studies indicate that NOR-1 agonists may act as exercise mimetics, other evidence suggests they would rather be obesogenic and could accelerate atherosclerosis. A transgenic mouse model overexpression NOR-1 in adipocytes developed a complex pathogenic phenotype with impaired glucose metabolism, dyslipidemia, cardiac function abnormalities, and behavioral

changes (Walton et al., 2016). In support of these observations, others demonstrated that NOR-1 is induced during adipocyte differentiation, and its expression is closely associated with obesity (Veum et al., 2012). NOR-1 activity has some controversial roles in the vascular system. On the one hand, NOR-1 is highly expressed in atherosclerotic plaques and has been shown to promote vascular smooth muscle cell proliferation (Saucedo-Cardenas and Conneely, 1996; D. Liu et al., 2003; Hanna et al., 2012; Hilgendorf et al., 2014; Y. W. Hu et al., 2014). Paradoxically, NOR-1 inhibits inflammation in these cells by suppressing NFκB signaling. In vascular endothelial cells, NOR-1 is induced by VEGF (D. Liu et al., 2003), and NOR-1 knockdown inhibits VEGF-induced cell growth (Martinez-Gonzalez et al., 2003; Rius et al., 2006). NOR-1 further regulates the vascular system by binding an NGFI-B RE in the promoter of the vascular cell adhesion protein 1 (*VCAM1*) gene (Y. Zhao et al., 2010).

Stimulation of mouse pancreatic beta cells with endoplasmic reticulum stressors, such as thapsigarin and palmitate, induces *Nr4a3* expression suggesting a possible role of NOR-1 in modulating insulin production (W. Gao et al., 2014). Intriguingly, NOR-1 knockout mice display higher beta cell mass and glucose tolerance (Close et al., 2019). In both human islets and INS cells, pro-inflammatory cytokines and elevated glucose induce NOR-1 expression. Furthermore, overexpression of NOR-1 in these cells triggered apoptosis. Finally, individuals with T2D displayed elevated NOR-1 expression, suggesting that NOR-1 signaling is a disrupter of glucose homeostasis (Close et al., 2019). In sum, these data indicate that cardiovascular therapeutic benefits of NOR-1 targeting would likely be achieved by inhibiting rather than activating the receptors.

5. NOR-1 in Cancer. Simultaneous abrogation of NOR-1 and NGFI-B in mice led to the development of AML (Mullican et al., 2007; Ramirez-Herrick et al., 2011). HDAC-induced apoptosis in AML cells induced NOR-1 expression, suggesting this receptor may mediate tumor suppression (L. Zhou et al., 2013). In nasopharyngeal carcinoma, NOR-1 overexpression hampered cell proliferation and colony formation (Nie et al., 2003; W. Li et al., 2011). However, the roles of NOR-1 on tumor suppression may not be consistent across all cancer types. For instance, NOR-1 is one of the few receptors overexpressed in both ER+ and ER− breast tumors, and its expression is higher in triple-negative breast cancer than in luminal tumors (Muscat et al., 2013; Z. Y. Yuan et al., 2014). Likewise, hepatocellular carcinoma cells express high levels of NOR-1 (Vacca et al., 2013).

Our understanding of NOR-1 is mainly based on gene expression analyses or genetic engineering techniques and is primarily limited by the lack of tools to study its biology. There is currently no known NOR-1 ligand other than prostaglandin A2 (Kagaya et al., 2005), an arachidonate metabolite that binds to many other proteins. Further understanding of NOR-1, especially its clinical significance, will require the generation of selective ligands to enhance or block its activity. The latest information on NOR1 and its ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=99).

VI. Subgroups V and VI

LRH-1 and GCNF are representative members of Subgroups V and VI, respectively. In this section, we will summarize recent studies that dissected their interaction with coregulators and DNA REs that shed light on the role of LRH-1 in diabetes and intestinal inflammatory disease and the possible links between GCNF and various cancers. For LRH-1, we will also highlight attempts to design hybrid phospholipid mimics that were found to be potent agonists.

A. Liver Receptor Homolog 1 (NR5A2)

LRH-1, an emerging drug target (J. M. Lee et al., 2011; Bayrer et al., 2018) for NAFLD, T2D, and intestinal inflammatory disease, was initially cloned as a regulator of albumin and hepatitis virus gene expression (Tsukiyama et al., 1992; Becker-Andre et al., 1993). The expression of LRH-1 is restricted in the liver, pancreas, intestines, and ovary, consistent with being involved in the regulation of BA biosynthesis, glucose metabolism, de novo lipogenesis, reverse cholesterol transport, sterol homeostasis, and embryonic development (Fernandez-Marcos et al., 2011; J. M. Lee et al., 2011; C. Zhang et al., 2013; Stein et al., 2014). This orphan NR has a large hydrophobic LBP, and initial studies suggested that without an exogenous ligand, the LBD maintains a constitutively active conformation (Sablin et al., 2008). However, phospholipid species were bound to the LBP when LRH-1 was purified in bacteria (Ortlund et al., 2005).

Monomeric LRH-1 acts as a transcriptional activator that recognizes the DNA consensus sequence AGGTCA and regulates *Oct4* gene expression, a TF that maintains the pluripotency of ESCs by binding to a 9-nt RE consisting of a YCA (Y = pyrimidine), followed by an NR half-site (AGGCCR; R = purine) (Gu, Goodwin, et al., 2005; Solomon et al., 2005). This NR contains an additional 20-amino acid extension after the C-terminal extension called the Ftz-f1 motif, a unique attribute of the NR5A family (Ingraham and Redinbo, 2005). The said *fushi tarazu* motif (after its *Drosophila* equivalent) was shown to be necessary for binding coactivator proteins (Solomon et al., 2005).

In this, we will focus on studies on LRH-1 that structurally dissected its interaction with coregulators and elucidated the conformational mechanism driving gene transcription. Next, we highlight its

clinical utility in treating cardiometabolic disorders and inflammatory bowel disease (IBD). Finally, we will discuss recent advancements in the search for LRH-1 modulators.

1. Interaction of LRH-1 with Coregulators. The transcriptional activity of LRH-1 depends on promoter accessibility via its interaction with coregulators, which either have the chromatin-remodeling ability or promote the recruitment of other proteins with such function. LRH-1 recruits coactivators that contain an LXXLL motif at the LBD interaction surface formed by helix 12 packed against helices 3 and 4 (Nagy and Schwabe, 2004). The receptor uses the same interaction surface to interact with Subgroup 0 atypical NRs SHP and DAX1, which suppress LRH-1 activity in the liver (Goodwin et al., 2000; Sablin et al., 2008). Like other NR5A receptors, LRH-1 helix 12 is oriented in an active conformation in X-ray crystal structures, suggesting its lack of ability to recruit corepressors, such as SMRT and NCoR, which require switching of helix 12 from the active conformation to an "inactive" corepressor binding form (Ingraham and Redinbo, 2005). As expected, recombinant LRH-1 loaded with copurified bacterial lipids did not bind SMRT, despite showing specific dose-dependent repression by this corepressor in vivo (P. L. Xu et al., 2003). Ligand binding to LRH-1 alters coregulatory preference. For instance, apo LRH-1 displayed low micromolar K_d for SRC1, SRC2, and a peptide derived from SHP without binding with PGC1α. Musille et al. found that when bacterial lipids bind to LRH-1, the K_d for SRC1 is unaffected, while the binding of SRC2 improved 10-fold and SHP peptide binding was weakened by a factor of 12 (Musille et al., 2012). The interaction of PGC1α to LRH-1 AF surface was analyzed in great detail (Mays et al., 2017). Beyond its role in oxidative metabolism, this coactivator also controls BA production (J. Lin et al., 2005). PGC1α is more sensitive than SRC2 at detecting ligand-bound states of LRH-1. PGC1α only binds LRH-1 when an agonist is present, while SRC2 binds to both the apo and ligand-bound states of the receptor (Musille et al., 2012). However, unlike SRC2, the first crystal structure of LRH-1 bound to PGC1α did not show perturbation of the distal portion of the LBD or induce allosteric signaling to the NR AF surface. In molecular dynamics (MD) simulations, PGC1α induced coordinated structural rearrangements throughout the entire AF surface, while SRC2 induced weaker signaling at this surface but induced allosteric perturbations emanating from the helix 6/β-sheet region to the AF surface (Mays et al., 2017). Combined X-ray crystallography and MD identified an unexpected allosteric network that provides a nexus between the alternate AF region and classic AF2 and confers coregulatory selectivity. The strength of coregulator affinity is dependent on this communication pathway (Musille et al., 2016).

2. LRH-1 in Diabetes. Hepatic lipid accumulation is tightly linked to insulin resistance and T2D (Cusi, 2009). Since increasing BA levels can reduce liver lipid content (M. Watanabe et al., 2004) and LRH-1 promotes BA production, increasing LRH-1 activity has been proposed as a therapeutic strategy to combat hepatic steatosis and associated health complications, such as insulin resistance (Mataki et al., 2007; J. M. Lee et al., 2011). LRH-1 was also shown to protect pancreatic islets from apoptosis (Mellado-Gil et al., 2012). A study in a mouse model of diabetes showed that dietary dilauroylphosphatidylcholine (DLPC) lowered both serum lipid and blood glucose levels in an LRH-1-dependent manner (J. M. Lee et al., 2011). Moreover, DLPC promotes LRH-1-mediated transcription, increases recruitment of coactivators, and induces the expression of LRH-1 target genes.

Although antidiabetic effects conferred by DLPC treatment are striking, a high concentration of this agonist is required to activate the receptor—100 μM in vitro and 100 mg/kg twice daily in vivo (J. M. Lee et al., 2011). The LRH-1 agonist BL001 hampered the progression of hyperglycemia and pancreatic inflammation by dampening the immune response in a murine model of type 1 diabetes (Cobo-Vuilleumier et al., 2018). Besides, Miranda et al. showed that HFD-fed LRH-1 knockout mice developed liver injury, hepatic steatosis, and glucose intolerance, and their phenotype was reversed by expressing wild-type human LRH-1 (D. A. Miranda et al., 2018).

3. LRH-1 in Intestinal Inflammatory Disease. IBD is a chronic disorder characterized by severe gastrointestinal inflammation leading to structural damage of the gut epithelial lining. LRH-1 is a crucial regulator of the intestinal epithelia and was shown to be expressed in intestinal crypts that harbor intestinal stem cells (Botrugno et al., 2004). This receptor contributes to the renewal of epithelial cells by modulating the Wnt/β-catenin pathway (Botrugno et al., 2004; Yumoto et al., 2012). Genome-wide association meta-analyses of IBD patients revealed a significant correlation between LRH-1 and IBD (de Lange et al., 2017). Heterozygous and conditional knockout of LRH-1 in animals resulted in high susceptibility to colitis and defective epithelial proliferation (Botrugno et al., 2004; Coste et al., 2007). Moreover, the lack of LRH-1 substantially decreased glucocorticoid synthesis in mouse intestine and human colon cancer cell lines (Atanasov et al., 2008; Sidler et al., 2011), which consequently led to severe intestinal inflammation (Mueller et al., 2006; Coste et al., 2007). Mice lacking LRH-1 in the gut had hampered Notch signaling, increased cell death in intestinal crypts, altered gut mucosal cell composition, and weakened the epithelial barrier. Overexpression of human LRH-1 in

these animals rescued epithelial integrity and ameliorated inflammation-induced damage in intestinal organoids (Bayrer et al., 2018).

4. LRH-1 Modulators. The endogenous ligands LRH-1 remain unknown, but the receptor binds an assortment of phospholipids (PLs) in vitro, which may account for some residual constitutive activity (Ortlund et al., 2005; Sablin et al., 2008). When administered exogenously, several PCs have demonstrated the ability to activate LRH-1 above basal levels both in vitro and in vivo, particularly medium chain length, saturated PCs such as diundecanoyl-phosphatidylcholine and DLPC (J. M. Lee et al., 2011). DLPC treatment decreased the concentration of hepatic and circulating lipids, improved BA synthesis, ameliorated insulin sensitivity, and improved glucose homeostasis, but these outcomes were negated upon knocking out LRH-1, thereby revealing receptor-dependent effects (J. M. Lee et al., 2011).

Structural studies of DLPC interaction with LRH-1 uncovered a peculiar ligand binding mode, where the phospholipid binds near a solvent-exposed surface mediated by polar interactions of phosphate headgroup with several residues at the mouth of the LBP—namely, G421, Y516, and K520—and is further stabilized by hydrophobic interactions of the PL "tails" (Musille et al., 2012). However, PCs are not ideal pharmacological agents due to their plasticity, susceptibility to hydrolysis, and ability to be assimilated into membranes that may affect biologic processes modulated by membrane fluidity (Ridgway, 2013). Moreover, high concentrations of DLPC agonists are required to activate LRH-1 (J. M. Lee et al., 2011). Thus, there is a need to develop stable small molecules that mimic the PL-driven activation of LRH-1 but with a substantially improved potency.

Another roadblock that hindered synthetic LRH-1 modulator development is the large and highly lipophilic LBP of this receptor. As expected, only a handful of chemical scaffolds have demonstrated the ability to modulate LRH-1 activity. To date, the most potent LRH-1 synthetic agonists are aryl-substituted hexahydropentalene (6HP) analogs (Whitby et al., 2006). One of the first derivatives with this scaffold, GSK8470, induces LRH-1 target genes but fails stability tests at acidic conditions (Whitby et al., 2006). The X-ray crystallography structures of the GSK8470-bound LRH-1 helped develop another analog, RJW100, whose interaction in the LBP is likely entropically driven as it is mediated by water molecules (Mays et al., 2016). Although both ligands bind the same LBP, their binding orientations are dramatically different, and RJW100 has substantially improved chemical stability while retaining LRH-1 activity (Whitby et al., 2011; Mays et al., 2016). Flynn and coworkers developed a series of novel LRH-1 agonists that contain three regions: the 6HP core of RJW100, modular alkyl linkers that confer hydrophobic interactions, and polar groups that interact with PC headgroup (Flynn et al., 2018). The phospholipid mimics are found to be a highly effective class of LRH-1 agonists, with one analog, 6HP-CA, reported as the most highly efficacious and potent (EC_{50} = 0.4 μM) LRH-1 agonist ever reported (Flynn et al., 2018). The latest information on SF-1 and its ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=100).

B. Germ Cell Nuclear Factor (NR6A1)

GCNF, also known as RTR or NR6A1, is an orphan NR involved in regulating early embryonic development and reproduction (A. C. Chung et al., 2001; Lan et al., 2002). In adult mice and humans, GCNF-mRNA tissue-specific expression is limited to the ovary and testis. The receptor was named as such because of its robust and restricted expression in germ cells (Hirose et al., 1995; Kapelle et al., 1997; Agoulnik et al., 1998). Meanwhile, in the embryo at gastrulation, GCNF shows broad expression, which is eventually restricted mainly to the burgeoning nervous system (Susens et al., 1997; A. C. Chung et al., 2001). Because of its peculiar structure, a separate subfamily (Subgroup VI) was created for GCNF. Like the REV-ERBs, GCNF does not contain a typical AF2 domain and is characterized as a transcriptional repressor mediated by interaction with corepressors, which to date appears to be independent of ligand binding to the NR (F. Chen et al., 1994; Mullen et al., 2007). The endogenous ligand for GCNF has not yet been identified, and studies show that receptor activity is modulated via regulation of its gene expression (Gurtan et al., 2013; Krill et al., 2013; H. Wang et al., 2013). Recombinant GCNF binds as a homodimer to DR0 REs or DRs of AGGTCA with no spacing between half sites (H. Greschik et al., 1999). However, endogenous GCNF does not homodimerize but instead exists as a part of a large structure called the transiently retinoid-induced factor. Atypically for an NR, GCNF binds to REs as an oligomer (Gu, Morgan et al., 2005).

1. GCNF Regulates ESC Pluripotency and Embryonic Development. One of the direct targets of GCNF is Oct4, a critical TF that maintains the pluripotency of ESCs (Fuhrmann et al., 2001). Aside from GCNF, a number of other NRs also regulate Oct4 expression by binding to associated REs within promoter regions, including LRH-1, steroidogenic factor 1, and RAR (Barnea and Bergman, 2000; Fuhrmann et al., 2001; Gu, Goodwin et al., 2005). The first crystal structure of GCNF DBD-Oct4 DR0 was recently published and revealed two subunits bound in a head-to-tail manner on opposite sides of the recognition sequence (Weikum et al., 2016). GCNF is an enticing therapeutic target for biomarking and manipulating stem cells because of its crucial role in regulating Oct4 and other pluripotency factors (Mullen et al., 2007; Akamatsu et al., 2009; H. Wang et al., 2013). For instance, during

mouse embryogenesis, repression of Oct4 by GCNF was shown to be crucial for stem cell differentiation (A. C. Chung et al., 2001; Gu, LeMenuet, et al., 2005). In mouse ESCs and iPSCs, GCNF represses Oct4 by binding to DR0 REs within the promoter. Upon binding to DR0, GCNF recruits DNA methyltransferases and methyl-binding proteins, thereby promoting Oct4 gene methylation to inhibit its expression during mouse ESC differentiation (N. Sato et al., 2006; H. Wang et al., 2013). During gastrulation, there is a dramatic increase in GCNF expression and a concomitant decrease in Oct4 expression (A. C. Chung et al., 2001; Lan et al., 2002).

GCNF is crucial for normal embryonic development, and its silencing leads to embryonic lethality by embryonic day (E) E10.5 with abnormalities such as defective forebrain development, aberrant midbrain-hindbrain boundary, and unusual posterior truncation (A. C. Chung et al., 2001; Lan et al., 2002; A. C. Chung et al., 2006). Strikingly, knocking out GCNF results in the loss of Oct4 suppression in somatic cells after gastrulation, a phase usually marked by Oct4 silencing (Fuhrmann et al., 2001). Furthermore, Wang et al. showed that GCNF directly represses Oct4 in both undifferentiated and differentiated human ESCs, and the knockdown of GCNF by small interfering RNA resulted in the unhampered expression of Oct4 upon inducing human ESC differentiation with ATRA. Moreover, the same study showed that overexpression of GCNF globally alters the gene expression profile in undifferentiated and differentiated human ESCs (H. Wang et al., 2016).

2. Possible Roles of GCNF in Cancer. Human CRIPTO-1 plays a crucial role in regulating embryonic development and various stages of tumor progression (Klauzinska et al., 2014). CRIPTO-1, which is highly expressed in undifferentiated cells, is rapidly suppressed upon inducing differentiation with RA (Mitsui et al., 2003). In adult cells, CRIPTO-1 expression is very low but dramatically high in disparate tumors, where it is identified as a robust oncogene (Strizzi et al., 2005). A study on the differentiation of the human teratocarcinoma cell line, NT2, showed that CRIPTO-1 is directly repressed by GCNF. In vitro experiments revealed that GCNF binds directly to a DR0 RE within the CRIPTO-1 promoter and that the repression of CRIPTO-1 depends on the GCNF recognition of the DR0 site (M. Hentschke et al., 2006). Moreover, a pseudogene of CRIPTO-1 on the X chromosome, CRIPTO-3, is also regulated by GCNF (M. Hentschke et al., 2006). Another study that attempted to unravel the mechanisms of CRIPTO-1 during tumorigenesis showed that GCNF strongly suppressed CRIPTO-1 in NTERA-2 human embryonal carcinoma cells (Bianco et al., 2013). Moreover, CRIPTO-1 is highly expressed in the majority of human breast tumors, which is in disagreement with its low expression in breast cancer cell lines. Meanwhile, GCNF is only expressed in 40% of breast carcinomas. Nevertheless, a positive linear correlation was found between CRIPTO-1 and GCNF expression in these tumors. Co-expression of CRIPTO-1 and GCNF in human invasive ductal breast carcinomas suggests that GCNF may regulate CRIPTO-1 expression in these cancer cells (Bianco et al., 2013).

Aside from possible links to breast cancer, GCNF is also regarded as a novel member of the cancer-testis antigen family (Scanlan et al., 2004). A study that analyzed 303 cases of prostate cancer post-prostatectomy found that gene silencing of GCNF resulted in G0/G1 phase cell cycle arrest and decreased metastasis and invasiveness of prostate cancer cells 22RV1. In contrast, overexpression of GCNF substantially promoted tumor growth in vivo (G. Cheng et al., 2016). Moreover, suppression of GCNF reversed the EMT in DU145 and PC3 cell lines, while overexpression of GCNF accelerated the EMT process in the 22RV1 cell line. Finally, GCNF played a crucial role in the migration and invasion of prostate cancer cells, making this receptor a novel biomarker for prostate cancer recurrence post-prostatectomy (G. Cheng et al., 2017).

GCNF was also identified as a novel regulator of lipid metabolism in hepatoma. Lipogenesis is required for the growth of most tumors as lipids are essential constituents of cancer cell lipid bilayer membrane rapidly expanding during cancer proliferation and metastasis and provides signaling molecules to block oxidative stress-induced cell death. Wang et al. showed that GCNF knockdown resulted in elevated lipid accumulation and insulin-induced proliferation and migration of HepG2 cells. Moreover, GCNF silencing resulted in increased expression of fatty acid synthase and diglyceride acyltransferase-2 in HepG2 cells, two rate-limiting lipogenic enzymes that have been shown to promote cancer development (Y. Wang et al., 2019). The latest information concerning GCNF and its ligands can be obtained on the IUPHAR guide to pharmacology website (https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=101).

VII. Summary and Conclusions

A wide range of processes are regulated by NRs, so it is not surprising that their anomalous regulation results in the development and progression of diverse pathologic conditions, including cancers, metabolic disorders, neurologic diseases, and defective embryonic development, among others. Most of these receptors can be pharmacologically modulated, making NRs enticing biologic targets for therapeutic intervention, where countless modulators (i.e., agonists, antagonists, inverse agonists, etc.) have been designed. Indeed, one in six FDA-approved drugs targets at least one of the 48 human NRs (Santos et al., 2017). Although NR targeting ligands led to significant advances in the medical field, adverse effects are recurring roadblocks, limiting their

clinical utility and slowing NR drug development (Santos et al., 2017). The primary goals of NR research are to unravel their cell type-specific functions and to design drugs that specifically modulate the activity of target receptors while minimizing cross-reactivity with other receptors.

For instance, the development of most dual and pan PPAR agonists has been abandoned; however, the possible and established success of a few putative (pioglitazone) and known (bezafibrate, saroglitazar, and chiglitazar) members of this class demonstrates their clinical utility. In addition, while the concept of selective NR modulation has been around for decades, developing such compounds for clinical use has been challenging. Examples of clinically approved biased NR drugs that offer substantially improved profiles over nonbased drugs are limited (raloxifene, for instance), and modulators targeting other NRs such as PPAR, TR, GR, and AR have met with significant challenges for clinical development. The limited success of such drugs and the lack of understanding of the physical mechanisms underlying selective modulation have led to questioning the quest for selective NR modulators (Clark and Belvisi, 2012). Despite the difficulty and uncertainty in biased drug development, the success of raloxifene targeting ER, as well as several G protein-coupled receptor agonists that are putative-biased drugs, have been approved or are in clinical trials (J. S. Smith et al., 2018), thus supporting the rationale and nourishing the motivation to pursue NR ligand development (Kenakin, 2018). Structural biology approaches, as well as advances in our ability to examine global gene expression alterations induced by various putative NR modulators, continue to provide a solid conceptual base for selective NR modulation with biased drugs and guide future biased drug development.

It is also important to note that various cellular environment factors modulate NR function. For example, ER regulates diverse physiologic programs via gene induction and repression. The selection of target genes, directionality of gene regulation, and magnitude of response are determined by a complex interplay of several factors (Chodankar et al., 2014). These factors include the activating hormone ligand and DNA binding that together modulate ER structural conformation, as well as the local regulatory environment of each gene. The local regulatory environment comprises chromatin conformation influenced by cell-specific enhancer-promoter interactions via DNA looping and other bound TFs. Together, these cellular environmental determinants influence the recruitment of, and requirement for, specific coregulators that regulate transcription complex assembly to induce a biologic response.

Despite the aforementioned challenges, some NR-targeting drugs are still among the most widely used and commercially successful. Steroid receptors and TRs have been targeted clinically for many years. Additionally, for example, fibrates (PPARα) and TZDs (PPARγ) are FDA-approved drugs for treating hyperlipidemia and T2D, respectively, and bexarotene and alitretinoin, both targeting the RXRs, are employed in oncology (Moore et al., 2006).

Several NRs are still classified as "orphan" as their endogenous ligands are yet to be identified. The hunt for small molecule compounds that modulate the function of these orphan targets remains a very active arena of research that will usher in a new era in drug discovery. Indeed, identifying biologic processes and ligands that activate several orphan NRs provided remarkable insight into a wide range of physiologic phenomena, including circadian rhythm, metabolism, inflammation, and ESC renewal. Illuminating the complex NR networks, such as the cellular function and genes that they regulate, will help further the understanding of the onset and progression of various diseases, which will guide the design of future drugs with higher potency, specificity, and, hence, therapeutic value.

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