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Nuclear Receptors, Mitochondria, and Lipid Metabolism

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Abstract

Lipid metabolism is a continuum from emulsification and uptake of lipids in the intestine to cellular uptake and transport to compartments such as mitochondria. Whether fats are shuttled into lipid droplets in adipose tissue or oxidized in mitochondria and peroxisomes depends on metabolic substrate availability, energy balance and endocrine signaling of the organism. Several members of the nuclear hormone receptor superfamily are lipid-sensing factors that affect all aspects of lipid metabolism. The physiologic actions of glandular hormones (e.g. thyroid, mineralocorticoid and glucocorticoid), vitamins (e.g. vitamins A and D) and reproductive hormones (e.g. progesterone, estrogen and testosterone) and their cognate receptors are well established. The peroxisome proliferator activated receptors (PPARs) and Liver X receptors (LXRs), acting in concert with PPARγ Coactivator 1α (PGC-1α), have been shown to regulate insulin sensitivity and lipid handling. These receptors are the focus of intense pharmacologic studies to expand the armamentarium of small molecule ligands to treat diabetes and the metabolic syndrome (hypertension, insulin resistance, hyperglycemia, dyslipidemia, and obesity). Recently, additional partners of PGC-1α have moved to the forefront of metabolic research, the Estrogen-related Receptors (ERRs). Although no endogenous ligands for these receptors have been identified, phenotypic analyses of knockout mouse models demonstrate an important role for these molecules in substrate sensing and handling as well as mitochondrial function.

Keywords

Estrogen-related receptor; Peroxisome-proliferator associated receptor; liver; X receptor; mitochondria; lipid metabolism

Nuclear Hormone Receptors

Nuclear hormone receptors (NRs) generally function as ligand-activated transcription factors that regulate the expression of specific genes related to reproduction, development and metabolism. Conserved functional domains of NRs, such as the DNA binding domain (DBD), ligand binding domain (LBD), N- and C-terminal transcriptional activation domains (AF-1 and AF-2, respectively) define this class of transcription factors (Evans 1988). Their disparate physiologic roles are determined by diversity in both ligand and DNA binding specificities, as well as in specific interactions with co-activator and co-repressor molecules that combinatorially mediate transcription (Glass and Rosenfeld 2000; Kressler et al. 2002). Models of transcriptional activity are dominated by conformational changes in chromatin that alter access of permissive factors to promoter regions and subsequently nucleate

transcriptional machinery (Chen et al. 2001). NRs classically affect these processes as *cis*-acting ligand-responsive switches to facilitate nucleation of factors to enhance or repress transcription. However, evidence suggests that in the absence of ligand, transcriptionally inactive NRs are not passive and may act in *trans* to sequester factors involved in other transcriptional pathways—expanding the physiologic role of NRs beyond either chromatin or ligand binding (Reichardt et al. 1998; Lee et al. 2003; Ogawa et al. 2004).

To date, 48 and 49 members of the NR superfamily have been identified in humans and mice, respectively (Mangelsdorf et al. 1995; Bookout et al. 2006). The first receptors to be cloned, the endocrine nuclear hormone receptors, were discovered in an effort to define the mechanism of action of known hormones, such as: the amino-acid-derived thyroid hormone; the steroidal glucocorticoid, mineralocorticoid, and sex hormones; and the vitamins A and D. Several of these endocrine receptors, e.g. thyroid (TR), estrogen, (ER) and Vitamin D (VDR) receptors have established or emerging roles for influencing metabolic and mitochondrial function, reviewed elsewhere (Weitzel et al. 2003; Chen et al. 2005; Roy et al. 2007). Subsequent to the molecular identification of classical endocrine receptors, additional members of the nuclear hormone receptor superfamily, so called “adopted orphan receptors”, were discovered to respond with low-affinity to physiologic ligands derived from dietary and metabolic sources, such as bile salts, fatty acids and eicasanoids, present in concentrations (micromolar) orders of magnitude higher than classic endocrine hormones (nanomolar). Both the endocrine and adopted orphan receptors may have evolved from a phylogenetically ancient transcriptional regulator that underwent multiple duplications and divergences. As a result, the NR superfamily is divided into two broad groups: 1) the transcription factors for which physiologic ligand-dependent activities have been identified; and 2) factors for which physiologic ligands have yet to be identified: the orphan nuclear receptors (Escriva et al. 2004). Unlike the endocrine receptors that generally translocate from the cytosol to the nucleus upon ligand binding, the orphan and adopted orphan receptors tend to be constitutively nuclear. Because most receptors appear to be physically capable of binding small molecules and profoundly influence metabolic function, there has been great interest from both biomedical research and the pharmaceutical industry to control their function in treating endocrine and metabolic diseases (Chawla et al. 2001).

Metabolic Control by NRs

Today one in three adults in the US is obese—an increase of 75% over the last 25 years (Flegal et al. 2002). In addition metabolic disorders associated with obesity have risen, such as hypertension, dyslipidemia, insulin resistance and glucose intolerance that are components of the metabolic syndrome. These endocrine disturbances increase cardiovascular risk and all-cause mortality by 6-7% (Ford 2005). Over the next fifty years, life expectancy may level off or decline due to the health burden of obesity-related illness presenting in younger populations, as well (Olshansky et al. 2005). To address these impacts, public health awareness of meal choices and portions, and physical exercise are foremost. However, for those already affected and refractory to diet and exercise changes, pharmacologic modification of metabolism provides an opportunity to prevent mortality and morbidity associated with diabetes, cardiovascular disease and the metabolic syndrome (Evans et al. 2004; Barish et al. 2006).

While the metabolic syndrome is multifactorial, insulin resistance may be at its core (Eckel et al. 2005; Grundy 2005). Insulin resistance is associated with altered glucose production in liver, elevated blood glucose and insulin, and reduced glucose uptake in fat and muscle by insulin. Less well appreciated are the derangements in lipids that occur. Free-fatty acids (FFAs) are elevated in circulation and are taken up by insulin target tissues where they may directly interfere with insulin signaling (Medina-Gomez et al. 2007). Furthermore, the

adipose depots elaborate inflammatory adipokines and cytokines that negatively impact insulin sensitivity and systemic metabolism (Kershaw and Flier 2004).

The increased prevalence of obesity and associated metabolic syndrome has driven intense interest in nuclear receptors that can favorably alter body composition, lipid profiles and insulin sensitivity. At the forefront of pharmacologic treatments of metabolic syndrome are the PPARs that serve as ligands for broadly used fibrates and thiazolidinediones, as well as promising pre-clinical compounds. In addition, LXRs and the orphan receptors ERRs appear to be viable targets for metabolic disorders. However the interactions of these molecules and the side effects of their pharmacologic activation are complex and will require additional explanation before long term treatments are implemented. This is highlighted in chronic treatments that influence inflammation which may produce untoward consequences as seen with glucocorticoids, COX inhibitors (e.g. rofecoxib/Vioxx) and possibly rosiglitazone (Avandia; Lago et al. 2007).

PGC-1α

Transcription factors, including nuclear receptors, are highly dependent on coactivator molecules to affect transcriptional control of physiologic processes. Mitochondrial biogenesis and respiration are highly dependent on the transcriptional coactivators, PGC-1α and β, and their interacting factors (Puigserver et al. 1998; Wu et al. 1999; Lehman et al. 2000; Lin et al. 2002; Kelly and Scarpulla 2004; Arany et al. 2007; Sonoda et al. 2007). In addition, many physiologic, hormonal and dietary cues are transduced into adaptive protein changes via the transcriptional coactivator PGC-1α. The activities are most notable in highly metabolic tissues, such as brown adipose tissue, heart, skeletal muscle, liver and the CNS, where PGC-1a regulates the central characteristics of these differentiated tissues: thermogenesis, contractile force, oxidative fiber types, gluconeogenesis and beta-oxidation, and emerging roles in the CNS such as ROS adaptation and apoptosis. (Puigserver et al. 1998; Herzig et al. 2001; Lin et al. 2002; Puigserver et al. 2003; Rhee et al. 2003; Yoon et al. 2003; Arany et al. 2005; St-Pierre et al. 2006; Handschin et al. 2007). While named for its interaction with PPARγ, many of these PGC-1-dependent adaptations appear to be largely dependent on ERRs and other metabolic transcription factors that are independent of PPAR/RXR (Puigserver et al. 2003; Rhee et al. 2003; Schilling et al. 2006; Alaynick et al. 2007; Huss et al. 2007; Villena et al. 2007).

PPARs

There are three isoforms of PPAR: PPAR, PPAR and PPAR. Expression of PPAR is greatest in tissues with active metabolism, such as BAT, liver, striated muscle, and kidney (Bookout et al. 2006). PPAR has a very broad expression pattern that made identifying its role more difficult. PPAR is highly expressed in fat, colon, placenta and macrophage (Rosen and Spiegelman 2000; Barish et al. 2005). Importantly, the PPARs act as obligate heterodimers with RXR to bind PPAR response elements consisting of direct repeats of AGGTCA separated by one nucleotide (DR1). PPARs have a large, promiscuous ligand binding pocket and in addition, are subject to RXR ligand activation by 9-cis-retinoic acid and synthetic agonists (Nolte et al. 1998; Xu et al. 1999).

Among the adopted orphan receptors, the most clinical knowledge has been gained about the physiology and mechanistic action of PPARs (Berger and Moller 2002). Currently, two PPAR agonist classes are in widespread use, the thiazolidinediones (TZDs) which activate PPAR and increase insulin sensitivity, and the fibrates (gemfibrozil, fenofibrate) which activate PPAR to reduce hepatic triglyceride production and increase hepatic fatty acid oxidation (Harris and Kletzien 1994; Forman et al. 1995; Lehmann et al. 1995; Willson et al. 1996a). In vivo, PPAR and ligands appear to be naturally occurring fatty acids and

eicosanoid arachidonic acid metabolites (Forman et al. 1997). Naturally occurring PPAR ligands appear to be nitrolinoleic acid and possibly prostaglandin J2 (Kliewer et al. 1995; Willson et al. 1996b; Schopfer et al. 2005). As these compounds are active at relatively high concentrations, some debate exists as to identity of *bone fide* PPAR ligands.

PPAR

PPAR controls the expression of several genes involved in fatty acid metabolism from transport across the cell membrane, intracellular binding (liver FABP), formation of acyl-CoA (FASN), to mitochondrial and peroxisomal β-oxidation, as well as microsomal ω-oxidation (ACOX, CYP4A1 and CYP4A6 genes, ACADM, and HMGCS1 and 2) (Desvergne and Wahli 1999). During a fast, when increased utilization of free fatty occurs, PPARα expression and activity promotes increased β-oxidation. In fact, while PPARα mice are relatively healthy when fed ad libitum, they have very poor tolerance for fasting and develop hypoglycemia, hypoketonemia and hypothermia (Kersten et al. 1999; Leone et al. 1999). In skeletal muscle, loss of PPARα is relatively mild, suggesting PPARδ and perhaps other factors may compensate (Muoio et al. 2002). However, PPARα is induced after exercise in human—as are some of its target genes (Horowitz et al. 2000). In the heart, which derives 70% of its energy from lipid in the adult, PPARα expression correlates with the fetal to adult transition, as does PGC-1α (Lehman and Kelly 2002). Furthermore, expression of PPARα is downregulated during pathological cardiac hypertrophy when a fetal metabolic preference for carbohydrate is reiterated and fatty acid oxidation declines (Barger and Kelly 2000).

PPAR

While loss of PPARγ results in a developmental elimination of adipose tissue in mouse, its role in mature adipocytes is less clear, although it is essential for adipocyte survival (Barak et al. 1999; He et al. 2003). Not only a repository of triglycerides, adipose-derived endocrine signals have profound global actions on metabolism by altering insulin sensitivity across tissues. Two isoforms of PPARγ, PPARγ1 (colon, retina, spleen, hematopoietic cells, liver, and skeletal muscle) and PPARγ2 (adipose) can respond to the same signals and activate the same target genes: aP2, LPL, ACS and CD36 (Rosen and Spiegelman 2001; Allen et al. 2006). The importance of PPARγ outside the adipose tissue is highlighted by mice with skeletal muscle-specific loss of PPARγ that had 80% reductions in insulin-stimulated glucose disposal rates that did not improve with TZD treatment (Hevener et al. 2003). Other muscle-specific studies, with different PPARγ mutations, showed some TZD sensitivity (Norris et al. 2003).

PPAR

The actions of PPARδ appear to be more similar to PPARα than PPARγ in favoring the oxidation of fats. In cell culture, UCP2, UCP3, H-FABP, FAT/CD36, LPL, ACS and CPT1 were demonstrated to be PPARδ target genes (Muoio et al. 2002; Dressel et al. 2003). Overexpression of PPARδ in fat produced a lean phenotype due to increased oxidation of fats in adipocytes and resulted in white adipose tissue (WAT) that took on some brown adipose tissue (BAT) characteristics (Wang et al. 2003) Cardiac metabolism is dependent on PPARδ and cardiomyocyte specific loss of PPARδ in mouse results in cardiomyopathy and reduced expression of β-oxidation genes (Cheng et al. 2004). Consistently, ligand treatment (GW610742X) helped preserve β-oxidation in a rat model of congestive heart failure (Jucker et al. 2007). Overexpression of VP16-PPARδ in skeletal muscle has profound effects, converting untrained animals into “marathon mice” with a substantial conversion of muscle to a slow-twitch form (Wang et al. 2004). While genetic introduction of VP16-PPARδ presents an extreme case, some components of this phenotype are reiterated by ligand treatments and exercise that hint at effective treatments for metabolic syndrome mediated by

PPARδ (Tanaka et al. 2003; Barish et al. 2006). For instance, patients with poor responsiveness to exercise and dietary changes may benefit from a 'jump start' in the form of PPAR agonists.

LXRs

Two additional RXR partners that can alter lipid handling are the receptors, LXR and LXR. Expression of LXR is greatest in fat, liver and macrophage (Repa and Mangelsdorf 2000; Bookout et al. 2006). In contrast, LXR is widely expressed. *In vivo*, LXRs are activated by physiologic concentrations of 22(R)-, 24(S)-, and 27-sterol metabolites in addition to 24(S), 25-hydroxycholesterol ligands (Janowski et al. 1996; Lehmann et al. 1997; Fu et al. 2001). Constitutively nuclear LXR/RXR partners bind LXR response elements of two AGGTCA repeats separated by four nucleotides (DR-4).

Several target genes for LXR, many of which are involved in cholesterol and fatty acid metabolism indicate that LXRs serve as global cholesterol sensors (Peet et al. 1998; Tontonoz and Mangelsdorf 2003). This is dramatically illustrated by CYP7A1, the rate limiting enzyme of bile synthesis in the liver, which is an LXR target gene. LXR-knockout mice have reduced Cyp7a1 expression and develop massive hepatic accumulations of cholesterol when challenged with a high-cholesterol diet (Peet et al. 1998). In contrast, LXR mice are relatively normal. Yet double knockout mice (LXR $^{-/-}$, $^{-/-}$) have a greater accumulation of cholesterol, suggesting some functional overlap (Alberti et al. 2001). Pharmacologic activation of LXRs activates lipogenic genes, sterol regulatory element binding protein 1c, SREBP-1c; fatty acid synthase, FAS; and steroyl-CoA desaturase 1, SCD-1—and elevates both hepatic and plasma triglyceride levels (Peet et al. 1998; Schultz et al. 2000).

RXRs

Because RXRs form obligate heterodimers with PPARs, LXRs, and other NRs, they have far reaching actions. There are three isoforms of RXR: RXRα, RXRβ, and RXRγ (Bookout et al. 2006). RXRα is broadly expressed with highest expression in the liver. RXRβ is also broadly expressed with relatively low expression in liver, while RXRγ has a more limited distribution with highest expression in striated muscle. Pharmacologic activation of RXRs by small molecule ligands or *rexinoids* may provide another avenue of intervention in the metabolic diseases of diabetes and obesity (Claudel et al. 2001; Desreumaux et al. 2001; Shulman and Mangelsdorf 2005). While rexinoids can mimic some of the ligand-dependent actions of their partners (e.g. PPARγ agonists pioglitazone and rosiglitazone) by increasing insulin sensitivity, they suppress the actions of thyroid hormone, increase triglycerides and decrease, rather than increase, body and fat mass (Mukherjee et al. 1997; Liu et al. 2002; Ferre 2004; Haffner et al. 2004; Ogilvie et al. 2004; Li et al. 2005). For example, treatment with the PPARγ-agonist, rosiglitazone, downregulated TNFα and upregulated GLUT4, MCP-1, SCD1 and CD36, while the rexinoid LG268 increased TNFα and had no effect or suppressed other genes in mouse (Singh Ahuja et al. 2001).

ERRs

The first orphan receptors to be cloned, ERRα and ERRβ, were joined years later by the identification of ERRγ (Giguere et al. 1988; Hong et al. 1999). These receptors all share an extended half-site motif TCAAGGTCA and can bind as monomers, dimers or heterodimers (Dufour et al. 2007). Because these receptors have very small ligand biding pockets, endogenous ligand discovery remains unlikely, although synthetic ligands have been developed and ERRα is blocked by diethylstilbestrol, while ERRβ and γ are blocked by tamoxifen (Coward et al. 2001; Greschik et al. 2002; Willy et al. 2004). The activity of

ERRs appears to be constitutive, with the ligand binding pocket stably arranged in an active conformation without ligand (Xie et al. 1999; Greschik et al. 2002; Greschik et al. 2004). Because ERRα is widely expressed in adult tissues, especially in tissues that utilize or can utilize fatty acid β-oxidation, many studies have addressed its role in cellular energetics (Luo et al. 2003). Loss of ERRβ results in placental defects and mid-gestational death of embryos, despite relatively limited expression in adult (Luo et al. 1997). ERRγ is highly expressed in tissues with high metabolic activity (e.g. heart, kidney, slow-twitch muscle, BAT and CNS) and loss of this receptor in mouse results in neonatal death, presumably due to motor defects that prevent feeding (Alaynick et al. 2007; Dufour et al. 2007).

ERRα

ERRα is involved in many aspects of lipid metabolism, likely by mediating actions of PGC-1α and -β (Kamei et al. 2003; Schreiber et al. 2003; Schreiber et al. 2004; Rodriguez-Calvo et al. 2006; Sonoda et al. 2007). In the mouse intestine, ERRα controls the ApoA-IV promoter and loss results in reduced uptake of lipids (Luo et al. 2003; Carrier et al. 2004). At the cellular level, defects in oxidative metabolism have been seen in ERRα null intestine, skeletal muscle, heart, and BAT (Carrier et al. 2004; Rodriguez-Calvo et al. 2006; Dufour et al. 2007; Huss et al. 2007; Villena et al. 2007). Several target genes have been identified by these studies including Ckmt2, Mcad, Sdha and Sdhb (Dufour et al. 2007).

ERRβ

Little is known about the physiologic role of ERRβ due to the confounds of mid-gestational lethality and placental defects. Tetraploid rescue experiments have produced adult animals with severe motor defects (Mitsunaga et al. 2004). Use of a floxed ERRβ allele and Sox2::Cre (which is not expressed in extraembryonic tissues) allowed the Mendelian generation of adult animals that displayed defects in inner ear morphology and endolymph formation (Chen and Nathans 2007). Perhaps the most surprising aspect of these and other nuclear receptor knockout mice is that despite similar DNA element affinities and coactivator interactions, in vivo compensation appears to be limited or absent. PPARγ, ERRγ and ERRβ all have lethal phenotypes that cannot be corrected by the remaining isoforms. However, it remains possible that pharmacologic perturbation of one receptor could be used to address processes controlled by related receptors. Given the roles of ERRα and ERRγ in mitochondrial and lipid metabolism and similarity of ERRs, ERRβ may play a yet unappreciated role in metabolic function.

ERRγ

ERRγ expression is linked with tissues with high metabolic activities, and loss of this receptor is detrimental in tissues examined to date. In the heart, loss of ERRγ appears to prevent a perinatal transition from carbohydrate-based fetal metabolism to lipid-predominant adult metabolism (Alaynick et al. 2007). Furthermore, it appears that ERRα and ERRγ act in concert to direct the oxidative metabolic program in heart (Dufour et al. 2007). Surprisingly, while loss of ERRα is relatively mild, loss of ERRγ results in reduced ventricular mass and increased mitochondrial DNA, even in heterozygous animals (Alaynick et al. 2007). Myocyte specific elimination of ERRγ may bypass the neonatal lethality of these animals and allow examination of ERRγ-dependent changes in the adult heart and skeletal muscles. To what extent ERRγ bears the transcriptional signaling of PGC-1α in a given tissue, relative to other ERRs and PPARs, awaits further study, as well.

Conclusions

The complex actions of nuclear receptors in regulating lipid metabolism can appear counterintuitive or deceptively mild when studied in knockout mice. The phenotype is not

simply loss of the receptor, however, but reflects the genome-wide compensatory reaction to that loss—especially in cases where very similar receptors remain. What occurs may represent a skewed stoichiometric ratio of target genes. As a consequence, levels of key enzymes and signaling molecules may exceed homeostatic safety margins where mild physiologic challenges or developmental transitions produce decompensation (Alaynick et al. 2007; Huss et al. 2007). Much remains to be learned about the actions of nuclear receptors from conditional loss of receptors by genetic methods as well as combinatorial uses of ligands to 'dial-in' metabolic treatments (Lalloyer et al. 2006; Schug et al. 2007).

The control of mitochondrial biogenesis and substrate utilization by these receptors is a complex issue as well. By mediating the action of PGC-1α and β, the PPARs and ERRs have global influences on mitochondria, increasing their numbers and oxidative capacities. How these receptors act combinatorially in specific cell types at particular times remains to be determined. It does appear however that each of these receptors controls a characteristic suite of genes that determine the genetic composition and metabolic function of mitochondria.

While diet and exercise often provide the best controls of metabolism, individuals who have pathologically, genetically, or behaviorally dysregulated metabolic function may benefit from treatments that activate nuclear receptor mediated metabolic pathways. By improving insulin sensitivity and lipid profiles, or synergistically improving exercise benefits, individuals may be better capable of avoiding a downward spiral of insulin-resistance and lipid accumulation.

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Abbreviations

ACADM	acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain
ACOX	acyl-Coenzyme A oxidase
ANT	adenine nucleotide translocator
APOA1	apolipoprotein A-I
APOE	apolipoprotein E
CD36	scavenger receptor class B
CKMT2	creatine kinase, mitochondrial 2
CPT-1	carnitine palmitoyltransferase
CS	citrate synthase
DGAT	diacylglycerol O-acyltransferase
ERR	estrogen-related receptor
FABP	fatty acid binding protein
FASN	fatty-acid synthase
FFA	free-fatty acid
HADHA	trifunctional protein, alpha subunit

HADHB	trifunctional protein, beta subunit
LDH	lactate dehydrogenase
LDLR	low density lipoprotein receptor
LPL	lipoprotein lipase
LXR	liver X receptor
MDH1	malate dehydrogenase
PCG	PPAR gamma coactivator
PPAR	peroxisome proliferator associated receptor
PDH	pyruvate dehydrogenase
PDK	pyruvate dehydrogenase kinase

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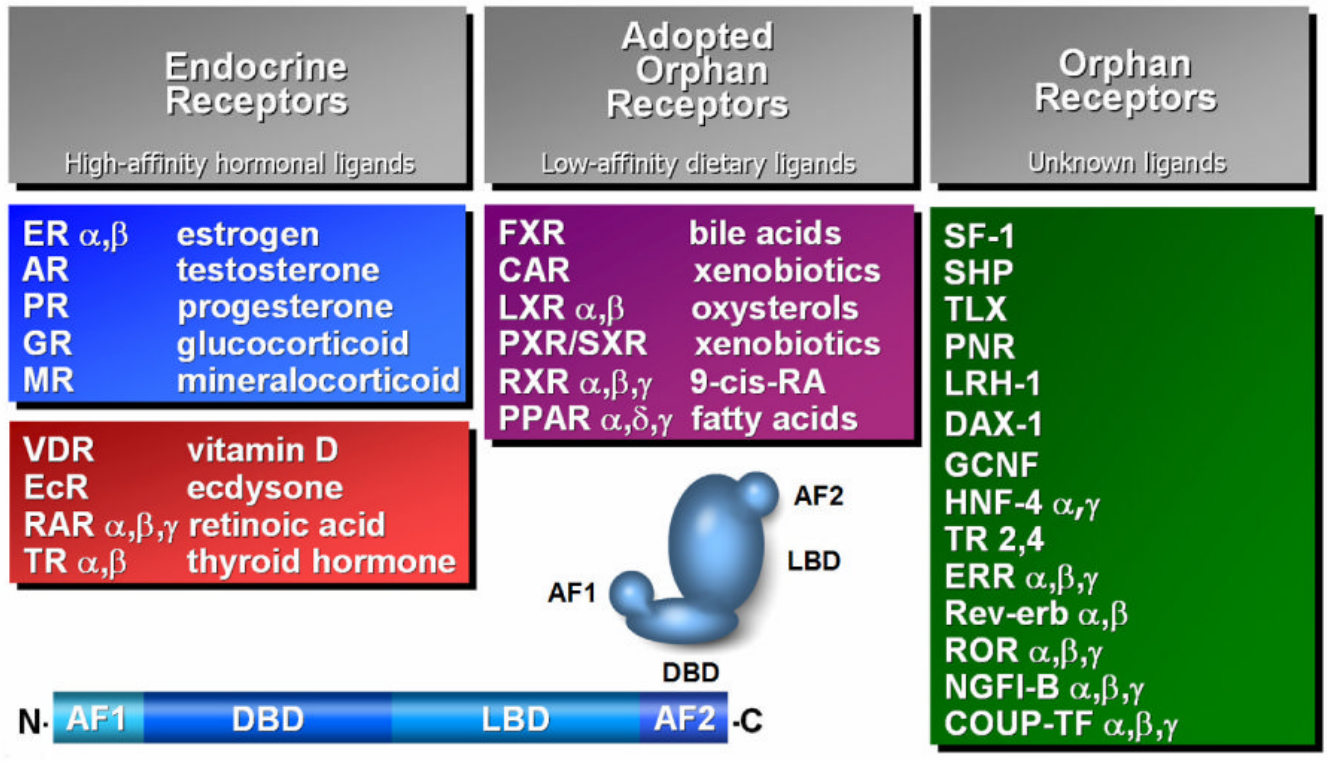

Figure 1. The Nuclear Receptor Superfamily

Nuclear hormone receptors can be divided into Endocrine, Adopted Orphan and Orphan subfamilies. The Endocrine receptors have high affinity ligands that are present in nanomolar concentrations, while Adopted orphan receptors have ligands present in the micromolar range. No physiologic ligands have been identified for the orphan receptors. Nuclear receptors share a common arrangement of an amino terminal Activation Function 1 (AF1), a DNA-Binding Domain (DBD), a Ligand Binding Domain (LBD) and a carboxy-terminal Activation Function 2 (AF2). Adapted from Chawla et al. 2001.

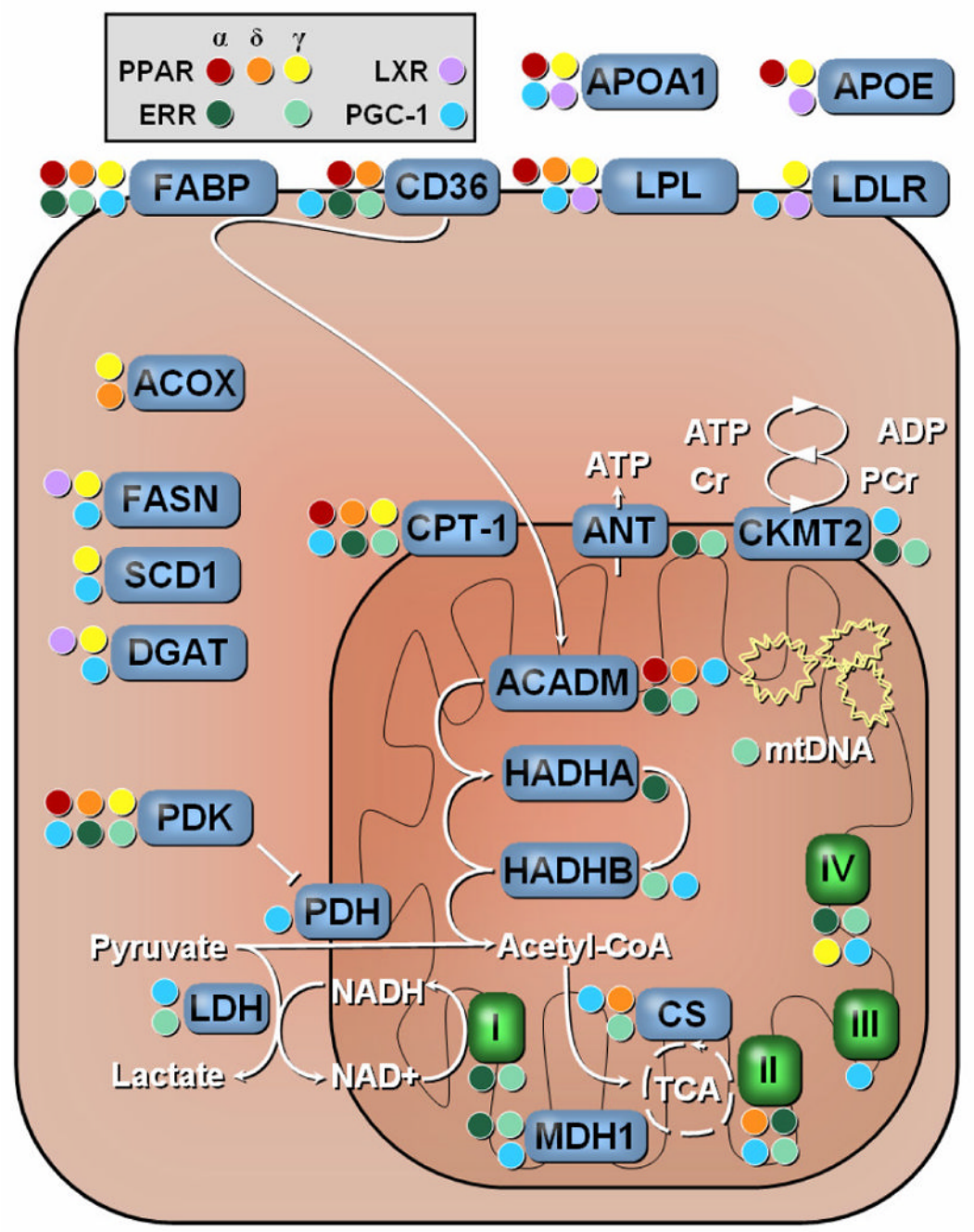

Figure 2. Nuclear Receptor Regulation of Metabolic Enzymes

The PPARs, ERRs and LXRs can influence the expression of several genes involved in lipid metabolism. Regulated processes include lipoprotein metabolism, fatty acid uptake, shuttling into mitochondria and fatty acid oxidation. Color-coded circles indicate regulation by a given receptor. I-IV, Electron transport chain complexes; ACADM, acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain; ACOX, acyl-Coenzyme A oxidase; ANT, adenine nucleotide translocator; APOA1, apolipoprotein A-I; APOE, apolipoprotein E; CD36, scavenger receptor class B; CKMT2, creatine kinase, mitochondrial 2; CPT-1, carnitine palmitoyltransferase; CS, citrate synthase; DGAT, diacylglycerol O-acyltransferase; FABP, fatty-acid binding protein; FASN, fatty-acid synthase; HADHA,

trifunctional protein, alpha subunit; HADHB, trifunctional protein, beta subunit; LDH, lactate dehydrogenase; LDLR, low density lipoprotein receptor; LPL, lipoprotein lipase; MDH1, malate dehydrogenase; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase. Adapted from Alaynick et al. 2007.