Nuclear Receptors and Epigenetic Regulation: Opportunities for Nutritional Targeting and Disease Prevention[1,2]

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ABSTRACT

Posttranslational modifications of histones, alterations in the recruitment and functions of non-histone proteins, DNA methylation, and changes in expression of noncoding RNAs contribute to current models of epigenetic regulation. Nuclear receptors (NRs) are a group of transcription factors that, through ligand-binding, act as sensors to changes in nutritional, environmental, developmental, pathophysiologic, and endocrine conditions and drive adaptive responses via gene regulation. One mechanism through which NRs direct gene expression is the assembly of transcription complexes with cofactors and coregulators that possess chromatin-modifying properties. Chromatin modifications can be transient or become part of the cellular "memory" and contribute to genomic imprinting. Because many food components bind to NRs, they can ultimately influence transcription of genes associated with biologic processes, such as inflammation, proliferation, apoptosis, and hormonal response, and alter the susceptibility to chronic diseases (e.g., cancer, diabetes, obesity). The objective of this review is to highlight how NRs influence epigenetic regulation and the relevance of dietary compound–NR interactions in human nutrition and for disease prevention and treatment. Identifying gene targets of unliganded and bound NRs may assist in the development of epigenetic maps for food components and dietary patterns. Progress in these areas may lead to the formulation of disease-prevention models based on epigenetic control by individual or associations of food ligands of NRs. *Adv. Nutr. 5: 373–385, 2014.*

Introduction

Nuclear receptors (NRs)[6] are a group of transcription factors that, through ligand binding, drive adaptive gene responses to changes in nutritional, environmental, developmental, pathophysiologic, and endocrine conditions (1). The NR superfamily includes endocrine, adopted orphan, orphan with evidence of natural and/or synthetic ligand, and orphan with no known ligand NR subclasses. Endocrine NRs bind the ovarian hormone receptors estradiol (ER) and progesterone, androgen receptor (AR), vitamin D receptor (VDR), retinoic acid receptor (RARα, RARβ, RARγ), retinoid acid receptor [retinoid X (RXRα, RXRβ, RXRγ)], glucocorticoid receptor (GR), mineralcorticoid receptor, and thyroid hormone receptor. The adopted orphan NRs are mediators of metabolic pathways and bind lipids [PPARα, PPARβ/δ, PPARγ; liver X receptor (LXRα, LXRβ)] and bile acids [BAs; farnesoid X receptor (FXR)]. The orphan NR subclass, for which there is evidence of natural and/or synthetic ligands, includes the small heterodimer

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[6] Abbreviations used: Ac, acetylated; AF-1, activation function domain-1; AF-2, activation function domain-2; AhR, aromatic hydrocarbon receptor; AP-1, activator protein-1; AR, androgen receptor; ARNT, AhR nuclear translocator; BA, bile acid; BAT, brown adipose tissue; BER, base excision repair; BRCA-1, breast cancer-1; CBP, cAMP-response element-binding protein; *COX-2*, cyclooxygenase-2; CpG, cytosine-phosphate-guanine; CYP1A1, cytochrome P450, family 1, subfamily A, polypeptide 1; CYP27B1, cytochrome P450, family 27, subfamily B, polypeptide 1; DAX1, dosage-sensitive sex reversal-adrenal hypoplasia critical region on chromosome X, gene 1; DBD, DNA binding domain; DNMT, DNA methyltransferase; EHMT-1, eukaryotic histone methyl transferase-1; ER, estrogen receptor; EZH2, enhancer of zeste homolog 2; FXR, farnesoid X receptor; FXRE, FXR response elements; GADD45, growth arrest and DNA damage 45; GLUT4, glucose transporter 4; GR, glucocorticoid receptor; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; HLCS, holocarboxylase synthetase; HMT, histone methyltransferase; H3K4, histone 3 at lysine 4; H3K9, histone 3 at lysine 9; H3K14, histone 3 at lysine 14; H3K27, histone 3 at lysine 27; H4K20, histone 4 at lysine 20; LXR, liver X receptor; MBD4, methyl-CpG binding domain-containing protein 4; me, methylated; me2, dimethylated; me3, trimethylated; MeCP2, methylated cytosine binding protein-2; NCoR, nuclear corepressor; NR, nuclear receptor; NSBP-1, nucleosomal binding protein-1; PAH, polycyclic aromatic hydrocarbon; PDK4, pyruvate dehydrogenase kinase 4; PEPCK, phosphoenol-pyruvate-carboxykinase; PGC-1α, PPAR coactivator 1α; pS2, human pS2; RAR, retinoic acid receptor; RXR, retinoid acid receptor; SHP, small heterodimer partner; Sin3A, Sin3 transcription regulator family member A; SMRT, silencing-mediator for retinoic and thyroid; SRC-1, steroid receptor coactivator-1; SWI/SNF, switch/sucrose non-fermentable; TDG, thymine DNA glycosylase; TZD, thiazolidinedione; VDR, vitamin D receptor; WAT, white adipose tissue; WY14,643, 2-[[4-chloro-6-[(2,3-dimethylphenyl) amino]-2-pyrimidinyl]thio]acetic acid; XRE, xenobiotic response element; 1,25$(OH)_2$-D3, cholecalciferol, 1,25-dihydroxycholecalciferol, 25-hydroxycholecalciferol; 25OH-D3-1α, 25-hydroxy vitamin D3-1α.

partner (SHP) and aromatic hydrocarbon receptor (AhR). The SHP binds retinoid-related molecules (2,3) and regulates BAs and lipid homeostasis (4). The AhR binds dietary (e.g., resveratrol, indol-3-carbinol), endogenous (e.g., PGs), and synthetic polycyclic aromatic hydrocarbon (PAH), dioxin (e.g., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin), and polychlorinated biphenyl compounds (5). Orphan NRs with no known ligands include the dosage-sensitive sex reversal-adrenal hypoplasia critical region on chromosome X, gene 1 (*DAX1*), whose mutation predisposes to X-linked adrenal hypoplasia congenital and hypogonadotropic hypogonadism (6). The DAX1 protein is a corepressor of FXR. Overexpression of DAX1 downregulates the expression of FXR target genes and interferes with BAs, TGs, and glucose metabolism (7).

It is well accepted that epigenetic mechanisms, i.e., changes in gene expression without modification in nt sequence, such as DNA methylation, histone modifications, and noncoding mRNAs, establish areas of active or repressed chromatin, which mediate adaptive responses to dietary, environmental, and developmental signals (8). Research evidence suggests that dietary compounds contribute to epigenetic regulation and phenotypic plasticity through both NRs and nongenomic pathways. For example, the soy compound genistein stimulates gene expression through induction of phosphoinositide 3-kinase/AKT, which in turn phosphorylates and represses the histone methyltransferase (HMT) enhancer of zeste homolog 2 (EZH2), thus reducing the amounts of the histone 3 trimethylated at lysine 27 (H3K27me3) repressive mark (9). In parallel, genistein induces transcription of estrogen-responsive genes by inducing the recruitment of ERα and cofactors with histone-modifying properties (e.g., p300) (10). Similarly, by engaging both cytosolic (i.e., extracellular signal-regulated kinase 2) and nuclear (i.e., RXR) mediators, retinoic acid modifies the epigenetic landscape and transcriptional regulation of genes involved in differentiation and embryonic development (11,12). Moreover, a large number of dietary ligands influence the epigenetic machinery by acting as methyl donors, cofactors, coenzymes, and regulators of chromatin-modifying proteins (13). Therefore, the full impact of diet–NR interactions on health and disease can only be appreciated by developing models that integrate all the pathways that impinge on epigenetic regulation (14). This review will focus on how the interplay between food compounds and NRs influences epigenetic regulation and the relevance of these interactions for disease prevention and treatment.

NR Structure and Regulation

The general structure of NRs comprises an amino-terminal activation function domain-1 (AF-1), a DNA-binding domain (DBD), a hinge region, a ligand-binding domain, and a C-terminal activation function domain-2 (AF-2) (**Fig. 1***A*). The ligand-binding domain comprises coregulator interaction domains. Through the DBD, NRs can bind directly to DNA as monomers, homodimers, or heterodimers (reviewed in references 15 and 16). For example, the ERα forms homodimers at estrogen response elements, whereas the FXR can form heterodimers with the RXR at FXR response elements

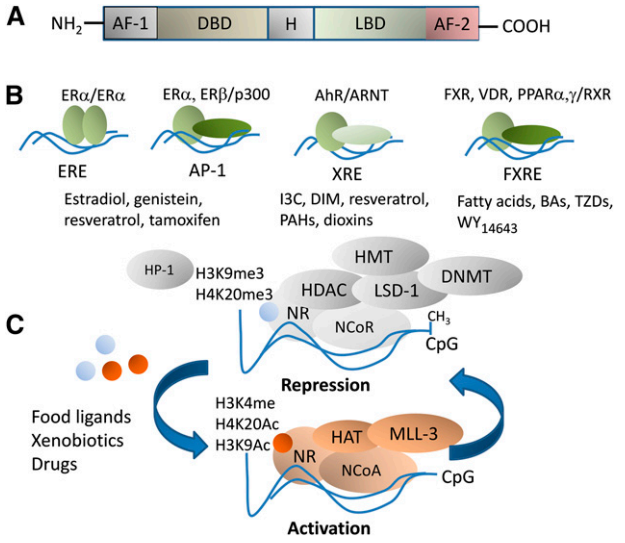

FIGURE 1 Nuclear receptor structure and coregulation by food ligands and nutritionally related xenobiotics and drug compounds. NRs share a general DNA structure comprising an amino-terminal AF-1, a DBD, an H, an LBD, and a C-terminal AF-2 domain (*A*). Examples of NR interactions within the coregulator interaction domains: the ERα forms homodimers at EREs; the ERα and ERβ can enhance or repress, respectively, transcription of genes containing AP-1 sites through interactions with DNA-bound Jun/Fos complexes; the AhR/ARNT heterocomplex binds DNA at XREs; the FXR forms heterodimers with the RXR at FXRE (*B*). Certain NRs function as promiscuous partners for various receptors. This is the case for the RXR that forms complexes at target promoters with FXR and PPAR, VDR, and retinoic acid receptor. Examples of food ligands are listed below each NR. The diagram depicts general models of repression and activation via CpG methylation and demethylation mediated by NRs (*C*). In the absence of ligands or when NRs are bound to antagonists, NRs are found in NCoR complexes with factors that possess DNMT and HDAC, HMT, and histone demethylase (e.g., LSD-1) properties. Certain covalent modifications placed by NR corepressors on histones are markers of silenced heterochromatin and include H3K9me3, histone 3 trimethylated at lysine 27, and H4K20me3. Chromatin is occupied by the repressive HP-1 factor. Binding of food ligands to NRs triggers the dismissal of NCoR complexes and the recruitment at the target promoter of NCoA complexes that comprise HMT (e.g., MLL-3) and HAT (e.g., cAMP-response element-binding protein/p300) factors. The latter possess enzymatic activities that place "active" histone acetylation marks on histones 3 and 4 (H3K9Ac, H4K20Ac). AF-1, activation function 1; AF-2, activation function 2; AhR, aromatic hydrocarbon receptor; AP-1, activator protein-1; ARNT, aromatic hydrocarbon receptor nuclear translocator; BA, bile acid; CpG, cytosine-phosphate-guanine; DBD, DNA binding domain; DIM, diindolylmethane; DNMT, DNA methyltransferase; ERE, estrogen response element; ERα, estrogen receptor-α; FXR, farnesoid X receptor; FXRE, farnesoid X receptor response element; H, hinge region; HAT, histone acetyltransferase; HDAC, histone deacetylase; HMT, methyltransferase; HP-1, heterochromatin protein-1; H3K4me4, histone 3 methylated at lysine 4; H3K9me3, histone 3 trimethylated at lysine 9; H4K20me3, histone 4 trimethylated at lysine 20; I3C, indol-3-carbinol; LBD, ligand-binding domain; LSD-1, lysine-specific demethylase-1; MLL-3, mixed lineage leukemia-3; NCoA, nuclear receptor coactivator; NCoR, nuclear corepressor; NR, nuclear receptor; PAH, polycyclic aromatic hydrocarbon; TZD, thiazolidinedione; VDR, vitamin D receptor; WY_{14643}, 2-[[4-chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl]thio]acetic acid; XRE, xenobiotic response element.

(FXRE). Certain NRs function as promiscuous partners for different receptors. This is the case for the RXR, which forms complexes at target promoters with the PPAR, VDR, RAR, and FXR. In addition, NRs can modulate gene expression through physical interactions with DNA-bound transcription factors. For example, the ERα and ERβ can enhance or repress, respectively, transcription of genes through interactions with DNA-bound activator protein-1 (AP-1) complexes (17) (Fig. 1*B*).

The physical interaction between NRs and cofactors influences the magnitude and direction of the transcriptional response (18,19). For instance, transcription by the ER, RAR (20), and PPARγ (15) is potentiated by interactions with the cofactors p160/steroid receptor coactivator-1 (SRC-1) and cAMP-response element-binding protein (CBP)/p300 through LXXLL-binding motifs (in which L indicates leucine and X indicates any amino acid) (20). Moreover, coregulator exchange contributes to gene-, cell-, and tissue-specific transcriptional regulation by NRs. For example, LXRα-regulated lipogenesis and cholesterol/BA homeostasis in the liver requires binding of LXRα through LXXLL motifs with the NR coactivator 6. However, NR coactivator 6 is not required for regulation of transcription by the ERα in the mammary gland (21). Conversely, repression of transcription by unliganded NRs is achieved through interactions with LXX I/H I XXX I/L motifs on nuclear corepressor (NCoR) and silencing-mediator for retinoic and thyroid (SMRT) factors (18).

NRs can also modify transcriptional regulation through interactions with *cis*-acting transcription factors. For example, the looping of the cytochrome P450, family 1, subfamily A, polypeptide 1 (*CYP1A1*) promoter region around histones facilitates interactions of DNA-bound AhR/AhR nuclear translocator (ARNT) complexes with the specificity protein 1 transcription factor recruited at adjacent sites and enhances transcription of the *CYP1A1* gene in response to AhR ligands (22,23). Examples of cooperativity between NRs and *cis*-acting transcription factors include those between the DNA-bound GR and the accessory nuclear factor-1 on the 11β-hydroxysteroid dehydrogenase (24) and phosphoenol-pyruvate-carboxykinase (*PEPCK*) genes (25). An example of negative *cis*-interaction is the recruitment of the activated AhR to a xenobiotic response element [XRE (5′-GCGTG-3′)] harbored in the breast cancer-1 (*BRCA-1*) gene, which displaces an ERα/p300 complex from an adjacent AP-1 site and represses estrogen-dependent activation of BRCA-1 expression (26). NRs may also repress transcription without direct binding to DNA through competition for ubiquitous cofactors as in the case of the *trans*-RA/RAR/RXR heterocomplex, which interferes with AP-1-dependent *trans*-activation by excluding the cofactor CBP (27). Similarly, the SHP orphan NR, which lacks a DBD, represses transcription through direct interaction with AF-2 coactivator domains on NRs or by stimulating the recruitment of NCoRs (4). Moreover, signaling pathways impart on NRs and cofactors posttranslational modifications (e.g., phosphorylation, methylation, and acetylation) that influence transcriptional activity. For instance, phosphorylation of p160 potentiates its coactivator functions on the AR and ER (28). Similarly, methylation and p300-dependent acetylation of the ERα protein potentiate its transcriptional activation of estrogen-responsive genes (29).

The cyclical recruitment of NRs and cofactors at target promoters contributes to transcriptional control (30). This is the case for the VDR on the 25-hydroxy vitamin D3 1α-hydroxylase (*25OH-D3-1α*) (31), the AR on the prostate specific antigen (32), the PPARδ on the pyruvate dehydrogenase kinase 4 (*PDK4*) (33), and the AhR on the *CYP1A1* (34) and cyclooxygenase-2 (*COX-2*) (35) genes. Similarly, ligands of the AhR direct the cyclical recruitment of p300 to the *COX-2* gene and its association with acetylated (Ac) histone 4 (H4) (35). Fluctuations in NR and cofactor recruitment fine-tune the duration of activation (or repression) and transcriptional rates of target genes. Thus, modeling the impact of food ligands for NRs on epigenetic regulation of target genes would require knowledge of the following: *1*) the presence and spatial arrangement of core binding motifs for NRs and cofactors; *2*) kinetics of recruitment of NR complexes; and *3*) the effects on expression and posttranslational modification of NRs and related cofactors.

Mechanisms of Epigenetic Regulation by NRs

Epigenetic repression

In the absence of ligands or when NRs are bound to antagonists, NRs are found in corepressor complexes with factors that possess histone deacetylase (HDAC), HMT, histone demethylase (HDM), and phosphatase enzymatic activities (36) (Fig. 1*C*). The NR cofactors Sin3 transcription regulator family member A (Sin3A), NCoR, and SMRT lock target genes in a repressed state by forming bridges with HDACs. NR corepressor complexes include the ATP-dependent switch/sucrose non-fermentable (SWI/SNF) nucleosome remodeling factors. Certain covalent modifications placed by NR corepressors on histones are markers of silenced heterochromatin and include histone 3 trimethylated at lysine 9 (H3K9me3), H3K27me3, and H4K20me3. The binding of heterochromatin protein-1 to H3K9me3 locks heterochromatin in a transcriptionally silent state (37). The transrepressive functions of certain NCoR complexes (e.g., tailless-like X receptor) require the presence of the HDM lysine-specific demethylase-1, which demethylates H3K4me2 and H3K4me (38).

Competition among NRs for coregulators with histone-modifying properties (e.g., p300, SRC-1) is a mechanism that contributes to epigenetic repression. For example, by "squelching" p300 from ERα complexes, the agonist-bound AhR represses transcription of DNA repair (e.g., *BRCA-1*) (26) and other estrogen-inducible genes (39). Similarly, the binding of vitamin D to VDR causes the dissociation of p300 and the recruitment of HDAC corepressor complexes on the *25OH-D3-1α* gene, hampering expression of 25OH-D3-1α and its participation in the de novo synthesis of vitamin D (40). Ubiquitin-mediated degradation of NCoRs is another mechanism that contributes to epigenetic repression by NRs (41). For example, agonist binding increases the affinity of PPARγ for NCoR/HDAC-3 repressor

complexes and prevents ubiquitin-dependent removal of NCoR and transcriptional activation of the NF-κB-inducible proinflammatory *COX-2* gene (42).

Epigenetic activation

For many genes, binding of agonists to NRs triggers the dismissal of NCoRs and the recruitment to the target promoter of coactivator complexes containing CBP and p300. The latter possess histone acetyltransferase (HAT) activities that place acetylation marks on H3 and H4 (H3K9Ac, H4K20Ac) (Fig. 1*C*). For example, transcriptional activation of the type 1 keratin KA11 (*KA11*) gene by IL-1β is accompanied by dismissal of NCoR from the AR bound to the KA11 promoter (43) Similarly, the estradiol-bound ERα induces transcription of the human pS2 (*pS2*) gene via dismissal of NCoRs and the ordered recruitment of activator complexes (44) comprising SRC-1 and HATs. These factors facilitate the acetylation and dimethylation of H3K14 and histone-4 at arginine-3 (H4R3) and the recruitment of transcription binding proteins and polymerase II, leading to activation of the *pS2* gene.

Histone modifications associated with transcriptional activation by NR include methylation of H3K4 (H3K4me) by the H3K4-methyltransferase mixed lineage leukemia-3 (38,45) and phosphorylation of H3 at serine 10. The later interferes with the binding of heterochromatin protein-1 to H3K27me3 and promotes nucleosomal opening and transcriptional activation (46). For example, elevation of phosphorylation of H3 at serine 10 and H3K9Ac are observed during early phases of ERα-induced transcription initiation (47).

The binding affinity of ligands toward NRs influences the dynamics of chromatin modifications at target genes. A study that examined the modulation of PPARγ transcriptional activity by insulin-sensitizing thiazolidinedione (TZD) compounds reported that pioglitazone and rosiglitazone were more effective than troglitazone in inducing the recruitment of PPARγ complexes to the PEPCK and PDK4 promoters and acetylation of PEPCK- and PDK4-associated histones (e.g., AcH4) (48). The stronger transcriptional effects of pioglitazone and rosiglitazone were mainly attributed to their higher binding affinity for PPARγ. Conversely, the preventive effects of resveratrol against transcriptional repression by the bound AhR of estrogen-inducible genes were related to formation of resveratrol/AhR heterocomplexes with lower affinity for XRE (49) and the agonist actions of resveratrol on the ERα (50) and related cofactors (e.g., p300) (51). Although the promiscuity of NRs for ligands with diverse binding affinity offers great variability and adaptability to environmental challenges, it also greatly expands the opportunities for the development of NR-based therapeutic strategies with food ligands (**Table 1**).

Cytosine-phosphate-guanine (CpG) methylation and demethylation at target promoters

Hypermethylation of cytosines comprised in CpG islands and its propagation through DNA replication have been related to gene silencing, whereas demethylation of CpGs has been linked to gene activation (52). Enzymes implicated in maintenance and de novo DNA hypermethylation are, respectively, DNA methyltransferase (DNMT)-1, and DNMT-3a and DNMT-3b, respectively (53). DNMT-1, but not DNMT-3a and DNMT-3b, and methylated cytosine binding protein-2 (MeCP2) recruit the biotin protein ligase holocarboxylase synthetase (HLCS) (54), leading to the assembly of a multiprotein gene repression complex comprising HDAC-1, NCoR, and the eukaryotic histone methyl transferase-1 (EHMT-1). The binding between HLCS and EHMT-1 is facilitated by the HLCS-dependent biotinylation of K161 in EHMT-1 (55). The close proximity between HLCS and histones facilitates the HLCS-dependent biotinylation of histone H3 and H4 (56). Nevertheless, biotinylation of histones is a rare event (≤0.001% of histone H3 and H4) and does not account for the repressive role of biotin on gene expression (57–59), in particular of repeats, which appears to be caused primarily by the HLCS-containing multiprotein complex (54). Repression of repeats is necessary for maintenance of genome stability, whereas chromosomal abnormalities have been reported in biotin-depleted human cell cultures (60).

DNMTs physically bind to HMTs and HDACs, providing a mechanistic link between transcriptional repression via DNA hypermethylation and histone methylation and deacetylation. In the case of the ERα-inducible *pS2* gene, cycles of CpG methylation alternate with cycles of CpG demethylation at the pS2 promoter. The hypermethylation of CpGs occurs at the end of each productive transcription cycle and corresponds to the corecruitment of MeCP2, SWI/SNF, DNMT-1, and DNMT-3a/3b. Conversely, transcriptional activation by the ERα, GR, and VDR has been linked to stimulation of CpG demethylation at the pS2 (61,62), tyrosine aminotransferase (63), and cytochrome P450, family 7, subfamily B, polypeptide 1 (64) promoter, respectively.

Whereas the mechanisms of DNA methylation have been established clearly, the processes that lead to active DNA demethylation remain an area of active investigation (53). Previous models of demethylation included the following: *1*) the enzymatic removal of the methyl group from 5-methylcytosine; *2*) nt excision repair involving the growth arrest and DNA damage 45 (GADD45) protein and XPG, a 3′ endonuclease; *3*) direct base excision repair (BER) of 5-methylcytosine by DNA glycosylases [i.e., thymine DNA glycosylase (TDG)] and methyl-CpG binding domain-containing protein 4 (MBD4); *4*) and deamination and repair of 5-methylcytosine via TDG and BER to replace the mismatched T with a C (53,65–68). Evidence that GADD45 family members interact with many food-related NRs, such as RXRα, RARα, ERα, PPARα, PPARβ, and PPARγ, suggest that nt excision repair-based CpG demethylation plays an important role in epigenetic regulation by common dietary compounds. However, the role of GADD45 in demethylation is still debated, and mounting evidence now offers a model for a complete cycle of methylation and demethylation that involves 4 steps: *1*) CpG methylation by DNMTs; *2*) iterative oxidation of methylated cytosine by 10-11 translocation enzymes; *3*) excision of methylated cytosine by TDG to generate

TABLE 1 Food ligands of nuclear receptors and influence on epigenetic regulation[1]

Food compound	Metabolic/epigenetic effects
ER	
Genistein, daidzein, equol	Potent activators of ERβ and ERα promoters through regulation of DNMT expression and enhanced HAT activity (122)
Resveratrol	Increases ER promoter methylation and inhibits HDAC (150)
EGCG	Induces chromatin remodeling by altering histone acetylation and methylation status leading to ER reactivation (47)
I3C	Disrupts interaction between ERα and Sp1 on promoter of the *hTERT* gene (151)
AR	
EGCG	Lowers AR acetylation and activation by inhibiting HAT activity (152)
DIM	Reverses epigenetic silencing of miR-34a in prostate cancer, inducing inactivation of the AR (153)
AhR	
Resveratrol	Prevents BRCA-1 promoter hypermethylation and silencing (49,126)
EGCG	Inhibits binding of AhR to XRE in endothelial cells (154); directly inhibits DNMT by binding to catalytic subunit (122)
DIM, I3C	Abrogate dioxin-induced recruitment of AhR and AcH4 to the COX-2 promoter (35)
Quercetin, kaempferol, genistein, daidzein, apigenin	Inhibit AhR binding to XRE of target genes, such as CYP1A1 (123)
PPARα/γ	
Resveratrol	Activates PPARs in vitro and in vivo leading to reduced COX-2 expression (155)
PPARα	
Eicosanoids	Regulate β-oxidation genes in liver; inhibit NF-κB transcription in heart (156)
PPARγ	
Arachidonic acid	Increases adipocyte differentiation in brown adipose tissue (156)
Genistein	Promotes adipogenesis at concentrations >1 μmol/L through mechanisms involving downregulation of ER-mediated transcription (156)
Daidzein and equol	Activate PPARγ at lower concentrations than genistein (157)
CLA	Inhibits adipogenesis and inflammation, promotes osteoblastogenesis (158)
PPARβ/δ	
PUFAs	Increase FA oxidation (156)
PGs	Lower TGs and free FA amounts in adipose tissue (156)
RXR	
9-*cis* RA	Binding to an NR partner (e.g., FXR, LXR, PPAR, RAR, TR, or VDR) promotes recruitment of cofactors and HATs that lead to transcriptional activation (159)
Lithocholic acid	
Phytanic acid	
VDR	
Vitamin D	Binding to VDR influences recruitment of coactivators or repressors and transcription of target genes (160–162)
Curcumin	Activates heterodimer formation with RXR and recruitment of coactivator SRC-1 (163)
FXR	
BAs	Increase interaction with NCoA6 (LXXLL motif) (126)
EGCG	Inhibits recruitment of coactivator SRC-2 to FXR and transcription of target genes in the intestine (7)
LXR	
Resveratrol	Increases RNA polymerase recruitment to the LXR promoter (164)
EGCG	Reduces expression of LXR in 3T3-LI liver cells (165)
Genistein	Increases promoter activity in rat liver, leading to insulin sensitization and improved lipid homeostasis (166)

[1] AcH4, acetylated histone-4; AhR, aromatic hydrocarbon receptor; AR, androgen receptor; BA, bile acid; BRCA-1, breast cancer-1; COX-2, cyclooxygenase-2; CYP1A1, cytochrome P450, family 1, subfamily A, polypeptide 1; DIM, diindolylmethane; DNMT, DNA methyltransferase; EGCG, epigallocatechin 3-O-gallate; ER, estrogen receptor; FXR, farnesoid X receptor; HAT, histone acetyltransferase; HDAC, histone deacetylase; hTERT, human telomerase reverse transcriptase; I3C, indole-3-carbinol; LXR, liver X receptor; LXXLL, L indicates leucine and X indicates any amino acid; miR-34a, microRNA-34a; NCoA6, nuclear receptor coactivator 6; NR, nuclear receptor; RA, retinoic acid; RAR, retinoic acid receptor; RXR, retinoid X receptor; Sp1, specificity protein 1; SRC-1, steroid receptor coactivator-1; SRC-2, SRC-1, steroid receptor coactivator-2; TR, thyroid receptor; VDR, vitamin D receptor; XRE, xenobiotic response element.

an abasic site; and *4*) placement of unmodified cytosine by BER (69–71). Evidence that TDG interacts with RAR, RXR, and ERα (72–74) further highlights the role of food-related NRs in epigenetic control via CpG demethylation.

Epigenetic Modifications Induced by Dietary and Nutrition-Related Ligands of NRs in Disease and Cell Fate Determination

PPAR

PPARα, PPARβ, and PPARγ play a key role in FA and glucose metabolism. PPARα is a binding target for several FAs, including palmitic acid, oleic acid, linoleic acid, CLA, arachidonic acid, EPA, DHA, and the PG metabolite 15D-J2 (75) (Table 1). PPARα is expressed primarily in liver, heart, and skeletal muscle. Gene targets for PPARα encode enzymes that contribute to FA oxidation: *1*) acyl-CoA synthetase; *2*) carnitine palmitoyl-transferase-1; *3*) acyl-CoA oxidase; *4*) very-long-chain and medium-chain acyl-CoA dehydrogenase; and *5*) FA transport protein. Also, PPARα activates its own expression through binding to a hepatocyte nuclear factor-4α-binding element harbored in the PPARα promoter (76).

PPARα. Gestational exposure to a protein-restricted diet elevates PPARα expression by lowering PPARα promoter CpG methylation in hepatic (77) and heart (78) tissue of rat offspring. Conversely, maternal supplementation with folic acid induces hypermethylation of the *PPARα* gene in liver tissue of offspring (79). These observations suggest that maternal nutrition influences epigenetic regulation of PPAR-regulated pathways in offspring.

Nonalcoholic fatty liver disease is a condition characterized by increased lipid influx into the liver and de novo hepatic lipogenesis. The hepatic accumulation of TGs has been linked to increased association of the repressive histone mark H3K9me3 on the *PPARα* gene and lowering of PPARα expression (80). Methyl-donor deficiency is a condition that has been related to impaired FA oxidation and decreased expression of PPARα. For example, administration during pregnancy and lactation of a methionine- and choline-deficient diet led to hypomethylation of the PPAR coactivator 1α (PGC-1α) protein and its reduced stimulation of PPARα expression in liver tissue of rat offspring (81). Thus, dietary disturbances (e.g., methyl-donor deficiency) may contribute to the pathogenesis of fatty liver by reducing expression of PPARα through epigenetic mechanisms. Conversely, targeting of PPARα with the synthetic agonist 2-[[4-chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl]thio]acetic acid (WY14,643) has been proposed as an option for the management of hypertriglyceridemia. The treatment with WY14,643 ameliorated liver insulin resistance, exerted anti-inflammatory effects, and activated β-oxidation enzymes in a rodent model of hepatic and muscle steatosis (82). Unfortunately, the benefits of lipid-lowering interventions based on WY14,643 and other agonists of PPARα could be offset by increased cancer risk. For example, increased PPARα expression was correlated with tumor development in humans, raising some concerns that constitutive hyperactivation of PPARα may exert tumor-promoting effects (83). In a rodent model (SV129 mice), the long-term exposure (5 mo) to WY14,463 increased liver cell proliferation and global hypomethylation but decreased the amounts of the repressive H4K20me3 mark. The latter changes were not observed in SV129/*PPARα*$^{-/-}$ mice. These data suggested a positive role for PPARα-mediated epigenetic regulation in tumorigenesis (84). As a result, more experimental evidence is needed to establish whether or not therapies based on dietary or synthetic agonists of PPARα pose increased cancer risks to humans through the induction of undesirable epigenetic changes (85).

PPARγ. In mammals, white adipose tissue (WAT) plays a prominent role in storing excess energy in the form of TGs but also plays essential roles as an endocrine organ through secretion of leptin and adiponectin and metabolism of sex steroids and glucocorticoids (86). Resident macrophages in WAT are a meaningful source of inflammatory cytokines, such as TNF-α and IL-6. An increase in circulating amounts of these macrophage-derived factors in obesity leads to a chronic low-grade inflammatory state that has been linked to the development of insulin resistance and diabetes (87).

There are 2 known PPARγ splice variants, PPARγ1 and PPARγ2. Expression of the PPARγ1 isoform is higher in WAT, intestine and spleen. PPARγ2 is expressed preferentially in WAT and brown adipose tissue (BAT). The activation of PPARγ with the synthetic agonist rosiglitazone shifts the fate of pluripotent adipose-derived stem cells toward BAT (88). In addition, manipulation of PPARγ signaling in WAT produces gene expression representative of BAT and improves glucose tolerance in murine cell cultures and in mice, respectively (89).

Ligands of PPARγ comprise common dietary FAs (linoleic acid, arachidonic acid, EPA, DHA), metabolites (15d-PGJ2), synthetic TZDs, and nonsteroidal anti-inflammatory drugs (90,91). Genes induced by PPARγ include those that regulate FA (e.g., FA-binding protein and lipoprotein lipase) and carbohydrate (*PEPCK*) metabolism (92). Chromatin-modifying cofactors that colocalize with PPARγ comprise p300/CBP, SRC-1, and jumonji histone demethylase 2A (JHDM2A), an HDM. Histone marks associated with activation of transcription by PPARγ are H3K4me2, H3K4me3, H4K20me1, acH3K9ac, and acH3K27. Conversely, the association of PPARγ with HDACs (HDAC-1 and HDAC-3), nuclear corepressors (NCoR-1, NCoR-2, and SMRT), and HMTs [SET domain, bifurcated 1 (SETDB1) and histone-lysine-N-methyltransferase (SUV39H1)] has been linked to transcriptional repression. Repressive histone marks associated with promoter recruitment of PPARγ include H3K9me2, H3K9me3, H3K27me2, and H3K27me3 (93).

The epigenetic silencing of the *PPARγ* gene by MeCP2- and EZH2-containing repressive complexes is a biomarker of colorectal cancer progression and adverse patient's outcome (94). Hepatic reactivation of PPARγ expression via repression of EZH2 and MeCP2 functions has been documented for the dietary compounds rosmarinic acid and baicalin (95). Intrauterine growth restriction is a condition that, in neonatal rat lung, reduces expression of PPARγ by lowering the amounts of the HMT su(var)3-9, enhancer of zeste, trithorax, domain 8 (setd8) and H4K20me on the *PPARγ* gene. The latter effects are ameliorated in offspring by maternal supplementation with DHA (96).

A factor related to PPARγ that controls lipid metabolism is the PPARγ coactivator PGC-1α. In skeletal muscle, the acute exposure to a heavy lipid load (e.g., palmitate) reduces PGC-1α expression through DNMT-3b-dependent non-CpG methylation of the PGC-1α promoter and impairs FA oxidation (97). Conversely, exercise induces acute expression of PGC-1α, PDK4, and PPARδ in skeletal muscle via reduced CpG methylation of the respective promoters (98). This cumulative evidence illustrates the contribution of epigenetic modification through DNA methylation at the *PGC-1α* gene in the regulation of lipid metabolism by FAs and exercise in skeletal muscle.

TZDs are a group of insulin sensitizers, of which, troglitazone induces transcription of the *PPARγ2* gene through placement of the active H4K20me1 mark on the PPARγ2

promoter (99). The induction of expression of PPARγ2 is linked to CpG demethylation of the PPARγ2 promoter in differentiated 3T3-Ll adipocytes (100). Similarly, the transcriptional activation of the glucose-dependent insulintropic polypeptide receptor and *PEPCK* genes with synthetic ligands of PPARγ is related to increased association of AcH3 and AcH4, respectively, with the glucose-dependent insulintropic polypeptide receptor and PEPCK promoters (48,101). Because certain TZDs, such as rosiglitazone, induce severe health side effects, such as myocardial infarction (102,103), future studies should examine whether or not feeding of certain food compounds alone or in combination with antidiabetic drugs offer safer alternatives for epigenetic activation of PPARγ networks and lowering of circulating glucose in patients with diabetes.

ER

The ER is expressed in 2 isoforms, α and β. The ERα stimulates proliferation in reproductive organs (104). The estradiol-bound ERα recruits cofactors that possess HAT (p300, p160s), HMT (e.g., protein arginine methyltransferase 1), and HDM (e.g., lysine-specific demethylase-1) enzymatic activities. Conversely, ERα bound to antagonists (e.g., tamoxifen) associates with NCoR-1 and SMRT. The latter recruit nucleosome remodeling and deacetylase complexes that repress transcription. Amounts of NCoR-1 are usually lower in invasive breast cancers, implying that changes in epigenetic control linked to NCoR-1/HDACs may contribute to transition to more invasive phenotypes (105).

The activation of ERβ leads to transcriptional repression of ERα target genes through either the sequestration of cofactors for the ERα or formation at target genes of complexes that repress ERα-dependent transcription. For example, the genistein-bound ERβ triggers the recruitment of the cofactor GR interacting protein-1, which antagonizes the activation of ERα responsive promoters (106). The contribution of ERβ to epigenetic regulation appears to be gene and tissue specific. In differentiated mouse embryonic fibroblasts, ERβ induces hypomethylation of the glucose transporter 4 (GLUT4) promoter and restores *GLUT4* gene transcription (107). Conversely, in prostate cancer cells, ERβ stimulates the recruitment of corepressor complexes containing NCoR, mSin3A, and HDAC-1 and the CpG methylation of the glutathione *S*-transferase P1-1 promoter (108).

Isoflavones are a class of phytoestrogens with higher (~10-fold to 30-fold) binding affinity for ERβ compared with ERα (e.g., genistein > biochanin A > daidzein). The phytoalexin resveratrol also binds to the ERα and ERβ but with ~7000-fold lower affinities compared with estradiol (109). Through epigenetic mechanisms, isoflavones exert tumor-protective or -promoting effects in ER-positive mammary tissue depending on the timing of exposure. In rodent models, the prenatal and neonatal exposure to genistein increased the incidence of carcinogen-induced mammary tumors (110) and uterine adenocarcinoma (111), respectively. The tumor-promoting effects of neonatal exposure to genistein in uterine tissue have been related to constitutive stimulation of hypomethylation and expression of the nucleosomal binding protein-1 (*NSBP-1*) gene (112). Notably, the *NSBP-1* gene encodes for a member of the high-mobility group nucleosome-binding proteins that reduce compaction of chromatin and enhance transcription. The NSBP-1 protein is expressed at high amounts in cancer cells, whereas the knockdown of the *NSBP1* gene inhibits tumor growth in nude mice but induces G_2/M cell cycle arrest and apoptosis (113).

In adult life, genistein may increase breast cancer risk through epigenetic silencing of RARβ2. The latter mediates the anticancer effects of retinoic acid. DNA hypermethylation of the *RARβ2* gene was observed in nipple aspirates obtained from premenopausal women supplemented for 1 menstrual cycle with phytoestrogens (90.6 mg/d genistein, 36.4 mg/d daidzein, and 1.8 mg/d glycitein) and plasma amounts of genistein >600 μg/L (114). The DNA methylation rate of *RARβ2* is generally higher in breast tumors and precancerous breast lesions compared with normal breast tissue (115).

Some of the preventive effects of genistein and daidzein against ERα-positive breast cancer have been related to activation of BRCA-1 expression via reversal of CpG methylation at the *BRCA-1* gene (116). Genistein mimics the stimulatory effects of estradiol on BRCA-1 (26,117) and triggers the association of p300, SRC-1, and AcH4 with the BRCA-1 promoter (118,119). Moreover, genistein may exert anticancer effects in endocrine tissue through epigenetic reactivation of ERα (120) and repression of DNMT-3b expression (121).

The antidiabetic effects of daidzein and its metabolite equol have been attributed to the induction of GLUT4 expression by ERβ through reduced CpG methylation at the GLUT4 promoter (107). Similarly, studies that focused on the anticancer effects of the phytoalexin resveratrol reported that it reduced promoter methylation of the phosphatase and tensin homolog gene in ERα-positive MCF-7 breast cancer cells (122,123). Overall, these examples suggest a role for polyphenols, such as genistein, resveratrol, and daidzein, as modifiers of cancer and diabetes risk through epigenetic regulation of genes targeted by the ER.

AhR

Ligands of the AhR include environmental dioxins and PAHs, a multitude of dietary compounds (e.g., resveratrol, kaempferol, and indol-3-carbinol), and metabolites (i.e., PGs) (reviewed in references 5,123). In the absence of ligands, the AhR is found in the cytoplasm in association with the chaperone proteins heat shock protein 90, HBV X-associated protein 2 (XAP2), and p23. The binding of ligands to the AhR displaces XAP2 and favors migration of the bound AhR to the nucleus in which it interacts with ARNT, of which 3 different isoforms (ARNT-1, ARNT-2, and ARNT-3) have been identified. After nuclear release of heat shock protein 90, the AhR/ARNT heterocomplex binds to core XREs and activates the expression of phase I and phase II enzymes. Phase I enzymes comprise CYP1A1,

cytochrome P450, family 1, subfamily B, polypeptide 1, and cytochrome P450, family 1, subfamily A, polypeptide 2, which produce chemically reactive species. The latter are substrates for detoxification by phase II enzymes, such as NAD(P)H:quinine oxidoreductase and UDP-glucuronosyltransferase-1A6 (123). The role of CpG methylation in differential regulation of CYP1A1 and cytochrome P450, family 1, subfamily B, polypeptide 1 expression by the AhR has been documented clearly in breast and hepatic cells (124).

In addition to its putative role in detoxification, the AhR regulates transcription of estrogen-responsive genes (125). For example, in the absence of agonists, the AhR coactivates the ERα and is necessary for estrogen-dependent activation of BRCA-1 transcription (26). Conversely, in the presence of agonists (i.e., PAHs, dioxins), the bound AhR is recruited to XREs harbored in the BRCA-1 promoter and antagonizes ERα-dependent stimulation of BRCA-1 expression. The latter effect is paralleled by increased CpG methylation of the BRCA-1 promoter and association of HDAC-1, DNMTs (DNMT-1, DNMT-3a, and DNMT-3b), and H2K9me3 with the *BRCA-1* gene (49). Among many dietary ligands of the AhR, resveratrol is a prototype food compound that overrides the placement of repressive marks by AhR agonists on the *BRCA-1* gene (126).

VDR

Through epigenetic mechanisms, the VDR directs the expression of genes involved in vitamin D and bone tissue remodeling. The cholecalciferol, 1,25-dihydroxycholecalciferol, [1,25(OH)2-D3]-bound VDR heterodimerizes with RXR at VDR response elements [(A/G)G(G/T)TCA] and recruits SWI/SNF chromatin remodeling (e.g., BRG-1) and HAT factors (e.g., CBP/p300, SRC-1) that activate transcription of the 25-hydroxy vitamin D3-24-hydroxylase (cytochrome P450, family 24, subfamily A, polypeptide 1) and osteopontin genes (31). The cytochrome P450, family 24, subfamily A, polypeptide 1 enzyme and osteopontin maintain vitamin D and bone tissue homeostasis, respectively, through the conversion of 25OH-D3 and $1,25(OH)_2$-D3 into hydroxylated degradation products and stimulation of bone cell survival. Conversely, the recruitment of the RXR/VDR–$1,25(OH)_2$-D3 heterocomplex to a VDR-interacting repressor bound to an E-box (CANNTG) harbored in the cytochrome P450, family 27, subfamily B, polypeptide 1 (CYP27B1) promoter represses CYP27B1 transcription (40). The CYP27B1 enzyme catalyzes the 1α-hydroxylation of vitamin D3. The transrepression of CYP27B1 transcription by the VDR/VDR-interacting repressor heterocomplex involves the recruitment of HDACs, Sin3A, NCoR, DNMTs, and MBDs on the *CYP27B1* gene. The CpG demethylation and derepression of the CYP27B1 promoter is induced by the parathyroid hormone through PKC-dependent phosphorylation of the DNA glycosylase MBD4 and BER mechanisms (127,128). Therefore, dietary ligands of VDR coordinate calcium and bone tissue metabolism by altering the epigenetic code of genes involved in vitamin D metabolism.

FXR

Endogenous ligands of FXR are the primary BAs chenodeoxycholic and cholic acid and the secondary metabolites deoxycholic acid and lithocholic acid. The chenodeoxycholic acid is the BA with the highest binding affinity for FXR (EC_{50} of 10–50 μmol/L). Conversely, the absence of a 7α-hydroxy group in deoxycholic acid and lithocholic acid or placement of a 12α-hydroxy group in CA reduces the binding affinity of these compounds for FXR, which directs transcription as a monomer, homodimer, or through heterodimerization with RXR. The activated FXR represses transcription of genes involved in BA synthesis (cytochrome P450, family 7, subfamily A, polypeptide 1) and gluconeogenesis (glucose-6-phosphatase). Conversely, it enhances the transcription of genes involved in BA shuttling [ileal bile acid-binding protein and metabolism (*SHP*)] (reviewed in reference 129).

Reduced FXR expression is found in intestinal epithelial cells with activated Wnt (wingless-type MMTV integration site family) signaling (130), human colon carcinoma (131), rodent colorectal cancers carrying a mutated adenomatous polyposis coli gene, and humans with familial adenomatous polyposis. FXR induces the expression of tumor suppressor (*p21*) and proapoptotic (FA synthase) but represses expression of antiapoptotic (B-cell CLL/lymphoma 2) and *TNF*-α, genes. Also, FXR tethers the transcription factor p65, thus hampering the ability of NF-κB to activate proinflammatory (e.g., *COX-2* and inducible nitric oxide synthase) genes (132).

The SHP and the bile salt export pump genes are targets for epigenetic regulation by the FXR. Under conditions of low exposure to BAs, the FXR is deacetylated by sirtuin 1, and transcription of SHP is repressed. Conversely, the activation of FXR by BAs induces the coordinate recruitment of p300 to the FXR/RXR complex, release of sirtuin 1, and association of AcH3K9 and AcH3K14 with the SHP promoter (133,134). Similarly, FXR activation with the synthetic compound 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]benzoic acid (GW4064) increases the association of AcH3K9 and AcH3K14 with the SHP promoter (135). FXR-dependent transactivation of the bile salt export pump gene requires histone methylation by the H3K mixed lineage leukemia-3 (136) and H4R3 protein arginine methyltransferase 1 (137) methylases. A posttranslational modification of FXR that increases binding of the FXR/RXR complex to FXRE and expression of FXR target genes is methylation of lysine 26 by the methylase histone-lysine N-methyltransferase SET domain 7/9 (SET7/9) (138). The latter enzyme also methylates the ERα at lysine 302 (139). These data clearly corroborate the role of epigenetic mechanisms in FRX-dependent transcriptional regulation of genes involved in maintenance of BA homeostasis.

Significance and Future Perspectives

The field of epigenetics finds its roots in the pioneering theories of Conrad Hal Waddington (140) and others (141), who developed the concept that the epigenotype is the

sum of the mechanisms that bridges the gap between genotype and phenotype (142). Research findings discussed in this review highlighted the notion that NRs influence the epigenotype, and thus the phenotypic response, by directing gene expression through the recruitment to target promoters of factors that possess chromatin, histone, and DNA-modifying properties. The ability of NRs to affect gene expression via epigenetic mechanisms would be sequence specific, i.e., via direct binding to core elements (i.e., XRE, VDR response element, FXRE, etc,) or to factors (i.e., AP-1, specificity protein 1) bound to DNA motifs. The precise sequence of the core motifs and their spatial arrangement would determine the specificity, strength, and impact of NRs–response element interactions on gene expression (143). Therefore, the identification and cataloging of binding sequences would greatly improve our understanding of how unliganded and food-bound NRs contribute to the epigenotype associated with chronic diseases. Notably, NRs interact promiscuously with many food ligands (Table 1). Therefore, future research should examine how synergies and antagonisms between food components and drugs for NRs influence the epigenotype and response to disease therapy. For example, studies reported that the efficacy of breast cancer therapies based on the ERα antagonist tamoxifen was augmented by the food isoflavone and ERα ligand genistein (144). Conversely, the treatment with the PPARα agonist fenofibrate prevented glucocorticoid-induced hyperinsulinemia of mice fed a high-fat diet but potentiated the anti-inflammatory effects of the GR on NF-κB. These examples provide the rationale for the development of combination therapies for the management of chronic disorders, such as breast cancer and chronic inflammation (145). Hence, future research should help clarify why diseased cells/tissues that share the same genotypes with healthy ones have different epigenotypes and predict their response to therapies based on food ligands of NRs.

Finally, it is relevant to highlight that epigenetic events, such as DNA methylation, may be imprinted through somatic transmission or even exert transgenerational effects if they affect the germ line (146). Nevertheless, unlike genetic changes (i.e., mutations), DNA methylation is reversible. For example, reversal of DNA hypermethylation has been documented for genistein on the *RAR*β (147) and *ER*α (148) and for epigallocatechin 3-O-gallate on the *RAR*β (149) genes. Whereas the anticancer effects of genistein and epigallocatechin 3-O-gallate may be due to combinatorial actions on NRs and other factors that influence epigenetic control, we suggest that vast opportunities exist for nutritional therapy of disease-related epigenotypes using food ligands of NRs.

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