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ERR α : a metabolic function for the oldest orphan

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Abstract

Estrogen receptor related receptor (ERR) α was one of the first identified (1988) orphan nuclear receptors. Many of the orphan receptors identified after ERR α were deorphanized in a timely manner and appreciated as key transcriptional regulators of metabolic pathways. ERR α , however, remains an orphan. Nevertheless, recent studies have defined regulatory mechanisms and transcriptional targets of ERR α , allowing this receptor to join ranks with other nuclear receptors that control metabolism. Notably, mice lacking ERR α show defects when challenged with stressors that require a 'shift of gears' in energy metabolism, such as exposure to cold, cardiac overload or infection. These findings establish the importance of ERR α for adaptive energy metabolism, and suggest that strategies targeting ERR α may be useful in fighting metabolic diseases.

Introduction

The nuclear receptor (NR) superfamily comprises a large number of ligand-regulated transcription factors that play important roles in development, reproduction and metabolism [1]. Cloning of cDNAs encoding nuclear receptors for known hormones, e.g. steroid hormones, was soon followed by the identification of structurally related proteins that had no known ligands and were classified as orphan receptors [2]. Estrogen receptor related receptors (ERR) α and β were the first orphan receptors described [3], followed by more than 30 other family members. The subsequent identification of ligands for many of these orphan receptors offered insights into their physiologic functions, and provided necessary experimental tools. For example, the recognition of lipids and known antidiabetic drugs as ligands of peroxisome proliferator activated receptors (PPARs), oxysterols as ligands of the liver X receptor, and bile acids as ligands of the farnesoid X receptor, enabled the elucidation of the role of these receptors in lipid, cholesterol and bile acid metabolism, respectively [4,5].

Even though ERR α was the first orphan NR identified, its role in metabolism has been appreciated only recently. Most initial studies focused on the roles of ERR α in estrogen signaling, cancer, bone differentiation and development. Such studies have been covered in other reviews [6-10] and will not be discussed here. This review focuses on the role of ERR α in regulating diverse aspects of oxidative metabolism, and the physiologic contexts where this role becomes important.

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The ERR family

ERR α is one of three members of the ERR family. ERR α , ERR β and ERR γ (NR3B1–3, also known as ERR1–3) possess the typical structural features of NRs: a central zinc finger DNA-binding domain that is highly conserved among the three members and enables recognition of DNA sites bearing TNAAGGTCA sequences (also known as ERR response elements or ERREs); a conserved C-terminal domain with a putative ligand binding domain (LBD) and interaction surfaces for coactivators and corepressors; and a less conserved N-terminal region [6]. Despite their similarity to estrogen receptors, ERRs are not activated by estrogens or estrogen-like molecules. Instead, ERRs attain active LBD conformations in the absence of ligand, consistent with the notion that these receptors are constitutively active [11–13]. For ERR α in particular, screening and structure-guided design efforts have identified synthetic inverse agonists that inhibit ERR α function, but no agonists, suggesting that ERR α may stay an orphan [14–17].

Regulation of ERR α : the roles of PGC-1 α and PGC-1 β

If small molecule ligands are not required to activate ERR α , how is ERR α function controlled? Insights into the regulation of ERR α came from studies of the transcriptional coactivators (Box 1) PGC-1 α and PGC-1 β , which integrate nutrient and energy state signals and control the expression of genes important for mitochondrial biogenesis, oxidative metabolism, oxidative stress responses and, in the case of PGC-1 α , gluconeogenesis [18,19]. The ability of PGC-1 coactivators to induce target genes relies on their recruitment at target genomic regulatory sites via physical interactions with nuclear receptors and other transcription factors [18,19]. In the case of nuclear receptors, PGC-1 amphipathic helices that bear LxxLL-type motifs bind a hydrophobic groove in the receptors' LBD. Given the conserved nature of the LBD across the NR family, it is not surprising that PGC-1 α and PGC-1 β interact with ERR α . However, several observations suggest that the interactions of PGC-1 α/β with ERR α are of unique importance for ERR α and PGC-1 function.

First, PGC-1 α has a protein interaction surface that is dedicated specifically to the ERRs. PGC-1 α harbors three LxxLL motifs, two of which, (L2 and L3), serve as NR interaction sites [20–24]. The L2 site bears a consensus LxxLL motif, similar to ones found in other receptor coactivators, and interacts with most NRs, including the three ERRs. The L3 site is an ERR-dedicated site, with an atypical LLxYL motif that interacts potently and specifically with the ERRs [23–25]. The ERR-specific L3 site suggests that ERRs are not in competition with other NRs for binding PGC-1 α , and may have the 'undivided attention' of this coactivator. Moreover, the ERR-specific site has enabled the construction of PGC-1 α mutants that interact only with ERRs, and that have been used as powerful tools to dissect the role of ERRs versus other NRs downstream of PGC-1 α [24,26].

Second, ERR α , which is a weak activator of transcription in cells with low PGC-1 activity and where other NRs are transcriptionally active, is transformed to a potent transcriptional activator when PGC-1 α or PGC-1 β is introduced into the system [23,24,27]. The striking dependency of ERR α on PGC-1 coactivators likely reflects the much higher affinity of ERR α for PGC-1 over other widely used NR coactivators [13,25], and suggests that ERR α activity is primarily controlled by interaction with 'protein ligands,' such as PGC-1 α and PGC-1 β , rather than small molecule ligands.

Third, PGC-1 α regulates not only the activity but also the expression levels of ERR α [24]. This results from ERR α binding to conserved ERREs in its own promoter, inducing transcription in a positive autoregulatory loop upon activation by PGC-1 α [28–30]. Consistent with the ability of PGC-1 coactivators to induce ERR α expression, ERR α mRNA levels are highest in tissues that have high levels of PGC-1 α or PGC-1 β , such as brown adipose tissue, heart, kidney,

small intestine and skeletal muscle [19,24,31-34]. Moreover, ERR α mRNA levels are increased in response to physiologic signals that induce PGC-1 α expression, such as fasting in liver [34], cold exposure in brown adipose tissue and muscle [24] and exercise in skeletal muscle [35].

In summary, ERR α is activated by interactions with PGC-1 coactivators and, therefore, by tissue- and physiological state-specific signals that determine PGC-1 α/β levels and activity (Figure 1). Additional signals are likely to impact ERR α function via other mechanisms, including ERR α phosphorylation and sumoylation [36-39]. Importantly, ERR α also interacts with the corepressor (Box 1) RIP140, which can suppress ERR α -dependent transcription and is thus likely to antagonize PGC-1 α/β function at ERR α target genes [40] (Figure 1).

Cellular function of ERR α : regulation of energy metabolism genes

The finding that ERR α is activated by PGC-1 α/β has given insights into the cellular and physiologic context of ERR α function and suggested a role for ERR α in PGC-1 signaling. Indeed, several studies have established not only that ERR α , like PGC-1 α/β , regulates the expression of energy metabolism genes, but also that ERR α is a key downstream effector of PGC-1 α/β . First, whereas PGC-1 α mutants that lack the ability to interact with all NRs (including ERRs) fail to induce expression of energy metabolism genes, PGC-1 α mutants that allow interaction with ERRs but not other NRs are as efficient as wild-type PGC-1 α in enhancing gene expression [26,41]. Second, inhibition of ERR α activity by either siRNA or an ERR α inverse agonist impairs the ability of PGC-1 α to induce expression of energy metabolism genes and enhance mitochondrial biogenesis and oxidative capacity [26,29]. Conversely, overexpression of ERR α in primary cardiomyocytes, which express endogenous PGC-1 α/β , induces many PGC-1 target genes involved in substrate utilization and energy production [42]. Interestingly, while ERR α overexpression in cells lacking endogenous PGC-1 α and PGC-1 β fails to induce target gene expression, consistent with a requirement for PGC-1 co-activators (Figure 1), overexpression of a chimeric, constitutively active form of ERR α bearing the VP16 activation domain bypasses this requirement and induces mitochondrial gene expression and biogenesis [26]. Collectively, these and later studies have established that ERR α activated by PGC-1 α or PGC-1 β induces genes with roles in lipid transport [42,43], fatty acid oxidation [24,26,29,41-44], TCA cycle [24,41,44-46], oxidative phosphorylation [26,29,41,42,44-46], mitochondrial biogenesis [26,44], mitochondrial dynamics [35,47] and oxidative stress defense [45] (Figure 2 and Table 1). Accordingly, ERR α , depending on the cell type, has been shown to promote lipid uptake and oxidation, mitochondrial biogenesis, respiratory capacity and ROS production, and to inhibit glucose oxidation [26,29,42,43,46,48].

The effects of ERR α on expression of metabolism genes are mediated by direct and indirect actions at the promoters of these genes. Bioinformatic analyses show a statistically significant enrichment of motifs corresponding to ERREs in genes induced by PGC-1 α [29]. The direct action of ERR α , as opposed to other NRs that recognize the same motif, is supported by the detection of endogenous ERR α binding at these sites [35,42-44,48,49]. Furthermore, the functional significance of some of these ERREs has been validated *in vitro* by showing that these response elements confer ERR α - and PGC-1 α -dependent regulation of reporter genes in transfection assays [26,42,43,47-51]. In addition to direct actions, ERR α can enhance mitochondrial gene expression indirectly by inducing the expression of other transcriptional regulators of mitochondrial genes, such as NRF1, the GABP α subunit of GABP/NRF2, and PPAR α [29,42] (Figure 2). The ability of ERR α to induce these transcription factors, which may be cell-type specific [24,44], is likely to expand the spectrum of ERR α -dependent genes, as well as increase the magnitude of regulation for genes where ERR α acts both directly and indirectly.

The role of $ERR\alpha$ as a regulator of energy metabolism has been confirmed and broadened by the unbiased identification of genome-wide direct targets of $ERR\alpha$ in the heart, a tissue that expresses high levels of all three ERRs [49]. Using chromatin immunoprecipitation (ChIP) and genomic DNA arrays (ChIP-on-chip), Dufour *et al.* detected $ERR\alpha$ binding at the promoters of a large number of energy metabolism genes, as well as genes involved in energy sensing, amino acid and carbohydrate metabolism, Ca^{+2} homeostasis, contractile function and other cellular processes. Strikingly, a comparison of $ERR\alpha$ and $ERR\gamma$ binding revealed largely similar target genes, suggesting a great overlap in the function of ERRs and implicating $ERR\gamma$, and likely $ERR\beta$, in the regulation of cellular energy metabolism [49]. It is too early yet to tell the extent to which all targets identified by ChIP-on-chip are positively regulated by $ERR\alpha$ and $ERR\gamma$. The expression of many of them is not decreased in the hearts of $ERR\alpha$ null mice, which may be due to compensation by $ERR\beta$ and/or $ERR\gamma$ [49,52]. It will be interesting to combine genome-wide ChIP and expression analyses in a cell system where there is no compensation by other ERRs, to elucidate the positive and negatively regulated $ERR\alpha$ targets.

Most of the studies have focused on the ability of $ERR\alpha$ to activate energy metabolism genes. However, $ERR\alpha$ can also act as a repressor [53]. At least two distinct modes of repression by $ERR\alpha$ have been observed in the context of metabolism. First, $ERR\alpha$ can act as a downstream effector of the corepressor RIP140 [40,54]. RIP140 acts as the antithesis of PGC-1 α , suppressing many of the energy metabolism genes that PGC-1 α activates [55] (Figure 1). In fact, the ability of RIP140 to repress expression of Glut4 and SDHB (identified as direct ERR targets [49]) relies on endogenous $ERR\alpha$ [54]. Thus, $ERR\alpha$ may function as a sensor of energy demand signals by interpreting the relative levels and activity of PGC-1s versus RIP140, and accordingly acting as an activator or repressor, possibly in a gene-specific manner (Figure 1). A different mode of repression has been shown in the case of the gluconeogenic/glyceroneogenic gene PEPCK, where $ERR\alpha$ binding at a complex response element inhibits PGC-1 α recruitment and PEPCK induction [56]. It is not clear why $ERR\alpha$ at the PEPCK promoter does not recruit PGC-1 α , as at other ERREs. One possibility is that the sequence of the PEPCK ERRE and/or the proximity to other elements directs $ERR\alpha$ binding as a monomer, which cannot recruit PGC-1 α [36,57].

Physiological function of $ERR\alpha$: lessons from mouse models

Mice genetically engineered to lack $ERR\alpha$ have been instrumental for understanding the physiological role of $ERR\alpha$ in the regulation of energy metabolism. Initial characterization of $ERR\alpha$ null mice showed them to be viable and fertile, with no gross anatomical alterations except for a small but significant decrease in adipose mass [58]. Gene expression analyses revealed modest decreases in the expression of some $ERR\alpha$ metabolic targets, but also upregulation of others and no evident organ malfunction [42,43,58]. $ERR\alpha$ null mice are not only lean but also resistant to high fat diet-induced obesity, a phenotype that does not appear congruent with the role of $ERR\alpha$ in promoting mitochondrial oxidative function. Given the multitude of transcription factors that regulate energy metabolism genes [59] and the fact that $ERR\alpha$ function is context (tissue- and signal-) dependent, the apparent lack of phenotype, other than the resistance to diet-induced obesity, may not be so surprising. Still, the cellular role of $ERR\alpha$ downstream of PGC-1 α and PGC-1 β suggested an important role for $ERR\alpha$ in metabolic adaptations to signals of increased energy demands. Indeed, three studies in the last year have shown roles for $ERR\alpha$ in the adaptation to stressful states that require increased use of energy stores.

In the first study, $ERR\alpha$ null mice were shown to be deficient in maintaining their core body temperature when exposed to cold [44]. Adaptive thermogenesis in rodents relies on heat production in brown adipose tissue (BAT), which is rich in mitochondria and expresses high levels of PGC-1D, PGC-1 β and $ERR\alpha$. Brown adipocytes of $ERR\alpha$ null mice have decreased

expression of FAO, TCA cycle and OxPhos genes, decreased mitochondrial mass and oxidative capacity, and increased lipid accumulation. Despite the normal induction of genes important for thermogenesis, such as uncoupling protein 1 and deiodinase 2, *ERR α* null mice become hypothermic when exposed to even mild cold (13°C) temperatures, reflecting their decreased capacity for respiration, and thereby, for the generation of energy necessary for thermogenesis [44].

In the second study, *ERR α* was shown to be important in the heart for the bioenergetic and functional adaptation to cardiac pressure overload [52]. In the absence of stress, hearts of *ERR α* null mice show deregulated expression of several energy metabolism genes but normal myofibrillar structure, mitochondrial morphology and mass, and contractile function. When challenged with increased workload imposed by chronic pressure overload, *ERR α* null hearts develop signs of heart failure, such as chamber dilatation, left ventricular systolic dysfunction, wall thinning and fibrosis. At the bioenergetic level, *ERR α* null hearts have a decreased capacity for ATP synthesis and exhibit defects in their high energy phosphate reserves after E-adrenergic stimulation or ischemia/reperfusion [52]. At the gene expression level, the role of *ERR α* in maintaining expression of energy metabolism genes becomes accentuated in chronically overloaded hearts, suggesting that defects in expression of these genes underlies the energetic defect and the development of contractile dysfunction [52].

The third study using *ERR α* mice reveals a key role for *ERR α* in IFN- γ stimulated oxidative metabolism in macrophages [46]. IFN- γ activates the antimicrobial actions of macrophages by inducing the expression of a wide range of genes. It also induces the expression of PGC-1 β , *ERR α* and genes important for mitochondrial metabolism, and enhances respiration. *ERR α* is required for the IFN- γ induced metabolic response. *ERR α* null macrophages show compromised mitochondrial gene induction, an inability to increase mitochondrial respiration and mitochondrial ROS, and decreased clearance of the intracellular bacterial pathogen *Listeria monocytogenes* in response to IFN- γ . As a result, *ERR α* null mice, and wild-type mice whose bone marrow-derived cells are *ERR α* null, have impaired survival when infected with *L. monocytogenes* [46].

The common theme in all three studies is that *ERR α* null mice are unable to mount proper responses to stressors that require shifts in energy production or utilization (Figure 3). Although small, the bioenergetic defects are significant and compromise organismal survival. By extension, it can be hypothesized that *ERR α* null mice show defects in other states of high energy demands, e.g. physical exercise. Indeed, *ERR α* null mice show decreased physical activity and decreased capacity for exercise when running on treadmills (J.A.V. and A.K., unpublished data). It will be interesting to test other paradigms, e.g. whether small defects seen in intestinal lipid absorption of *ERR α* null mice [43] are accentuated in states requiring increased nutrient absorption.

Do these findings mean that *ERR α* function is not important for basal energy metabolism? And why are *ERR α* null mice lean and resistant to high fat diet-induced obesity? Although the answers to these questions are not yet clear, the following observations give some insights. First, increased expression of other regulators, as seen with *ERR β* and PGC-1 α in heart [42, 52], may compensate for the lack of *ERR α* and mask *ERR α* function in basal energy metabolism. Overcompensation by *ERR β* /PGC-1 α or differences in genes targeted by *ERR α* and *ERR β* may also contribute to the increased expression of some *ERR* targets and the lean phenotype in *ERR α* null mice. Second, the role of *ERR α* in specific tissues or under particular physiological states may promote energy intake and storage. Such a role is consistent with the notion of *ERR α* as a factor that enables the organism to cope with energetically stressful states, e.g. by ensuring availability of energy stores. In line with this role, *ERR α* null mice show defects in intestinal lipid absorption and decreased lipid stores in WAT [43,58]. *ERR α* may

act with PGC-1 α to promote transcription of genes with roles in lipid transport [42,43] in the intestine, where ERR α and PGC-1 α are highly expressed, and/or act with the corepressor RIP140 to suppress energy expenditure genes [54] in WAT, where RIP140 levels are high. Finally, it is possible that effects of ERR α on development and differentiation, e.g. by ERR α promoting adipogenesis [60], might underlie some of the phenotypes in the ERR α null mice.

Concluding remarks

In the last five years, extraordinary progress has been made in our understanding of ERR α function. In response to activation by PGC-1 α and/or PGC-1 β , ERR α regulates genes important for mitochondrial biogenesis and function. Mice lacking ERR α show tissue- and signal-specific defects in mitochondrial biogenesis and respiratory capacity, leading to cold sensitivity, cardiac malfunction and susceptibility to infection. Mitochondrial dysfunction and/or decreased PGC-1 α/β levels have been associated with insulin resistance, type 2 diabetes, cardiovascular disease and neurodegenerative disorders [61-65]. The contribution of ERR α to these disorders is not yet clear. Neither is it known whether increases in ERR α activity could have any harmful effects. Nevertheless, the expectation is that enhancing ERR α activity should enhance mitochondrial oxidative metabolism, as well as the oxidative stress defense system, and benefit patients suffering from such diseases. The emerging evidence that ERR γ shares the ability to regulate energy metabolism genes further raises expectations for the therapeutic potential of ERR agonists. It is clearly essential to understand the specific roles and contributions of each ERR to mitochondrial function in different tissues and physiological states.

Box 1: Coactivators and corepressors

Coregulators interact with DNA-binding transcription factors and assist them in the regulation of transcription of target genes. Coregulators that promote the activation of gene transcription are referred to as coactivators. Conversely, corepressors assist transcription factors to repress gene expression. Coactivators and corepressors do not bind DNA by themselves.

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Glossary

ACO2, aconitase 2
 ATP5B, ATP synthase, H⁺ transporting, mitochondrial F1 complex, beta subunit precursor
 ChIP, chromatin immunoprecipitation
 CPT1b, carnitine palmitoyltransferase 1b (muscle)
 CYCS, cytochrome c, somatic
 ERR, estrogen-receptor related receptor
 ERRE, ERR response element
 FAO, fatty acid oxidation
 GABP, GA binding protein
 GLUT4, glucose transporter 4 (insulin responsive)
 IDH3A, isocitrate dehydrogenase 3, alpha subunit
 LBD, ligand binding domain
 MCAD, medium-chain acyl-CoA dehydrogenase
 MFN, mitofusin
 NR, nuclear receptor

NRF, nuclear respiratory factor
 OxPhos, oxidative phosphorylation
 PEPCK, phosphoenol pyruvate carboxykinase
 PGC, PAR gamma coactivator
 PPAR, peroxisome proliferator activated receptor
 PRDX3, peroxiredoxin 3
 RIP140, receptor-interacting protein 140 (also known as nuclear receptor interacting protein 1 or NRIP1)
 SDHB, succinate dehydrogenase complex, subunit B
 SOD, superoxide dismutase
 TCA, tricarboxylic acid
 TIM, translocase of inner mitochondrial membrane

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Figure 1.

ERRα is regulated by protein-protein interactions with coregulators. The ability of ERRα to affect gene expression is controlled by its association with specific coregulators, such as the coactivators PGC-1α and PGC-1β and the corepressor RIP140. Consequently, ERRα activity is regulated by the tissue- and physiologic state-specific signals that regulate levels and activity of PGC-1α/β and RIP140. For example, ERRα is a positive regulator of the TCA cycle gene IDH3A in brown adipose tissue, which expresses high levels of PGC-1α/β, but a negative regulator of the OxPhos gene SDHB in white adipocytes, which express high levels of RIP140 [44,54]. Gene-specific factors, such as the type of ERRE sequence and the proteins binding in the vicinity of the ERRE, may also contribute to the ability of ERRα to interact with PGC-1α/β versus RIP140.

Figure 2.

ERRα regulates genes important for mitochondrial biogenesis and oxidative metabolism. ERRα acts as a downstream effector of PGC-1α and PGC-1β in the regulation of expression of genes with roles in fatty acid oxidation, the TCA cycle, oxidative stress responses, mitochondrial biogenesis and dynamics, and oxidative phosphorylation (OxPhos). It acts both directly on genes encoding mitochondrial structural components and enzymes, as well as indirectly by enhancing expression of other transcriptional factors, such as PPARα, NRF1 and NRF2/GABP, that regulate these pathways.

Figure 3.

ERRα function *in vivo* is important for adaptive metabolic responses under conditions of increased energetic demand. Mice lacking ERRα show compromised responses to stresses imposed by exposure to cold, cardiac overload, and bacterial infection. In all three cases, a decreased capacity for oxidative metabolism leads to reduced fitness [44,46,52]. A role for ERRα in skeletal muscle is supported by findings that ERRα null mice have a reduced capacity for exercise (Villena and Kralli, unpublished data). ERRα may have additional roles in other states, as indicated by the increased expression of the gluconeogenic/glyceroneogenic enzyme PEPCK in livers of fed mice [56].

Table 1

ERR α target genes in metabolism

Metabolic pathway	Gene	Regulated by ERR α in	Direct target in	Promoter study?
Fatty acid oxidation	Acadm (Mcad)	HeLa [24], SAOS2 [26], C2C12 [29], MDA-MB-231 [15], BAT [44], heart [49] HL-1 atrial myocytes [49], soleus muscle [42], BAT [44], heart [52]		Yes [23]
TCA cycle	Cpt1b	MEFs [45], BAT [44]	BAT [44]	–
	Aco2	Macrophages [46]; BAT [44]	BAT [44], macrophages [46]	–
	Idh3a	SAOS2 [26], HepG2 [41,56], macrophages [46]; BAT [44]	BAT [44], macrophages [46]	–
	Sdhb	Macrophages [46]	Macrophages [46]	–
OxPhos	Sdhb	Macrophages [46]	Heart [49], macrophages [46]	–
	Atp5b	SAOS2 [26], HepG2 [41,56], macrophages [46]; liver [56], BAT [44], heart [49], macrophages [46]		Yes [26]
	Atp5 g3	Macrophages [46]	Macrophages [46]	–
	Coq7	Macrophages [46]	Macrophages [46]	–
	Cox8a	Macrophages [46]	Macrophages [46]	–
	Cyts	SAOS2 [26], HepG2 [41,56], MEFs [45], macrophages [46]; BAT [44], heart [52]	BAT [44], heart [49], macrophages [46]	Yes [26,49]
	Ndufs7	Macrophages [46]	Macrophages [46]	–
Mitochondrial transport	Timm13a	Macrophages [46]	Macrophages [46]	–
Mitochondrial dynamics	Slc25a4 (Ant1)	HepG2 [41], heart [52]	Heart [49], macrophages [46]	–
	Mfn2	SAOS2 [35]	SAOS2 [35], HeLa [47]	Yes [47]
Regulator of metabolism	Esrra	C2C12 [29], MDA-MB-231 [15],	Heart [49]	Yes [28,29]
	Ppara	HepG2 [41], BAT [44], heart [52]	L6 myoblasts [42]	Yes [42]
	Gabpa (Nrf2A)	C2C12 [29], FAO hepatoma [29], MEFs [45]	Heart [49], macrophages [46]	Yes [29]
	Nrip1 (Rip140)	3T3-L1 [66]	3T3-L1 [66]	Yes [66]
Lipid transport	Apoa4	Intestine [43]	Caco-2 [43]	Yes [43]
neogenesis	Gluco/Glycero-Pck1 (Pepck) *	H4IIE hepatoma cells [56]; liver [56]	H4IIE [56]	Yes [34,56]

ERR α targets shown here are ones with roles in metabolism, regulated by endogenous ERR α (i.e. genes whose expression is reduced, as determined by quantitative RT-PCR, in cells when ERR α is inhibited by siRNA or the inverse agonist XCT790, cells derived from ERR α null mice, or tissues of ERR α null mice) and directly recognized by ERR α (i.e. direct ERR α targets, as determined by quantitative ChIP). Target genes whose ERRE-containing regulatory regions have been tested for conferring ERR α /PGC-1 regulation to reporter genes in transient transfections are indicated by 'yes' under 'promoter study'. Notably, some targets are regulated by ERR α in a cell-type specific manner. For example, Acadm is not regulated by ERR α in macrophages [46] and Gabpa is not regulated by ERR α in SAOS2 [26] and macrophages [46].

* Pepck is repressed by ERR α (all other targets shown here are activated by ERR α).