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Review

Constitutive activities of estrogen-related receptors: Transcriptional regulation of metabolism by the ERR pathways in health and disease

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ABSTRACT

The estrogen-related receptors (ERRs) comprise a small group of orphan nuclear receptor transcription factors. The ERRα and ERRγ isoforms play a central role in the regulation of metabolic genes and cellular energy metabolism. Although less is known about ERRβ, recent studies have revealed the importance of this isoform in the maintenance of embryonic stem cell pluripotency. Thus, ERRs are essential to many biological processes. The development of several ERR knockout and overexpression models and the application of advanced functional genomics have allowed rapid advancement of our understanding of the physiology regulated by ERR pathways. Moreover, it has enabled us to begin to delineate the distinct programs regulated by ERRα and ERRγ that have overlapping effects on metabolism and growth. The current review primarily focuses on the physiologic roles of ERR isoforms related to their metabolic regulation; therefore, the ERRα and ERRγ are discussed in the greatest detail. We emphasize findings from gain- and loss-of-function models developed to characterize ERR control of skeletal muscle, heart and musculoskeletal physiology. These models have revealed that coordinating metabolic capacity with energy demand is essential for seemingly disparate processes such as muscle differentiation and hypertrophy, innate immune function, thermogenesis, and bone remodeling. Furthermore, the models have revealed that ERRα- and ERRγ-deficiency in mice accelerates progression of pathologic processes and implicates ERRs as etiologic factors in disease. We highlight the human diseases in which ERRs and their downstream metabolic pathways are perturbed, including heart failure and diabetes. While no natural ligand has been identified for any of the ERR isoforms, the potential for using synthetic small molecules to modulate their activity has been demonstrated. Based on our current understanding of their transcriptional mechanisms and physiologic relevance, the ERRs have emerged as potential therapeutic targets for treatment of osteoporosis, muscle atrophy, insulin resistance and heart failure in humans.

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1. Introduction

This review highlights the current understanding of the molecular mechanisms and physiology of the estrogen-related receptor (ERR) family of orphan nuclear receptor transcription factors. Since the discovery of ERRs involvement in metabolic regulation the interest in the field has expanded into areas in which metabolic reprogramming is a fundamental aspect of biology, such as the relationship to growth and differentiation. ERRs are of great interest for their potential involvement in metabolic dysregulation in diseases that will also be discussed. The review will reveal the novel functions of the ERR isoforms emphasizing physiologic studies using novel genetic models and small molecule ligands. The literature related to ERR involvement in cancer, including regulation of tumor and microenvironment metabolism, cell cycle and proliferation, epithelial–mesenchymal transition, and metastatic mechanisms is extensive and deserves an independent review. Indeed, excellent reviews have discussed these topics in depth as well as the chemotherapeutic potential for drugs that target the ERR pathway [1–4]. Therefore, the topic of ERRs and cancer will not be directly covered in this manuscript.

2. The ERR subfamily of constitutively active nuclear receptors: The basics

The superfamily of nuclear receptors (NRs) includes the endocrine receptors that mediate the actions of steroid hormones, thyroid hormones, and the fat-soluble vitamins A and D, as well as a large number of so-called orphan nuclear receptors [5]. The name of "orphan nuclear receptor" indicates that their ligands and/or target genes and physiological functions were initially unknown. With the progress of research, many of the orphan receptors become "adopted" [6] by the discovery and characterization of their ligands and target genes. The estrogen-

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related receptors (ERRs) are among orphan receptors whose physiological ligands remain elusive.

The ERRs were initially discovered using a cDNA library screen to identify novel steroid receptors on the basis of similarity within the DNA binding domain sequence of the human estrogen receptor α (ERα) [7]. Two unique clones found in the kidney and heart cDNA libraries encoded previously unknown proteins with the conserved features of steroid hormone receptors and were designated estrogen-related receptor α (ERRα) and ERR β (ERRβ). Subsequently, the third isoform ERR γ (ERRγ) was identified, first through its linkage with Usher's syndrome locus [8], then functionally by yeast two-hybrid screening using the NR coactivator GRIP1 as the bait [9]. The ERRs comprise the NR3B group, ERRα (NR3B1, *ESRRA* gene), ERRβ (NR3B2, *ESRRB* gene) and ERRγ (NR3B3, *ESRRG* gene), which clusters by structural relatedness with the NR3 subfamily of steroid receptors, including the ERs, progesterone, androgen, mineralocorticoid, and glucocorticoid receptors [10]. Apart from the main isoforms, ERRβ and ERRγ also have several splice variants that show distinct developmental and tissue specific expression patterns, but it is unclear what distinct roles these splice variants play in organs where they are being expressed [11–13]. It became evident early on in their characterization that ERRs, which share only 30–40% homology with ERα in the ligand binding domain, do not bind or respond to endogenous estrogens or their derivatives and were therefore designated as orphan receptors [7,14].

ERRs have structural features typical to NRs as summarized in Fig. 1. These include an activation function (AF)-1 domain, a DNA-binding domain (DBD), a ligand-binding domain (LBD), and an AF-2 domain. The N-terminus contains the AF-1 domain, which confers weak ligand-independent transcriptional activation in most NRs. The ERRβ and ERRγ isoforms share a high degree of structural relatedness overall and notably in the N-terminal region, which is typically poorly conserved even among receptors in the same subfamily/group. In addition, the N-terminal/AF-1 domain of all 3 ERR isoforms contains conserved motifs subject to posttranslational phosphorylation and sumoylation, which regulates transcriptional activity [15,16].

The ERR DBDs contain two highly conserved zinc finger motifs that target the receptor to a specific DNA sequence (TCAAGGTCA) termed ERR response element (ERRE). All three members of the ERR subfamily share an almost identical DBD. It is not surprising then that many genes can be targeted by more than one of the ERR isoforms. Furthermore, it has been shown that ERRs can bind to the ERRE as a monomer, homodimer or as a heterodimer composed of two distinct ERR isoforms [17,18]. The proportion of ERREs within target genes bound by the different ERR complexes is not known, but likely varies by cell type, cellular proliferation and differentiation states and in response to cell stimuli. Distinct ERR complexes will have different gene recognition or transcriptional activity, but the details of these molecular mechanisms remain to be defined. Despite a high degree of amino acid similarity in the DBDs of ERRs and ERα (e.g. hERRα, 68% identity), ERRs do not bind strongly to perfect palindromic ER response elements. However, ERRs have been found to share some target genes with ERα [19–22]. Most commonly ERRs occupy half-sites that are part of a multi-site module that mediates the response to estrogens. Depending on the gene context, ERR and ER may cooperate to support full activation (e.g. lactoferrin) or may antagonize one another's activity (e.g. MAO-B) [21,22]. Finally, the affinity of ERRα for binding to ERREs is affected by the acetylation status of 4 Lys residues in the Zn^{2+} finger and C-terminal extension of the DBD mediated by the acetyltransferase PCAF and deacetylases, HDAC8 and SIRT1. By this mechanism, these cofactors may link metabolic status with the control of ERRα target gene selection [23].

The C-terminal LBD of the ERRs contains a well-conserved AF-2 helix motif that is essential for cofactor interactions. While typical NRs require ligand binding to enable gene activation, ERRs were found to activate transcription without the addition of exogenous ligands. This constitutive activity is due to a conformation adopted by the LBD in the absence of ligand that supports recruitment of NR coactivators, which is key for transcriptional activation by ERR [24,25]. The structure of ERRα and ERRγ LBDs shows that amino acids with bulky side chains occupy the ligand-binding pocket and, in effect, mimic a ligand bound conformation to favor cofactor binding. For instance, the ERRα LBD crystal structure reveals partial occupation of the putative ligand-binding pocket by Phe328 causing the LBD to adopt an agonist conformation that binds a PPARγ coactivator-1α (PGC-1α) peptide [26]. Although the transcriptional activity of the ERRs is not agonist-dependent,

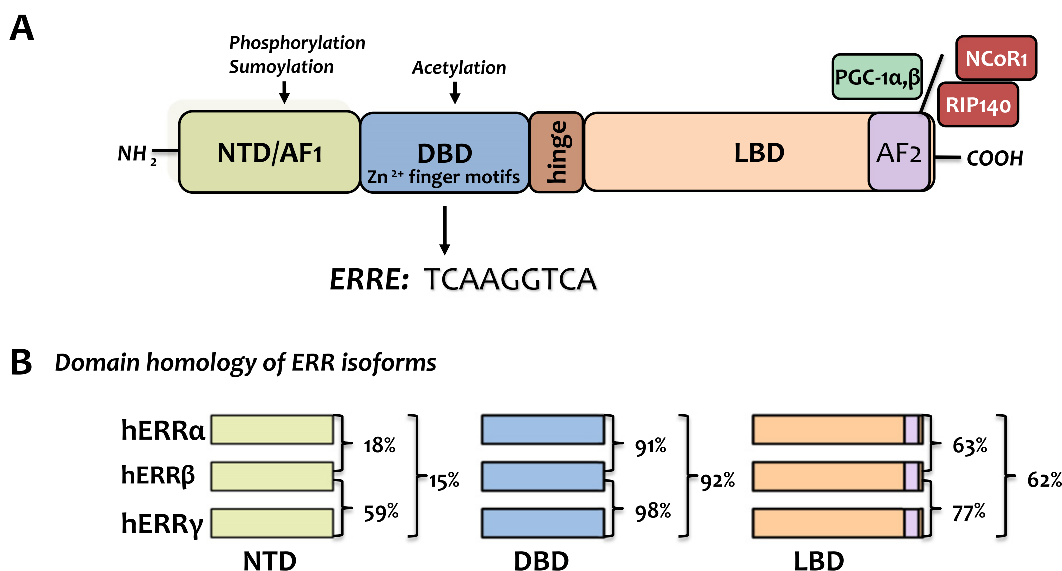

Fig. 1. Structural features and domain homology of Estrogen Related Receptors (ERRs). A: The structural organization of ERRs. The ERR structure is similar to other nuclear receptors (NRs). Each ERR contains an NH2-terminal region that holds a ligand-independent transcriptional activation function (AF-1), which is a subject of various post-translational modifications; a DNA-binding domain (DBD) containing two highly conserved zinc finger motifs; a hinge region that confers the protein flexibility needed for simultaneous receptor dimerization and DNA binding, and a ligand-binding domain (LBD) containing a conserved AF-2 helix motif. The LBD of ERR is responsible for constitutive activity due to its unique conformation that facilitates the recruitment of NR coactivators like PGC1α or corepressors such as RIP140 and NCoR1. B: Domain homology of ERRs isoforms. The three ERRs are almost identical in their DNA binding domains. Although the lowest homology between ERRs isoforms can be found in the N-terminal domain (NTD), the overall degree of structural relatedness is still high, when compared to other members of the NR family within their subfamily/group.

structural analyses revealed the presence of an open ligand-binding pocket ~220 Å^3 in ERRγ and ~100 Å^3 in ERRα that accommodates synthetic molecules to modulate transcriptional activity of ERRs [27–31]. Compound A and XCT790 are specific ERRα inhibitors that have been useful in demonstrating physiologic processes regulated by ERRα in cells and in vivo [32–34]. The synthetic ER modulator, 4-hydroxytamoxifen, and its analogs (e.g. GSK5182), have been identified as inverse agonists of ERRγ; while some phenolic acyl hydrazones are weak selective agonists for ERRγ [35–38]. Bisphenol A (BPA), an important environmental contaminant and endocrine disruptor, was long thought to exert its endocrine effects through binding to ERs. However, BPA binds to ERRγ with much higher affinity than it binds to ER, which may account for its biologic effects at very low concentrations [39,40]. The effects of BPA on zebrafish otolith development are observed at low concentrations comparable to levels of exposure in the environment and requires ERRγ expression, suggesting that ERRγ is the receptor target for this toxicant [41]. Structural analysis of the ERRγ LBD bound to BPA show that the compound stabilizes the transcriptionally active conformation of ERRγ that favors coactivator binding, consistent with BPA antagonism of inverse agonists, like 4-hydroxytamoxifen [39,42,43]. The ability of small molecules to bind with ERRs in an active conformation along with the emerging role for these receptors in metabolism suggests that natural ligands for ERRs likely exist. Regardless, a recent study demonstrating that ERRγ inverse agonists can reduce hepatic glucose production in a mouse model of obesity-related T2D [44] highlights the potential efficacy of ERR modulators in treating human disease and the priority for developing additional drugs that target ERRs.

3. Genomic studies reveal metabolic transcriptome of ERRs

Transcription factors modulate physiological events by regulating genes that control vital processes. Studying gene networks controlled by nuclear receptor activity is traditionally facilitated by the availability of pharmacological agents that activate or inhibit NR activities. Although this research tool is scarce in studying orphan receptors like ERRs, functional and physiological genomics are effective alternatives, which help to uncover the biology of orphan nuclear receptors. A group led by Vincent Giguère at McGill University has made substantial contributions to ERRs biology through their genomics work. Developments and improvements in chromatin immunoprecipitation techniques (ChIP) have led to the high resolution mapping of in vivo functional transcription factors binding sites. Chromosome and genome-wide analyses have shown that the ERR binding sites are more enriched in the promoter regions, whereas ligand bound nuclear receptors, such as ERα, are usually recruited to more distant regions from the gene promoters [45,46]. Although ERRα is able to bind ERα binding sites in ERα-positive and ERα-negative breast cancer cell lines, ERRα and ERα display strict binding site specificity and independent mechanisms of transcriptional activation [47]. Interestingly, although ERRs can compete efficiently for ERα binding sites (EREs) in vitro, ERRα binds specifically to ERREs and the competition for EREs only occurs when it also contains an embedded ERRE in vivo [48].

A ChIP-chip analysis on mouse heart revealed that ERRα and ERRγ occupy the promoter regions of genes involved in fuel sensing, substrate uptake, mitochondrial oxidative pathways, and contractile work. Furthermore, both ERRs can target other metabolic transcription factors and signaling proteins involved in nutrient and energetic signaling in muscle [49]. These were the first genome-wide studies to bring to light the involvement of ERRs in regulating many aspects of mitochondrial metabolism and in transducing metabolic signals to regulate energetic gene programs. Identification of ERRα and ERRγ binding sites and subsequent analysis of their close vicinity also revealed enrichment for binding sites for other transcription factors. Using motif-finding algorithms it was shown that the ERRα binding site neighborhood contains response elements for NRF-1, CREB, and STAT3 in the adult heart [49], suggesting possible functional association and/or direct molecular interaction between ERRs and various transcription factors. For example, ERRα can activate the peroxisome proliferator-activated receptor alpha (PPARα) gene expression via a direct binding of ERRα to the PPARα gene promoter. This contributes in part to the mechanism by which ERRα regulates energy metabolism in cardiac and skeletal muscle [50,51]. ERRs binding to specific DNA regions can also indirectly modify the expression of various genes. In a breast cancer study, it was found that ERRα is being recruited to DNA segments associated with the ERBB2 oncogene amplicon. Such close vicinity recruitment assists the co-binding of the coactivator PGC-1β and recruitment of RNA polymerase II to the ERBB2 gene promoter [45].

ChIP studies are not only useful for the confirmation of ERR target genes discovered previously using different approaches like gene expression analysis or bioinformatic techniques, but also to identify genetic controllers of ERRs. For example homeobox protein prospero-related homeobox 1 (Prox1) inhibits the activity of the ERRα/PGC-1α interacting with ERRα solely through its DNA-binding domain (DBD) [52]. This study also found that ERRα not only binds to genes encoding proteins of the ETC/Oxphos pathway but also to promoter regions within a cluster of genes encoding enzymes at every step in the glycolytic pathway, pyruvate metabolism, and TCA cycle [52].

ChIP-on-chip studies are particularly valuable because they directly demonstrate that many of the physiological changes observed in ERR knockout models are a consequence of direct binding of ERRs to key target genes. For example, disruption of the ERRγ gene blocks the transition from carbohydrate utilization to oxidative metabolism in the postnatal heart. And this effect is directly mediated by ERRγ regulation of a nuclear-encoded mitochondrial genetic network [53]. Using the same physiological genomic methodology, Tremblay and colleagues were able to demonstrate that genetic ablation of ERRα prevents the direct regulation by this orphan receptor of expression of channels involved in renal Na (+) and K (+) handling [54].

4. ERR constitutively interactions with metabolic coregulators

4.1. PGC-1 coactivators

The PGC-1 family of transcriptional coactivators integrates diverse pathways involving numerous NR and non-NR partners to activate mitochondrial biogenesis, fatty acid oxidation, glucose uptake and gluconeogenesis in various tissues [55,56]. A number of laboratories have characterized PGC-1α and PGC-1β as potent coactivators of ERRα and ERRγ [57–59]. Prior to the discovery of ERR/PGC-1 functional complexes, ERRα was implicated to play a role in metabolic regulation in tissues with high energy demands, such as heart and brown adipose (BAT), through regulation of the *Acadm* gene, encoding the mitochondrial β-oxidation enzyme medium chain acyl-CoA dehydrogenase (MCAD) [60,61]. Only with the coexpression of PGC-1α were ERRα and ERRγ able to maximally activate the transcription of *Acadm* and other ERRE-containing target genes [58]. In addition to ERRα, PGC-1α interacts with many other transcription factors, including PPARs, myocyte enhancer factor, nuclear respiratory factors, and FOXO1, to mediate its effects on mitochondrial biogenesis, mitochondrial oxidative pathways, glucose and fatty acid transport, glycolysis and gluconeogenesis [55,62].

Unlike other transcription factors that can complex with PGC-1, the capacity for ERRα to activate metabolic gene transcription appears to be mostly reliant on its interaction with PGC-1 coactivators. ERRα activation of metabolism is observed to occur most robustly where it is coexpressed with PGC-1α or PGC-1β, despite the ability of ERRα to interact with more ubiquitously expressed coactivators, such as the nuclear receptor coactivator (Ncoa) 1, Ncoa2, and Ncoa3 (also known at SRC-1, -2 and -3) as well as the less well understood proline-rich nuclear coactivators 1 and 2 [9,25,63]. Conversely, in some cell types ERRα has been shown to account for much of PGC-1α mediated effects on

mitochondria biogenesis through ERRα binding to the *Gapba* gene, which encodes the α subunit of the nuclear respiratory factor 2 (NRF-2) transcription factor [64,65]. Furthermore, ERRα directs PGC-1α-dependent activation of enzymes participating in most of the mitochondrial oxidative pathways via direct ERRα targeting of nuclear-encoded mitochondrial enzyme genes [49]. PGC-1α exerts regulatory control over ERRα expression through autoregulatory mechanism involving the polymorphic ERR responsive region in the *ESRRA* gene promoter [66]. Likewise, ERRα can regulate PGC-1α expression in skeletal myocytes by direct transactivation of *Ppargc-1a* gene through ERRE sites in the promoter [67,68].

4.2. RIP140 and NCoR1

The nuclear receptor cofactor RIP140 has been shown to have both corepressor and coactivator activities depending on the context of tissue, transcription factor, or gene target [69]. However, in previous studies RIP140 was shown to function exclusively as a corepressor with ERRs with functional implications in skeletal muscle, adipose tissues and heart. Mechanistically, RIP140 repression of ERRγ is target gene specific [70]. RIP140's interaction with ERRγ confers conformational constraints on the ERRγ complex, thereby directly influencing its binding profile and target gene recognition. In adipocytes, RIP140 functions through ERRα to repress genes involved in glucose uptake and mitochondrial TCA and respiratory chain, including SDHB and CoxVb [71]. RIP140 knockout mice are lean and resistant to high fat diet induced obesity; thus, they share some phenotypic features with the ERRα −/− mice, which was attributed, in part, to increased oxidative metabolism in white adipose [72]. RIP140 expression in skeletal muscle is low in oxidative myofibers and high in glycolytic fast-twitch fibers, opposite the pattern of ERRα and ERRγ expression. Nevertheless, loss of RIP140 function in knockout mice or by short-hairpin knockdown in myocytes enhances the expression of genes involved in mitochondrial biogenesis, oxidative phosphorylation and fatty acid oxidation (FAO) [73]. Conversely, RIP140 overexpression downregulates the same gene programs, which is partly attributable to the active repression of ERRs. A similar pattern of repression was seen in transgenic mice overexpressing RIP140 in the heart with downregulation of FAO and mitochondrial metabolism via the repression of ERRα or ERRγ [74]. Inhibition of a postnatal switch to oxidative substrate utilization and the resulting metabolic inflexibility results in postnatal hypertrophy, ventricular fibrosis, and reduced fractional shortening. This metabolic phenotype is similar to the post-natal heart metabolic profile of the ERRγ −/− mice [53] that will be discussed below.

Nuclear receptor corepressor 1 (NCoR1) is a ubiquitously expressed corepressor that can interact with a number of transcription factors through its multiple leucine-rich motifs in the carboxy-terminus of the protein [75]. Because NCoR1 lacks histone deacetylase activity, the complex mediates transcriptional repression through recruitment of additional complex proteins, including the histone deacetylase HDAC3 [76]. NCoR1 is down-regulated in MEFs in response to stimuli that promote fatty acid oxidation, including low glucose and insulin and treatment with exogenous fatty acids. In skeletal muscle NCoR1 expression is reduced by high fat diet, fasting and acute exercise in fast glycolytic and oxidative fiber types in vivo [77]. Muscle-specific deletion of NCoR1 ($NCoR1^{skm-/-}$) increases the percentage of fast-oxidative fibers in muscles comprised of both fast-glycolytic and fast-oxidative myofibers coordinated with increased mitochondrial density and oxidative metabolism. This metabolic and contractile reprogramming results in increased exercise endurance, myofiber force and fatigue resistance. NCoR1 deletion activates a subset of genes perturbed in muscle-specific PGC-1α knockout or overexpression models and directly occupies and deacetylates both PPARδ and ERRα/ERRγ target genes [77,78]. Interestingly, de-repression of mitochondrial TCA and electron transport/Oxphos genes in the NCoR1 −/− muscles can be achieved through the use of ERRα inverse agonists, suggesting that NCoR1 mediates repression in complex with ERRs. The current model favors the involvement of PGC-1α and NCoR1 as common cofactors for ERRα that confer opposing effects on the transcriptional activity of metabolic genes [78].

5. Expression patterns of ERRα and ERRγ and regulation of their expression under physiologic and pathologic conditions

5.1. Tissue distribution

Transcript profiling in mice has shown that ERRα is present in all tissues while ERRγ and ERRβ are widely expressed except that ERRβ is absent in the immune system and ERRβ and ERRγ are not detected in adult bone and skin [79]. ERRα and ERRγ expression is enriched in adult tissues that rely primarily on mitochondrial oxidative metabolism for ATP production, including heart, skeletal muscle, kidney and brown adipose tissue [12,50,58,60,61]. In situ hybridization in mouse embryos shows ERRα expression in the primitive heart at e8.5, in all regions of the heart at e10.5, and in the premuscular mass at e13.5 [80]. ERRγ is also expressed in fetal heart and skeletal muscle of mice and humans [12]. In the post-natal heart, ERRα expression dramatically increases in parallel with FAO enzyme genes coincident with the onset of oxidative metabolism [58,60]. ERRα and ERRγ are expressed in adult skeletal muscle but at much higher levels in postural muscles enriched with slow oxidative ("slow-twitch") myofibers compared to sprint muscles that are comprised predominantly of fast glycolytic ("fast-twitch") myofibers [50,81].

5.2. Regulation of ERR activity and expression by nutrient, energetic and growth signals

Consistent with their role in metabolism, ERRα and ERRγ expression and activity are highly regulated during development and in response to changes in nutrient and energy demands. In adult tissues, ERR isoforms are up-regulated by stimuli that increase overall tissue oxidative capacity or fatty acid utilization. In rodent models, we and others have observed that short-term and endurance exercise causes robust induction of ERRα and ERRγ transcripts in skeletal muscles comprised of fast-twitch glycolytic and fast-oxidative myofibers [82]. ERRα expression is also induced in human skeletal muscle by exercise [83]. Cold exposure upregulates ERRα expression in skeletal muscle as well as in brown adipose tissue of mice [59]. We have observed that cardiac ERRα expression is increased in models of cardiac lipid dysregulation, including streptozotocin-induced diabetes and in mice treated with etomoxir, which increases intracellular fatty acid concentrations by inhibiting muscle-carnitine palmitoyltransferase I (M-CPT I), a rate-limiting enzyme for transport of FA into mitochondria (Huss, unpublished observations).

The ERR-PGC-1α complex response to nutrient, hormonal, and energetic changes are mediated by numerous signal transduction pathways. Thus, ERRs contribute to a complex transcriptional network that transduces these signals to regulate broad metabolic gene programs in order to maintain energetic and substrate homeostasis. The activity and expression of PGC-1α are subject to regulation by multiple signaling pathways including AMPK, SIRT1, MAP kinases, β-AR/cAMP/PKA [84,85]. The involvement of ERRα and/or ERRγ as primary mediators of transcriptional effects downstream of PGC-1α regulation by many of these pathways has yet to be determined.

ERRα and ERRγ are also subjected to post-translational modifications, including phosphorylation, sumoylation, and acetylation, that affect the receptor's DNA binding and recruitment of coactivators [15,16,23,86]. However, the physiologic, nutrient and hormonal contexts in which these post-translational modifications occur and their relevance to effects on cellular metabolism have not been fully explored. Using the ERRα −/− mice, the activation of angiogenic factors by β-adrenergic receptor signaling and exercise-induced angiogenesis was

shown to be dependent on ERRα in skeletal muscle [87]. ERRα also mediates the cAMP/PKA dependent developmental and hormonal regulation of genes with specialized functions, such as surfactant protein-A in fetal type II lung cells [88]. Repression of ERRγ in liver by insulin is mediated via direct Akt phosphorylation, which triggers ERRγ translocation to the cytoplasm [89]. Counterregulation by glucagon/cAMP/PKA occurs by direct transcriptional activation of *Esrrg* gene by the cAMP response element-binding protein (CREB) and its coactivator CRTC2 [90]. In addition to coactivation by PGC-1α, ERRα expression is regulated by PGC-1α through an autoregulatory mechanism involving a multi-ERRE region within the human *ESRRA* promoter [66,91]. As might be predicted, the same region also binds ERRγ and mediates cross-regulation between the two factors [91]. This isoform cross-talk has not been thoroughly investigated but is likely to have physiologic relevance in skeletal muscle, heart and liver where they have known overlapping targets.

The mammalian target of rapamycin (mTOR) complex 1 is recognized as the central cellular pathway by which nutrients, growth factors, and energy sensing pathways are integrated to coordinate the downstream effectors protein and lipid biosynthesis, autophagy, cell cycle and transcription pathways [92,93]. A recent study by the Giguère laboratory provides evidence that the ERR transcriptional pathway links cellular energetics with the mTOR pathway [94]. Genome-wide ChIP-seq analysis revealed that mTOR bound to polymerase II-transcribed genes from several molecular/biological function classes, including the ubiquitination pathway, insulin signaling, and mitochondrial oxidation pathways. ERRα and mTOR have significant overlap in their target genes, including genes involved in the TCA cycle and lipogenesis, although they do not share the same DNA binding sites. Simultaneous ERRα and mTOR inhibition, using rapamycin treatment of ERRα −/− mice, reduces the expression of TCA enzymes in liver. As a result, citrate accumulates and is shuttled into the lipogenic pathway, which is upregulated in ERRα −/− liver, resulting in a fatty liver phenotype. Furthermore, mTOR was shown to regulate ERRα protein degradation through the ubiquitin–proteasomal pathway. Thus, the mTOR–ERRα axis involves both genomic and post-translational crosstalk.

Although these studies were performed in liver, it is possible that the same mechanism may also be functioning in other tissues. In skeletal muscle, activation of mTOR increases, whereas inhibition diminishes muscle oxidative capacity and expression of mitochondrial genes through modulation of PGC-1α, ERRα and NRFs [95]. mTOR regulates PGC-1α activation of candidate mitochondrial genes through its interaction with the transcription factor YY1, but not with ERRα or NRF-1. Although ERRα transcript expression is up-regulated by mTOR activation in myocytes, it is not clear whether mTOR has any direct effect on ERRα protein levels and target gene activation in muscle. The mechanism of ERRα-mTOR crosstalk, proposed by Chaveroux, et al., provides a testable model by which ERRα and ERRγ may coordinate metabolism and growth (proliferation and hypertrophy) in various tissues and in cancer. These findings are also consistent with the role of mTOR to interface with metabolic transcription factors in order to coordinate acute and long-term responses based on cellular growth status.

6. ERR regulation of differentiation and growth

Recent studies by a number of laboratories have demonstrated that ERRs contribute energetic support and play fundamental regulatory roles in growth programs. The involvement of insulin signaling has been extensively studied and the mechanisms are well-established. However, given the energetic requirements for addition of biomass in both proliferating cells and in quiescent cells undergoing hypertrophy, many laboratories have begun to focus on the involvement of metabolic pathways in the control of growth and differentiation. Indeed, mitochondrial biogenesis has been implicated in the regulation of neuronal, erythroblast and myoblast differentiation [96–98]. The major growth signaling program mTOR is subject to regulatory control by AMPK and SIRT to limit growth based on the availability of adequate energy to support cell proliferation or hypertrophic growth. As these signals are also upstream of ERR-PGC-1 pathway, the energy sensing networks coordinate gene programs regulating cellular energetics with cellular growth.

6.1. Regulation of ES cell pluripotency and self-renewal by ERRβ

Several years ago ERRβ was shown to substitute for Klf transcription factors in the transcription factor cocktail, comprising Oct4, Sox2, Klf4, and c-Myc, that can reprogram fibroblasts into pluripotent stem cells [99]. These findings stimulated intense interest in the fundamental role of ERRβ in embryonic stem cell (ESC) function. ERRβ is recognized to be important for growth of extra-embryonic tissues, including the placenta and is expressed in trophoblast stem (TS)-like cells, where it serves as a marker of undifferentiated TS cells [100,101]. In mouse ESCs the core set of pluripotency factors that maintain their undifferentiated state and self-renewal capacity include Oct4, Sox2, and Nanog [102,103]. ERRβ is coexpressed with these core factors in mESCs and occupies the same regulatory regions of target genes [103]. ERRβ expression declines with differentiation and its knockdown in mESCs results in loss of pluripotency [104,105]. Mechanistic studies have demonstrated that ERRβ is regulated by Nanog and can rescue pluripotency and self-renewal phenotype in *Nanog*−/− mESCs [106]. Consistently, ERRβ depletion abolishes leukemia inhibitory factor (LIF)-independent mESC self-renewal, a signature feature of Nanog regulation. ERRβ also directly interacts with Nanog, Oct4, and the nuclear receptor Dax1, another core transcription factor, bound to pluripotency genes as well as their own promoter regions to maintain the stem cell potential [107–111].

ERRβ recruits members of the Ncoa family of p160 coactivators (also known as SRC) to the pluripotency factor complexes and this interaction has been shown to facilitate RNA polymerase II binding to target gene promoters [112,113]. Ncoa3/SRC-3 coactivates ERRβ to regulate key self-renewal genes and is absolutely required for ERRβ to maintain mESC pluripotency and to induce somatic cell reprogramming [112]. Analysis of the mechanism by which ERRβ contributes to maintenance of mESC pluripotency revealed that ERRβ regulates the Dub3 deubiquitylase, which stabilizes Cdc25a to maintain relaxed G1/S checkpoints in pluripotent mESCs [114]. ERRβ upregulates Dub3 expression prior to G1/S transition. Interestingly, in the case of *Dub3* regulation ERRβ selectively recruits Ncoa1, which oscillates with mES cell cycle phase, to mediate a synchronized expression of *Dub3* and other genes [113]. ERRβ may selectively bind different Ncoa isoforms or splice variants in a context dependent manner to regulate pluripotency and self-renewal. Collectively, ERRβ has been established as a bona fide pluripotency factor and may have potential use in regenerative medicine as a target for controlling embryonic stem cell fate.

6.2. Regulation of skeletal myocyte differentiation by ERRs

Mitochondrial biogenesis is an integral component of the myogenesis program [97]. In myogenic models, inhibition of differentiation-associated mitochondrial gene expression or protein synthesis blocks myogenesis [115]. Recent studies have provided evidence that in addition to their importance in mitochondrial metabolism, ERRα and ERRγ may regulate additional programs that are fundamental in myocyte differentiation. The expression profile for ERR isoforms during myogenic differentiation supports distinct but potentially overlapping roles for ERRα and ERRγ in myotube formation and maturation. During differentiation in primary and C2C12 myocyte models, the PGC-1α and ERRα transcripts are coordinately up-regulated shortly after myoblasts exit the cell cycle, which is coincident with the onset of mitochondrial biogenesis [116]. In contrast, ERRγ is expressed in a later phase of myogenesis with peak expression coinciding with myotube maturation [117,118].

Our laboratory has investigated the role of ERRα in coordinating the metabolic and contractile gene programs during myogenesis in culture.

The early transition from proliferating myoblasts to fused, multinucleated myotubes is inhibited in primary myocytes isolated from hindlimbs of ERRα −/− mice. Transient activation of dual specificity phosphatase-1 (Dusp1) is essential for early deactivation of the ERK–MAP kinase pathway to allow transition from proliferating myoblasts and to initiate myotube formation; while in later stages ERK activation promotes myotube hypertrophy. The *Dusp1* gene is an ERRα target gene, so the early myogenic induction of Dusp1 expression and ERK inactivation is perturbed in ERRα −/− myocytes. Mature ERRα −/− myotubes have reduced sarcomeric structure, fewer mitochondria, and reduced fatty acid and glucose oxidative capacity. Growth inhibition is likely due to activation of the energy sensing AMP-dependent protein kinase (AMPK) in the late stage ERRα −/− myotubes, which increases phosphorylation of raptor and reduced mTOR activity (Murray and Huss, unpublished observations). Conversely, adenoviral overexpression of ERRα in C2C12 myoblasts increases mitochondrial biogenesis and causes precocious expression of skeletal muscle sarcomeric proteins, including myosin heavy chain and α2-actinin. Similarly in neonatal rat cardiac myocytes, ERRα overexpression elicits a physiologic growth program characterized by a switch in myosin heavy chain (MHC) isoform expression from the fetal βMHC to the adult αMHC, as well as induction of oxidative metabolic genes [49]. Thus, ERRα plays a complex role in regulating myocyte differentiation involving regulation of mitochondrial energetics and MAP kinase signaling. The associated effect on skeletal muscle regeneration in ERRα-deficient muscles will be discussed in the section addressing in vivo mouse models.

The effects of ERRγ on myocyte differentiation appear to be more closely linked with its role in mitochondrial metabolism. Primary ERRγ −/− myocytes form immature myotubes with reduced mitochondrial content secondary to inhibition of differentiation caused by excess reactive oxygen species production (ROS) [117]. The primary defect is caused by impaired mitochondrial complex I activity associated with a shift from long-chain fatty acid β-oxidation toward preferential oxidation of medium- and short-chain fatty acids in the mitochondria. The resulting ROS production activated FoxO1, FoxO3a and NF-κB and downstream atrophy pathways that targeted contractile proteins for proteasomal degradation.

6.3. Regulation of bone differentiation by ERRs

There is considerable evidence that ERRs have multiple complementary functions in skeletal physiology through the regulation of bone and cartilage formation [119]. Osteoblasts and osteoclasts work in concert to remodel bone during development and to replace bone after injury and in the context of normal bone turnover and maintenance in adults. Osteoblasts are bone forming cells that synthesize and secrete bone matrix proteins and signaling molecules. ERRα directly regulates genes encoding bone matrix proteins, including osteopontin and bone sialoprotein, and ERRα overexpression in primary rat calvarial cells promotes differentiation and expression of these bone-specific proteins [120–123]. Likewise, mesenchymal stem cells (MSC) isolated from the bone marrow of ERRα −/− showed impaired osteoblast differentiation and mineralization [121]. Paradoxically, osteoblasts from ERRα −/− mice have increased expression of osteoblastic markers and calcium deposition [124]. The differences may be due to the distinct models and differentiation stages evaluated or due to the potential contribution of ERRγ, which has been shown to negatively regulate BMP-2-induced osteoblast differentiation in vivo [125]. A recent study by the Vanacker group sheds light on the differential roles for ERRα in osteoblast lineage determination versus maturation [126]. In the whole body ERRα knockout, female mice are resistant to bone loss with aging and ovariectomy [127]. However, conditional Cola-Cre:ERRα$^{lox/lox}$ mice, in which ERRα expression is disrupted after early osteoblast lineage determination, show aging related loss of bone density similar to control mice. In contrast Cola-Cre:ERRα$^{lox/lox}$ are resistant to bone loss with ovariectomy. Thus, ERRα repressive effects on late osteoblast maturation are involved in bone loss induced by estrogen deficiency.

The counterpart to osteoblasts in bone remodeling, osteoclasts are specialized in bone resorption and have high energetic demand supplied by abundant mitochondria. Mitochondrial biogenesis is an integral component of the osteoclast differentiation program. Based on evidence from knockout models, ERRα and PGC-1β are essential for normal osteoclastogenesis through regulation of mitochondrial biogenesis and oxidation [128,129]. Impaired osteoclastogenesis in bone marrow derived MSCs from ERRα −/− mice is associated with a complete disruption of differentiation dependent induction of metabolic genes involved in fatty acid oxidation, TCA cycle and electron transport [129]. These results demonstrate a cell autonomous reliance of osteoclast differentiation on ERRα signaling. In vivo, ERRα −/− mice have a reduced number of osteoclasts in bone resulting in increased bone density due to the defect in bone resorption [129]. Similarly, PGC-1β −/− mice have abnormal osteoclasts (no decrease in number) with impaired bone resorbing activity [128]. Based on these observations, it was proposed that ERRs may also contribute to pathologic bone remodeling in aging and in the context of disease [130].

7. Linking gene regulation to function: analysis of ERR gain and loss-of-function models

The role of ERRs in regulating metabolic gene programs has been examined in several global and tissue-specific knockouts and overexpressing mice. These mice display phenotypes that support distinct but overlapping roles for ERRs in processes requiring oxidative processes, high energetic demand and changes in substrate utilization.

7.1. Adipose tissue and regulation of obesity/energy balance

In the initial characterization, the ERRα −/− mice were reported to have reduced adiposity and resistance to high-fat diet induced obesity [72]. White adipose tissue (WAT) mass is decreased in ERRα −/− mice coincident with increased FAO enzyme gene expression and decreased adipocyte size and lipid synthesis rates. Paradoxically, overall energy balance is the same or reduced in the mice since food consumption is unchanged and 24 h locomotor activity (i.e. voluntary wheel running) is actually lower [72,131]. Increased oxidation in WAT may contribute to the resistance to diet-induced obesity and insulin resistance observed in ERRα −/− mice. An additional mechanism of protection against diet-induced obesity in ERRα −/− mice may also involve downregulation of intestinal apolipoprotein A-IV and reduced dietary lipid absorption [132].

The impact of ERRα deficiency has been most dramatic in highly oxidative tissues that feature elevated ERRα expression, such as brown adipose tissue (BAT), activated macrophages, heart and skeletal muscle. In general, physiologic responses that rely on high mitochondrial reserve capacity or short-term induction of nuclear-encoded mitochondrial enzyme genes are defective or blunted in ERRα −/− mice. BAT is a specialized tissue involved in thermogenesis, which is stimulated by cold exposure and activation of β-adrenergic signaling. Activation stimulates uncoupled respiration in the mitochondria of BAT in part through induction of uncoupling protein 1 (UCP1), resulting in generation of heat to maintain core body temperature. ERRα −/− mice have lower mitochondrial density and reduced expression of mitochondrial FAO and respiratory chain enzyme genes but maintain UCP1 induction in response to β-adrenergic stimulation. Rather UCP1 is regulated by an ERRα-independent mechanism involving ERRγ (or ERRβ) activated by p38 MAPK downstream of the novel thermogenic factor, growth arrest and DNA-damage-inducible protein 45 gamma (GADD45g) [133]. Thus, impaired thermogenesis observed in the ERRα −/− is due to a primary defect in BAT mitochondrial metabolic reserve [134].

The physiologic role of ERRβ has been elusive and difficult to study since homozygous deletion of the *Esrrb* gene results in impaired

placental formation and death at 9.5–10.5 d.p.c. [100]. Recently two viable conditional ERRβ −/− mouse models were generated, one driving deletion in embryo and the other in the CNS. While these knockouts do not target the adipose tissue, they reveal a function for ERRβ in hypothalamic regulation of feeding behavior, satiety, whole body energy balance [135]. In the studies by Byerly and colleagues, the Sox2-Cre:ERRβ$^{lox/lox}$ mice in which ERRβ was knocked out in the developing embryo are lean with increased activity and basal metabolic rate. Despite this change in body composition, the mice consumed more food consistent with increased hypothalamic expression of neuropeptide Y (NPY) and agouti-related peptide (Agrp), neuropeptides that regulate feeding and energy expenditure. These results suggest that the phenotype originates in the CNS.

To test this notion the Nestin-Cre:ERRβ$^{lox/lox}$ mice the *Esrrb* gene was selectively disrupted in the developing nervous system. ERRβ expression is eliminated in neurons within the hindbrain, the CNS region with the highest ERRβ expression. Loss of ERRβ results in an increased lean:adipose mass ratio and increased energy expenditure despite increased feeding frequency. The feeding behavior is dissociated from NPY expression, which is reduced in Nestin-Cre:ERRβ$^{lox/lox}$ mice. Both of the ERRβ deficient mouse strains show a preference for carbohydrate metabolism as demonstrated by a higher respiratory exchange ratio and have enhanced insulin sensitivity. Interestingly, ERRγ expression was increased in both ERRβ −/− models, suggesting that some of the metabolic changes may be driven by ERRγ activation. Indeed, pharmacologic activation of ERRγ in the presence or absence of ERRβ reduced NPY expression, decreased satiety and increased feeding frequency [135]. The association between feeding behavior and NPY expression is complex, so the changes in NPY expression in these models may be secondary to altered glucose metabolism with enhanced insulin sensitivity or to changes in stress hormone (i.e. corticosterone) levels [136]. The counter-regulatory pattern of ERRβ and ERRγ has significant implications for the mechanism by which ERRs regulate CNS effects on whole body energy balance. The ERRβ and ERRγ homodimers may simply regulate expression of overlapping target genes, and ERRγ upregulation drives the observed gene expression changes in ERRβ null mice. Alternately, ERRβ:ERRγ heterodimers may be involved in differential regulation of target genes when their relative expression levels change. Thus, the expression ratio between ERRβ and ERRγ may be an important graded mechanism to modulate feeding behavior by altering the expression of genes that control satiety and whole-body energy balance.

7.2. Immune response

Activation of macrophages in the innate immune response triggers induction of mitochondrial electron transport enzymes and release of ROS to destroy phagocytosed pathogens. ERRα-deficient macrophages have impaired ROS production in response to INF-γ, associated with increased mortality in ERRα −/− in response to pathogen infection [137]. INF-γ mediated induction of mitochondrial gene expression is dependent on the ERRα-PGC-1β complex that is directly activated by the JAK–STAT1 pathway. The intracellular anti-oxidant defense includes enzymes localized either to the cytoplasm or mitochondria enabling metabolism of ROS at the site of production. ERRα −/− MEFs show reduced expression of mitochondrial antioxidant enzymes, superoxide dismutase 2, thioredoxin 2 and peroxiredoxins 3 and 5. Furthermore, PGC-1α-dependent regulation of the mitochondrial biogenesis and component metabolic enzymes is lost in ERRα −/− MEFs [138].

ERRγ has also been shown to control macrophage function indirectly through regulation of intracellular iron. In response to microbial infection hepatic expression of the hormone hepcidin is upregulated by ERRγ downstream on IL-6 signaling [139]. Hepcidin is the primary regulator of systemic iron homeostasis, controlling absorption in the gut and iron mobilization from liver stores [140]. During inflammation, hepcidin promotes cellular iron retention by interacting with the iron export protein ferroportin, resulting in increased macrophage intracellular iron and hypoferremia in the host. The increase in intracellular iron in macrophages in response to infection enhances growth of intracellular microbes, including *Salmonella* and *Legionella*. Treatment of mice with the ERRγ inverse agonist GSK5182 is able to blunt hepatic hepcidin expression in response to *Salmonella typhimurium* infection [139]. ERRγ inhibition also rescues hypoferremia, reduces microbial growth and improves survival of the infected mice. Based on the findings to date, ERRα and ERRγ isoforms have divergent effects on macrophage function.

Lymphocyte metabolic reprogramming is a fundamental component of T cell activation. ERRα has been shown to regulate genes involved in lymphocyte metabolism and activation [141]. Effector T cells (Teff) mainly utilize glucose; whereas Treg cells rely on mitochondrial oxidation of lipids as a source for ATP generation. Teff cell activation is accompanied by a metabolic reprogramming that favors aerobic glycolysis to support cell proliferation. ERRα protein is upregulated in response to Teff cell activation and ERRα transcriptional activity is required for maximal induction of genes involved in glucose and mitochondrial metabolism during activation. In ERRα −/− mice metabolic reprogramming in Teff cells is impaired, thereby reducing proliferation and inflammatory cytokine production in activated Teff cells. Inhibition of ERRα activity, either by treatment with XCT790 or in the ERRα −/− mice reduces mortality in an autoimmune encephalitis model due to modulation of the Teff response. Collectively, these studies support the targeting of ERRα to modulate lymphocyte and macrophage metabolism as an alternate strategy in regulating immune responses.

7.3. Cardiac phenotype

ERRα largely functions as a transcriptional activator in heart and oxidative skeletal muscles to drive oxidative metabolism, consistent with its functional interaction with PGC-1α, which is coexpressed with ERRα in these tissues. Despite overall reduced mass, the heart and skeletal muscles of ERRα −/− mice develop normally. The ERRα −/− hearts have a decreased expression of mitochondrial energetic gene programs [49] and in response to acute stimulation of contractile work, ERRα −/− hearts showed rapid depletion of phosphocreatine and delayed ATP recovery, suggesting a reduced energetic reserve and impaired mitochondrial function [51]. In response to a chronic pressure overload, ERRα −/− hearts exhibited accelerated metabolic decompensation and progression to contractile failure. The ERRα-of-function does not, however, directly regulate the hypertrophic growth response to pressure overload. In fact, ERRα −/− hearts are slightly smaller compared to wild-type, consistent with the role of ERRα in myocyte growth discussed above.

The whole body deletion of ERRγ has a dramatic effect on post-natal survival that is associated with defects in the heart and central nervous system [53]. Characterization of the cardiac phenotype reveals an essential role for ERRγ in post-natal metabolic reprogramming and ion transport in the myocardium. Normally, a switch in metabolic gene expression occurs right after birth to increase myocardial mitochondrial capacity and shift metabolism from reliance on glycolysis to fatty acid oxidation. In ERRγ −/− mice this gene reprogramming is disrupted resulting in reduced myocardial mitochondrial function and lactatemia. The mice also display arrythmogenic defects that are associated with downregulation of voltage-gated potassium transporters, such as *Kcne2*, which are direct ERRγ target genes. The ERRγ −/− mice exhibit dramatic slowing of ventricular depolarization conduction as well and delayed repolarization [53]. Through regulation of the same classes of genes, ERRγ deficiency reduces the expression of parietal cell surface markers in the stomach and impaired renal potassium uptake in the kidney [142]

In contrast, recent studies evaluating the effects of ERRγ gain-of-function in the adult heart reveals that the constitutive overexpression of ERRγ driven by the αMHC (*Myh6*) gene promoter is sufficient to trigger pathologic hypertrophy. In wild-type mice, ERRγ expression is

induced 2 weeks after introduction of the pressure overload, suggesting that ERRγ plays a functional role in the growth response. Indeed, hypertrophy is mediated in part by ERRγ induction of GATA4, an important transcription factor involved in regulating hypertrophic growth and fetal gene reprogramming [143]. Treatment with the ERRγ inverse agonist GSK-5182 blocks the effects of the ERRγ transgene on GATA4 gene expression and cardiac growth [144]. Likewise, GSK-5182 can also block growth, hypertrophic gene reprogramming and fibrosis in the context of pressure overload [144]. Additional studies consistently show that ERRγ is either unchanged or up-regulated early in pathologic hypertrophy but that with progression to heart failure ERRγ levels also decline [51,74,144,145].

A potential role for ERRβ in heart failure and re-activation of the fetal genes during pathologic growth was recently demonstrated during the characterization of a cardiac-enriched microRNA. ERRβ was identified as a direct target of miR-1-1 and miR-1-2, muscle-specific miRNAs that regulate cell proliferation and cardiac function [146]. The miR-1 double knockout (dKO) mice develop dilated cardiomyopathy with profound reduction in LV systolic function and die within 2 weeks of birth. ERRβ was evaluated as the miR-1 target involved in re-expression of the fetal metabolic and contractile program. Overexpression of ERRβ in cardiomyocytes increases expression of glycolytic and glycogen synthesis genes along with fetal isoforms of contractile genes including βMHC. Furthermore, glucose utilization and glycogen accumulation is enhanced in ERRβ expression cardiomyocytes. Cardiac-specific ERRβ transgenic mice develop LV dilatation and die of sudden cardiac death by 1 month of age similar to the miR-1 dKO phenotype. Although based exclusively on overexpression, this study raises the possibility that ERRβ may contribute to fetal gene regulation, mediating repression postnatally during transition to the adult program as well as re-activation of the program with pathologic hypertrophy.

7.4. Liver metabolism

Insulin and glucagon are primary hormones regulating glucose utilization/storage and synthesis in the fed and fasted states, respectively. Generally, in the fasted state cAMP/PKA signaling reduces glucose uptake and glycogen synthesis and stimulates gluconeogenesis and fatty acid β-oxidation. Insulin signaling through the insulin receptor/PI 3-kinase/Akt pathway increases glucose transport and glycogen and fatty acid synthesis. In the liver ERRα, ERRγ and PGC-1α are coordinately upregulated by fasting in normal mice [90,147,148]. ERRα and ERRγ have been shown to bind many of the same target genes involved in mitochondrial oxidative processes and in liver they also occupy the regulatory regions of gluconeogenic genes, including the *Pck1*, encoding the cytosolic Pepck isoform [90,149]. However the effects of ERRα and ERRγ on gene activity and the in vivo physiologic effects observed with selective disruption or overexpression are clearly divergent in liver.

ERRα regulates genes involved in hepatic mitochondrial biogenesis, ETC/Oxphos, glucose metabolism, fatty acid β-oxidation along with other mitochondrial processes in liver [52,150]. ERRα's dynamic regulation of these genes is affected by nutrient and acute and long-term fasting cues (i.e. insulin, glucagon) as well as to molecular clock inputs [131,149,151,152]. Activation of gluconeogenic genes downstream of PGC-1α occurs independent of ERRα and is, in fact, antagonized by ERRα in hepatocytes [149]. Indeed, in ERRα −/− mice Pepck and Glycerol kinase are upregulated in liver, demonstrating ERRα's repressive role in gluconeogenesis under fed conditions. By contrast, ERRα disruption downregulates mitochondrial oxidative genes and other metabolic pathways in liver, and as discussed above predisposes mice to hepatic steatosis [94,131,153]. Thus, despite ERRα mediating PGC-1α regulation of mitochondrial processes in fasted liver, ERRα is dissociated from PGC-1α effects on gluconeogenesis.

ERRγ has been demonstrated to regulate gluconeogenic genes and is responsive to nutrient signaling pathways downstream of fasting and re-feeding cycles analogous to other well-characterized transcription factors involved in this program [44,90]. The *Esrrg* gene is transcriptionally activated by the CREB-CRTC2 complex bound to CRE sites in its promoter. Thus, hepatic ERRγ and PGC-1α expression is coordinately upregulated by the same pathway [154]. ERRγ upregulation occurs after the acute fasting response, so activation of *Pck* and *G6pc* by ERRγ is additive with other gluconeogenic factors regulated post-translationally by cAMP/PKA [90]. Consistent with this mechanism, ERRγ is coactivated by PGC-1α through ERREs on *Pck* and other gluconeogenic genes. Systemically, ERRγ overexpression in the liver induces gluconeogenic genes and increases serum glucose in fasted mice. Thus, ERRγ contributes to hepatic gluconeogenic gene regulation with PGC-1α and its other transcription factor partners, including Foxo1 and HNF4α, to confer tight control downstream of nutrient signals [147,155,156].

The mechanisms that dictate selective regulation of mitochondrial functions over gluconeogenesis by ERRα have not been determined. In ERRα −/− mice the circadian patterns of metabolic genes are deregulated in liver, which may contribute to the derepression of gluconeogenic genes [131]. Furthermore, Pck and Gcpc are coordinately upregulated with ERRγ and PGC-1α at the same point of the diurnal cycle in ERRα deficient liver. PGC-1α activity is regulated by post-translational mechanisms that lead to selective activation/repression of gluconeogenic or mitochondrial genes [157]. In the fed state Akt inhibits PGC-1α activation of all genes, but S6K1 and cdc2-like kinase 2 specifically repress PGC-1α activity on gluconeogenic genes thereby shifting activation toward mitochondrial targets [158,159]. While the mechanisms by which these pathways inhibit PGC-1α coactivation of HNF4α or Foxo1 have been elucidated, whether their effects are mediated through ERRα and/or ERRγ is not fully understood.

7.5. Skeletal muscle

ERRα and ERRγ have overlapping roles in regulating skeletal muscle mitochondrial oxidative programs but analysis of genetic models suggests that the exact mechanisms may be distinct. Although the essential role for ERRα in mitochondrial biogenesis in adult skeletal muscle and during muscle regeneration has been demonstrated [160] (see discussion below), the role of ERRα in regulating muscle adaptations in response to physiologic and pathologic stimuli remains to be characterized using the muscle specific ERRα −/− mice. However, a recent finding using the whole body ERRα −/− strain of mice demonstrated that ERRα was essential for regulating transcriptional programs involved in oxidative metabolism and oxidative stress response. Thus ERRα-deficient mice had reduced basal metabolic oxidative capacity and were hypoactive and exercise intolerant [161].

Consistent with an essential role of ERRγ in directing the baseline metabolic program in skeletal muscle, ERRγ heterozygous mice (ERRγ+/−) have reduced mitochondrial function and expression of FAO enzyme genes in mixed fiber type muscles [81]. These metabolic changes result in reduced exercise performance and peak VO_{2max} in exhaustion trials. In our muscle-specific ERRγ −/− model, we observe increased ROS generation in the mitochondria that is associated with reduced ETC complex I activity [117]. We observed a defect in myogenesis in the same model but no baseline changes in mitochondrial number or citrate synthase activity, a marker of tissue mitochondrial capacity [117] (Huss, manuscript in preparation). Although ERRγ is induced in response to exercise in mouse models, whether ERRγ is necessary for the adaptive metabolic response to endurance exercise training in muscle is currently unknown. However, genetic activation of the ERRγ pathway in skeletal muscle, by overexpressing either wild-type ERRγ or an ERRγ-VP16 fusion, mimics some of the metabolic effects of endurance training, such as enhanced mitochondrial content and respiration, an increase in the proportion of fast-oxidative fibers, and angiogenesis. ERRγ overexpression enhances mitochondrial oxidation and drives a shift from type IIb to IIa myofibers in fast-twitch glycolytic

muscles, while slow-oxidative muscles show little response to ERRγ activation [81,162]. Activation of the oxidative myofiber program is accompanied by increased arterial density and blood flow at baseline [162]. As a result the ERRγ overexpressing muscles reperfuse more quickly after an ischemic event and are resistant to ischemic muscle damage [163]. Angiogenesis is stimulated in these muscles by upregulation of angiogenic gene programs, including Vegf, Fgf, and Ephrin A, independent of O_2 tension. While the enhanced angiogenesis may be secondary to ERRγ effects on oxidation, both ERRα and ERRγ are reported to directly regulate the *Vegfa* gene promoter through a conserved ERRE site, suggesting that ERRs may play a primary role in angiogenesis [87,162].

ERRs also affect skeletal muscle regeneration. Skeletal muscle regeneration in vivo is accompanied by mitochondrial biogenesis in order to match mitochondrial capacity with the energetic demands of growth as well as contractile activity of newly formed myofibers [164,165]. In injury-induced regeneration models, mitochondrial enzyme gene induction parallels the onset of differentiation within a myoblast pool derived from muscle precursor cells located in the basal lamina of muscle. Upregulation of ERRα and PGC-1 isoforms occurs at the onset of myogenesis in regenerating muscle [164,166,167]. Mouse models in which metabolic regulatory pathways are deficient or constitutively activated, including PGC-1α, calcineurin, and AMPK; exhibit coordinated changes to alter myopathy or regeneration phenotypes in concert with effects on mitochondrial function in skeletal muscle [168–172].

We have used a muscle-specific ERRα knockout model (M-ERRα −/−) to determine the role of ERRα in normal skeletal muscle regeneration and in directing the metabolic and fiber type profile of repaired myofibers. Although the metabolic phenotype of M-ERRα −/− mice has yet to be fully characterized, we observed reduced mitochondrial oxidative capacity in slow- and fast-twitch oxidative muscles, and a shift in substrate selection in muscle in M-ERRα −/− mice. Mitochondrial biogenesis and mitochondrial metabolic functional enhancement in response to physiologic and metabolic stimuli, including high fat diet and exercise, is blunted in these mice (McDonald and Huss, manuscript in progress). As mitochondrial biogenesis is required for myoblast differentiation and essential for efficient muscle regeneration, the M-ERRα −/− mice exhibit a dramatic defect in muscle repair in response to injury [160]. The levels of mitochondrial biogenesis factors, mtTFA, NRF-2a and PGC-1β are down-regulated in M-ERRα −/− muscles at the onset of myogenesis. Reduced mitochondrial energetic capacity in the context of growth stimulation results in ATP depletion and activation of the energy-sensing kinase AMP-activated kinase (AMPK). Even with an adequate energy supply, AMPK activation (i.e. genetic or pharmacologic activation) is sufficient to inhibit growth in cardiac and skeletal myocytes [173–176]. In the injury model we demonstrated that pharmacologic AMPK activation post-injury delayed muscle regeneration [160]. Importantly, ERRα expression is regulated by the AMPK pathway through induction of the *ESRRA* promoter, suggesting that ERRα controls gene regulation downstream of the AMPK pathway activation in many adaptive contexts (i.e. exercise, hypoxia, fasting). Collectively, the phenotypic difference among the ERR mouse models highlights the physiologic relevance of distinct programs regulated by ERRα and ERRγ that confer overlapping and complementary effects on metabolism and growth.

8. Dysregulation of the ERR transcriptional axis and association with disease etiology and pathology

8.1. Heart failure

In response to pressure overload the heart undergoes a compensated hypertrophy associated with metabolic and contractile reprogramming to maintain systolic function. With sustained stress the response progresses to a decompensated stage, associated with systolic and diastolic dysfunction due, in part, to mitochondrial dysfunction and energetic insufficiency [177]. ERRα expression is specifically down-regulated in a mouse model of pressure overload-induced left ventricular hypertrophy and the ERRα −/− mice progress more rapidly to heart failure in this model [51]. Thus, while ERRα deactivation promotes metabolic reprogramming during compensated hypertrophy, residual ERRα activity slows the rate at which mitochondria energetic capacity and contractile function declines. Subsequent studies have supported this hypothesis. Expression of ERRα and/or its PGC-1 coactivators is reduced in various rodent models of heart failure, including decompensated right ventricular hypertrophy and myocardial infarction models as well as in genetic models that display accelerated heart failure [74,145,178–180]. Likewise, PGC-1α −/− and PGC-1β −/− mice show accelerated heart failure in response to pressure overload, accompanied by an altered expression of metabolic genes corresponding to known ERR targets [181,182]. Importantly, ERRα and its target genes are down-regulated in human hearts with chronic congestive heart failure and in ischemic and idiopathic end stage failure [183]. Microarray gene expression profiles have demonstrated that alterations in ERRα target gene expression strongly correlate with LV ejection fraction and thus, are predictive for failing versus non-failing phenotypes in patient samples [184]. Thus, there is strong evidence for the involvement of ERRs in heart failure progression and therefore the potential that drugs targeting these pathways may provide a strategy to slow or prevent progression of heart failure.

The mechanisms that drive downregulation of the ERRα-PGC-1α regulatory axis in heart failure are not fully understood. It has been linked to upregulation of metabolic coactivators, including RIP140 and SIRT1, as well as microRNAs in the context of pathologic hypertrophy [74,178,185]. For example, a recent study demonstrated that cardiac-specific overexpression of microRNA-22, which targets PGC-1α, results in a hypertrophic cardiomyopathy and is accompanied by downregulation of ERRα and its target genes [186]. Direct inhibition of ERRα expression and transactivation may be mediated by SIRT1 and PPARα, which are up-regulated in some forms of hypertrophy. A SIRT1–PPARα complex was able to displace ERRα binding to ERRE sites and to repress genes involved in mitochondrial energy generation [187].

Insulin resistance in type 2 diabetes is a major risk factor for heart failure due to the metabolic and functional alterations in the diabetic heart, unrelated to the independent risk factors of hypertension and coronary artery disease. The pathogenesis of diabetic cardiomyopathy is related to myocardial triglyceride accumulation, increased β-oxidation and impaired glucose utilization [188]. In the insulin resistant heart PPARα activation by fatty acids, PGC-1α stimulation by AMPK, and impaired insulin signaling contribute to the metabolic profile.

A genome-wide association study identified genetic variants within the human *PPARA* gene promoter associated with mortality after acute coronary ischemia in diabetic patients [189]. Functional analysis showed reduced ERRα binding and transactivation of the protective *PPARA* promoter variant. The results of this study suggest that ERRα inhibition may confer some protection in the diabetic heart. The role of ERRα on metabolic gene programs and disease progression is likely to be distinct in diabetic cardiomyopathy compared to hypertrophy-associated heart failure. However, additional expression studies in patients and direct functional analysis using cardiac-specific ERRα-deficient models must be performed to understand how ERRα affects diabetic cardiomyopathy. Nevertheless, there is great interest in the potential for GWAS to reveal disease relevant variations in metabolic nuclear receptors and cofactors, including the ERRs, PPARs, and PGC-1, to allow the development of personalized approaches in treating diabetic cardiomyopathy as well as hypertrophy related heart failure [190].

8.2. Muscular dystrophies

Given the importance of ERRα and ERRγ pathways in myocyte differentiation and of ERRα in muscle regeneration, future studies should

address the involvement and the therapeutic potential of ERRs in mitochondrial and dystrophin-related myopathies. ERRα and ERRγ are down-regulated in human muscular dystrophy and in the dystrophin-deficient (*mdx*) mouse model of Duchenne's muscular dystrophy [191, 192]. Indeed, a recent study showed that skeletal muscle-specific ERRγ overexpression in the *mdx* mice blunted exercise-mediated muscle damage [192]. ERRγ overexpression enhanced mitochondrial oxidative capacity and activated angiogenesis factors, including Vegf and Hgf to increase blood flow in the *mdx* muscles. Slow oxidative fibers are more resistant to the contraction-induced damage in dystrophin-deficient models. Consistently, ERRγ overexpression, which increases proportion of type I fibers, protected against basal and post-exercise damage in the *mdx* mice [162,192]. In agreement, long-term pharmacologic activation of the AMPK pathway reversed mitochondrial dysfunction in *mdx* mice and increased the oxidative fiber number leading to improved sarcolemmal structural integrity and resistance to exercise-mediated damage [193,194]. The adaptive metabolic changes downstream of AMPK are mediated by activation and up-regulation of PGC-1α and ERRα [194]. We demonstrated that AICAR treatment increases ERRα expression and transcriptional activity in skeletal muscle, consistent with the notion that ERRs could be therapeutically targeted in the treatment of myopathies [160]. Oxidative myofibers are resistant to mechanical damage, have increased satellite cell populations, and are richly vascularized by virtue of their high expression of angiogenic factors, all of which contribute to resistance to muscle damage or accelerated repair. Thus, interventions that target gene programs that regulate the oxidative phenotype in muscles could provide an alterative strategy to prevent muscle loss in disease and aging.

8.3. Insulin resistance and type 2 diabetes

Type 2 diabetes is a complex disease that develops over a long period of time during which tissues become insulin resistant asynchronously and impose a progressive burden on the pancreas to produce and secrete higher amounts of insulin. The tissues of greatest importance in this process are the liver and skeletal muscle because they have the greatest impact on whole body glucose homeostasis. Modulation of ERRα or ERRγ activity either by genetic or pharmacologic means is shown to affect glucose tolerance and insulin resistance.

8.3.1. Hepatic insulin resistance

ERRα has the greatest influence on hepatic mitochondrial biogenesis and function and, therefore, susceptibility to mitochondrial dysfunction and oxidative stress with diet induced obesity. ERRα −/− mice are resistant to obesity on a high fat diet. Despite ERRα repression of gluconeogenic genes in liver, serum glucose levels are not elevated in ERRα −/− mice. Indeed, mice fed normal chow have reduced serum glucose and insulin, dependent on diurnal phase, which suggests improved insulin sensitivity [72,131]. Likewise, treatment of mice fed a high fat diet with the ERRα inverse agonist C29 prevents hyperlipidemia and improves insulin sensitivity compared to untreated DIO mice [195]. These protective effects are observed despite no difference in weight gain or adipose accumulation on the high fat diet. Remarkably, C29 exerts similar improvements in glucose tolerance and insulin sensitivity as the anti-diabetic drug rosiglitazone in Zucker diabetic fatty rats. The C29 effects correlate with altered hepatic expression of fatty acid metabolism and β-oxidation genes and mimic the pattern of transcript changes seen in ERRα −/− mice fed a high fat diet. On the other hand C29 treatment also exacerbates rapamycin-induced fatty liver, similar to the effects of ERRα deletion [94]. Lipid accumulation in the ERRα −/− liver is associated with reduced mitochondrial capacity to completely oxidize fats resulting in a shunting of citrate and acetyl-CoA to the biosynthesis pathway which is upregulated in rapamycin-treated ERRα −/− mice [94]. Thus, ERRα deficiency likely contributes to the hyperlipidemia and glucose intolerance observed in patients on chronic immunosuppressive therapy and potentially other metabolic effects associated with mTOR dysregulation.

A combination of hepatic insulin resistance, along with elevated serum glucagon that accompanies hyperinsulinemia due to pancreatic islet expansion, contributes to excessive production of glucose by the liver in diabetes. Hepatic ERRγ expression is upregulated in diabetic mouse models by cAMP activation of CREB-CRTC2, while reduced Akt activity allows nuclear localization of the receptor [89,90]. The interaction of ERRγ with the gluconeogenic factors, CREB, HNF4α, and Foxo1, which are key regulators of gluconeogenesis under normal conditions and in diabetes, and its physiologic relevance in the insulin resistant liver are not completely clear. Nevertheless, ERRγ overexpression prolongs glucose excursion time in glucose tolerance tests; while depletion of ERRγ in the liver effectively blunts hyperglycemia in db/db and DIO mice [44,90]. Thus, elevated ERRγ activity in diabetes may contribute to hyperglycemia. Importantly, systemic treatment with the ERRγ inverse agonist GSK5182 also reduces the expression of *Pck* and *G6pc* and significantly lowers fasting serum glucose levels in diabetic mice as effectively as the anti-diabetic drug metformin. Metformin inhibits PGC-1α activation of gluconeogenic genes [196], yet selective targeting of ERRγ has more robust effects. In fact, GSK5182 is more effective at lowering body weight, adipose mass, and hepatic lipid accumulation than metformin [44]. Despite its beneficial effects on metabolism, GSK5182 does not restore hepatic insulin signaling or alter gene expression in peripheral tissue (i.e. skeletal muscle).

ERRγ activation may also indirectly promote liver insulin resistance as a result of its effects on lipid metabolism. ERRγ activation of the *Lpin1* gene in liver causes diacylglycerol (DAG) accumulation, which inhibits insulin receptor signaling through activation of PKCε [197]. The well-characterized mechanism of insulin receptor inhibition involves Ser/Thr phosphorylation of IRS-1 by lipid activated PKC isozymes ϕ and ε that inhibits IRS-1 Tyr phosphorylation and activation of downstream kinases in response to insulin [198–200]. ERRα is also a target for PKCs in cancer cell models. Phosphorylation of ERRα within the DBD by PKCδ or PKCε enhances ERRα transcriptional activity and stimulates mitochondrial function [201]. Mechanistically, phosphorylation by PKCδ promotes binding of ERRα dimers to ERREs and recruitment of PGC-1α [86]. Although this mechanism has not been evaluated in liver, these DAG-dependent PKC isozymes are activated in livers of high fat diet fed and diabetic mice. Thus, it is interesting to speculate on whether PKCε activation by ERRγ shown to inhibit IR signaling might simultaneously regulate gene recognition and activity of ERRα in the liver. Overall, the current evidence suggests the ERRγ regulation of hepatic gluconeogenesis plays a prominent role in glucose homeostasis in normal and diabetic states and offers an attractive target pathway for anti-diabetes drugs.

8.3.2. Skeletal muscle insulin resistance

Insulin resistance in skeletal muscle precedes the onset of type 2 diabetes by many years and is a major risk factor for development of the disease. Increased intramyocellular lipids and lipid intermediates have been shown to inhibit insulin signaling and impair glucose uptake. A widely recognized model for how obesity and physical inactivity lead to insulin resistance involves a mismatch between intracellular lipids, which are in excess with a high fat diet and obesity, and the capacity to completely oxidize these substrates in the mitochondria. Elevated levels of incompletely oxidized lipid intermediates, diacylglycerols, acyl-carnitines and ROS, produced by overloaded mitochondria, have all been cited as the byproducts of the mismatch that lead to insulin resistance [202–204]. An influential study implicating mitochondrial dysfunction as a causative factor in insulin resistance used transcript expression profiling to show that reduced VO_2max in adult diabetics correlated with down-regulation of genes involved in mitochondrial ETC/Oxphos genes in skeletal muscle [205]. The expression of PGC-1α, PGC-1β, and NRFs was shown to be down-regulated in parallel with mitochondrial genes and enzyme activity in the context of obesity, insulin

resistance and type 2 diabetes in humans [64,206,207]. ERRs were implicated to mediate the effects of PGC-1 on metabolic gene expression in the skeletal muscle of diabetics, based on enrichment of ERREs in the promoters of genes discovered in the transcriptional profiling [64]. More importantly, recent ChIP-chip and ChIP-seq profiling definitively show that ERRs directly bind genes involved in all aspects of mitochondrial metabolism and recruits PGC-1 to activate many of these genes. In humans, reduced mitochondrial capacity is seen in the skeletal muscle of patients with frank diabetes. However, this correlation is less consistent in obese and insulin resistant patients or in healthy individuals with a family history of diabetes and may be confounded by effects of sedentary lifestyle and reduced aerobic fitness on skeletal muscle metabolism. Thus, whether mitochondrial dysfunction in skeletal muscle is the predisposing cause or is a concurrent defect that contributes to insulin resistance and the development of type 2 diabetes is still being debated [208]. Nonetheless, it is clear that overlapping mechanisms, including genetic (e.g., heritable genetic/epigenetic metabolic gene variants) and environmental (obesity, sedentary lifestyle) factors work together in various combinations to drive the metabolic defects observed in insulin resistance and type 2 diabetes.

A consistent observation in diabetic rodent models and in humans is that exercise improves insulin sensitivity through increased whole body energy expenditure and metabolic flexibility. As a major site of glucose utilization and a primary target of exercise-mediated metabolic reprogramming, skeletal muscle is responsible for many of the beneficial effects of exercise on systemic metabolism. Aerobic exercise increases basal and maximal O_2 consumption and stimulates glucose uptake in skeletal muscle. These effects result from increased mitochondrial number and oxidative enzyme activity, a shift from glycolytic to oxidative fiber types, greater arterial density and increased expression of glucose transporters driven by coordinated transcriptional pathways. [209]. There is renewed interest in the benefits of resistance exercise, which increases muscle mass and glycolytic capacity in fast-twitch muscles resulting in improved systemic metabolism and glucose homeostasis [210]. Enhanced skeletal muscle mitochondrial content or function in response to aerobic exercise has been shown to promote the complete oxidation of lipids and coupled respiration in the context of obesity, thereby reducing intermediates that inhibit insulin signaling and glucose metabolism [211,212]. PGC-1α and ERRα are up-regulated in response to exercise [83,213], and many signaling pathways regulate PGC-1α in this context, including AMPK, SIRT1, Ca^{2+}/calmodulin kinases, calcineurin, p38 MAP kinases [85,214]. ERRα may be up-regulated via a feed-forward mechanism whereby the ERRα/PGC-1α or ERRγ/PGC-1α complexes activate its expression through ERREs within the *ESRRA* gene promoter [66]. Furthermore, AMPK has been shown to upregulate ERRα via an independent mechanism involving Sp1 sites in the *ESRRA* promoter [183]. Thus, the mechanisms of ERRs regulation by exercise are complex and involve multiple transcription factor and signaling mechanisms. The adaptive metabolic effects of aerobic exercise can be mimicked in transgenic mouse models overexpressing PGC-1α, ERRγ, PPARδ, or Nur77 in skeletal muscle [162,215–218]. Thus, multiple overlapping regulatory programs converge to coordinate metabolic, excitation and contractile functions that respond to varied exercise stimuli. Not surprisingly, recent reports have shown that some nuclear receptors are dispensable for PGC-1α mediated metabolic adaptations [219]. Collectively, these studies support a therapeutic approach of selective targeting of metabolic regulators, such as the ERR pathway, to confer or enhance the metabolic benefits of exercise.

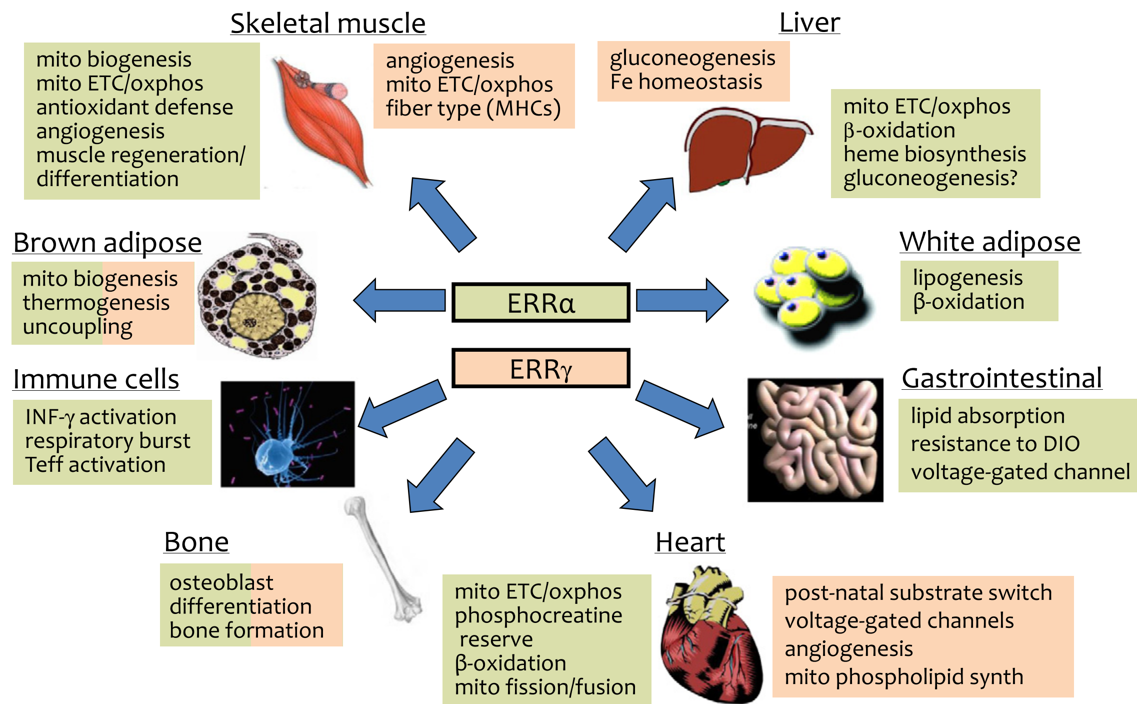

Fig. 2. ERRα and ERRγ functions in health and disease. ERRα and ERRγ regulate multiple aspects of physiology through tissue- and cell-specific effects. In the skeletal muscle, ERRα and ERRγ are expressed primarily in oxidative ("slow-twitch") myofibers, where ERRα regulates mitochondrial biogenesis, muscle regeneration/differentiation and along with ERRγ they modulate oxidative phosphorylation and angiogenesis. In the cardiac tissue, ERRγ plays an essential role in the transition from carbohydrate utilization to oxidative metabolism in the postnatal heart and in regulating voltage-gated potassium transporters. ERRα is also expressed in the heart, playing an important role in this tissue by driving lipid catabolism through regulation of mitochondrial metabolism. In the brown adipose tissue (BAT), ERRα signaling contributes to heat generation and in white adipose (WAT) to lipogenesis. In liver ERRγ predominantly regulates gluconeogenesis in response to fed/fasting cycle under normal conditions and contributes to hyperglycemia in diabetic conditions. ERRα regulates hepatic mitochondrial oxidation and lipid metabolism. Through crosstalk with mTOR, the ERRα pathway contributes to hepatic steatosis seen with rapamycin inhibition of mTOR. ERRα is expressed in epithelial cells of the small intestine and regulates apolipoprotein A-IV contributing to intestinal fat transport, which is a critical step in energy balance. In the immune system, in response to INF-γ, ERRα regulates the availability of reactive oxygen species (ROS) needed to destroy phagocytosed pathogens in activated macrophages, thereby playing a role in INF-γ elicited anti-pathogen defense. ERRα and ERRγ directly regulate genes encoding bone matrix protein in osteoblasts (bone forming cells). Additionally, ERRα is essential for normal osteoclastogenesis (bone resorption) through its regulation of mitochondrial biogenesis and oxidation.

9. Summary and perspectives

As typical members of the orphan receptors, ERRα and ERRγ are transcriptional factors that share functional domains typical to nuclear hormone receptors. In the meantime, ERRs exhibit some unique features such as their constitutive activities. Combined use ERR knockout mice and functional genomic analysis enable us to uncover the transcriptome of ERRs. Phenotypical analyses of the ERR knockout and transgenic mice in conjunction with cell-based studies have revealed the essential roles of ERRα and ERRγ in numerous metabolic pathways as summarized in Fig. 2. The metabolic pathways controlled by ERRs are implicated in physiologic and pathologic conditions. However, a key priority in the field is to delineate the distinct biological roles of ERRα and ERRγ and to characterize the mechanisms by which they mediate specific pathway regulation. Additionally, two critical remaining challenges are to discover the endogenous ERR ligands and to develop synthetic ERR modulators that can selectively target ERR isoforms. The ultimate goal is to use pharmaceuticals to harness the transcriptional benefits of ERRs to prevent and treat human diseases, such as the cardiovascular, muscle, and bone diseases and to reverse the pathologies linked with metabolic syndrome.

Transparency document

The Transparency document associated with this article can be found, in online version.

References

[1] G. Deblois, V. Giguere, Oestrogen-related receptors in breast cancer: control of cellular metabolism and beyond, Nat. Rev. Cancer 13 (2013) 27–36.
[2] G. Deblois, J. St-Pierre, V. Giguere, The PGC-1/ERR signaling axis in cancer, Oncogene 32 (2013) 3483–3490.
[3] F.E. May, Novel drugs that target the estrogen-related receptor alpha: their therapeutic potential in breast cancer, Cancer Manag. Res. 6 (2014) 225–252.
[4] S. Inoue, A. Misawa, Estrogen-related receptors in breast cancer and prostate cancer, Front. Endocrinol. 6 (2015).
[5] R.M. Evans, D.J. Mangelsdorf, Nuclear receptors, RXR, and the Big Bang, Cell 157 (2014) 255–266.
[6] S. Hummasti, P. Tontonoz, Adopting new orphans into the family of metabolic regulators, Mol. Endocrinol. 22 (2008) 1743–1753.
[7] V. Giguere, N. Yang, P. Segui, R.M. Evans, Identification of a new class of steroid hormone receptors, Nature 331 (1988) 91–94.
[8] J.D. Eudy, S. Yao, M.D. Weston, M. Ma-Edmonds, C.B. Talmadge, J.J. Cheng, W.J. Kimberling, J. Sumegi, Isolation of a gene encoding a novel member of the nuclear receptor superfamily from the critical region of Usher syndrome type IIa at 1q41, Genomics 50 (1998) 382–384.
[9] H. Hong, L. Yang, M.R. Stallcup, Hormone-independent transcriptional activation and coactivator binding by novel orphan nuclear receptor ERR3, J. Biol. Chem. 274 (1999) 22618–22626.
[10] C. Nuclear Receptors Nomenclature, A unified nomenclature system for the nuclear receptor superfamily, Cell 97 (1999) 161–163.
[11] F. Chen, Q. Zhang, T. McDonald, M.J. Davidoff, W. Bailey, C. Bai, Q. Liu, C.T. Caskey, Identification of two hERR2-related novel nuclear receptors utilizing bioinformatics and inverse PCR, Gene 228 (1999) 101–109.
[12] D.J. Heard, P.L. Norby, J. Holloway, H. Vissing, Human ERRgamma, a third member of the estrogen receptor-related receptor (ERR) subfamily of orphan nuclear receptors: tissue-specific isoforms are expressed during development and in the adult, Mol. Endocrinol. 14 (2000) 382–392.
[13] A.M. Tremblay, V. Giguere, The NR3B subgroup: an ovERRview, Nucl. Recept. Signal. 5 (2007) e009.
[14] J.P. Lydon, R.F. Power, O.M. Conneely, Differential modes of activation define orphan subclasses within the steroid/thyroid receptor superfamily, Gene Expr. 2 (1992) 273–283.
[15] A.M. Tremblay, B.J. Wilson, X.J. Yang, V. Giguere, Phosphorylation-dependent sumoylation regulates estrogen-related receptor-alpha and -gamma transcriptional activity through a synergy control motif, Mol. Endocrinol. 22 (2008) 570–584.
[16] E.H. Vu, R.J. Kraus, J.E. Mertz, Phosphorylation-dependent sumoylation of estrogen-related receptor alpha1, Biochemistry (Mosc) 46 (2007) 9795–9804.
[17] M.D. Gearhart, S.M. Holmbeck, R.M. Evans, H.J. Dyson, P.E. Wright, Monomeric complex of human orphan estrogen related receptor-2 with DNA: a pseudo-dimer interface mediates extended half-site recognition, J. Mol. Biol. 327 (2003) 819–832.
[18] J. Huppunen, P. Aarnisalo, Dimerization modulates the activity of the orphan nuclear receptor ERRgamma, Biochem. Biophys. Res. Commun. 314 (2004) 964–970.
[19] V. Giguere, The ERR in the estrogen pathway, Trends Endocrinol. Metab. 13 (2002) 220–225.
[20] R.J. Kraus, E.A. Ariazi, M.L. Farrell, J.E. Mertz, Estrogen-related receptor alpha 1 actively antagonizes estrogen receptor-regulated transcription in MCF-7 mammary cells, J. Biol. Chem. 277 (2002) 24826–24834.
[21] N. Yang, H. Shigeta, H. Shi, C.T. Teng, Estrogen-related receptor, hERR1, modulates estrogen receptor-mediated response of human lactoferrin gene promoter, J. Biol. Chem. 271 (1996) 5795–5804.
[22] Z. Zhang, K. Chen, J.C. Shih, C.T. Teng, Estrogen-related receptors-stimulated monoamine oxidase B promoter activity is down-regulated by estrogen receptors, Mol. Endocrinol. 20 (2006) 1547–1561.
[23] B.J. Wilson, A.M. Tremblay, G. Deblois, G. Sylvain-Drolet, V. Giguere, An acetylation switch modulates the transcriptional activity of estrogen-related receptor alpha, Mol. Endocrinol. 24 (2010) 1349–1358.
[24] S. Chen, D. Zhou, C. Yang, M. Sherman, Molecular basis for the constitutive activity of estrogen-related receptor alpha-1, J. Biol. Chem. 276 (2001) 28465–28470.
[25] W. Xie, H. Hong, N.N. Yang, R.J. Lin, C.M. Simon, M.R. Stallcup, R.M. Evans, Constitutive activation of transcription and binding of coactivator by estrogen-related receptors 1 and 2, Mol. Endocrinol. 13 (1999) 2151–2162.
[26] J. Kallen, J.M. Schlaeppi, F. Bitsch, I. Filipuzzi, A. Schilb, V. Riou, A. Graham, A. Strauss, M. Geiser, B. Fournier, Evidence for ligand-independent transcriptional activation of the human estrogen-related receptor alpha (ERRalpha): crystal structure of ERRalpha ligand binding domain in complex with peroxisome proliferator-activated receptor coactivator-1alpha, J. Biol. Chem. 279 (2004) 49330–49337.
[27] H. Greschik, R. Flaig, J.P. Renaud, D. Moras, Structural basis for the deactivation of the estrogen-related receptor gamma by diethylstilbestrol or 4-hydroxytamoxifen and determinants of selectivity, J. Biol. Chem. 279 (2004) 33639–33646.
[28] H. Greschik, J.M. Wurtz, S. Sanglier, W. Bourguet, A. van Dorsselaer, D. Moras, J.P. Renaud, Structural and functional evidence for ligand-independent transcriptional activation by the estrogen-related receptor 3, Mol. Cell 9 (2002) 303–313.
[29] J. Kallen, R. Lattmann, R. Beerli, A. Blechschmidt, M.J. Blommers, M. Geiser, J. Ottl, J.M. Schlaeppi, A. Strauss, B. Fournier, Crystal structure of human estrogen-related receptor alpha in complex with a synthetic inverse agonist reveals its novel molecular mechanism, J. Biol. Chem. 282 (2007) 23231–23239.
[30] L. Wang, W.J. Zuercher, T.G. Consler, M.H. Lambert, A.B. Miller, L.A. Orband-Miller, D.D. McKee, T.M. Willson, R.T. Nolte, X-ray crystal structures of the estrogen-related receptor-gamma ligand binding domain in three functional states reveal the molecular basis of small molecule regulation, J. Biol. Chem. 281 (2006) 37773–37781.
[31] K.S. Jin, J.K. Park, J. Yoon, Y. Rho, J.H. Kim, E.E. Kim, M. Ree, Small-angle X-ray scattering studies on structures of an estrogen-related receptor alpha ligand binding domain and its complexes with ligands and coactivators, J. Phys. Chem. B 112 (2008) 9603–9612.
[32] M.J. Chisamore, M.E. Cunningham, O. Flores, H.A. Wilkinson, J.D. Chen, Characterization of a novel small molecule subtype specific estrogen-related receptor alpha antagonist in MCF-7 breast cancer cells, PLoS One 4 (2009) e5624.
[33] M.J. Chisamore, H.A. Wilkinson, O. Flores, J.D. Chen, Estrogen-related receptor-alpha antagonist inhibits both estrogen receptor-positive and estrogen receptor-negative breast tumor growth in mouse xenografts, Mol. Cancer Ther. 8 (2009) 672–681.
[34] P.J. Willy, I.R. Murray, J. Qian, B.B. Busch, W.C. Stevens Jr., R. Martin, R. Mohan, S. Zhou, P. Ordentlich, P. Wei, D.W. Sapp, R.A. Horlick, R.A. Heyman, I.G. Schulman, Regulation of PPARgamma coactivator 1alpha (PGC-1alpha) signaling by an estrogen-related receptor alpha (ERRalpha) ligand, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 8912–8917.
[35] E.Y. Chao, J.L. Collins, S. Gaillard, A.B. Miller, L. Wang, L.A. Orband-Miller, R.T. Nolte, D.P. McDonnell, T.M. Willson, W.J. Zuercher, Structure-guided synthesis of tamoxifen analogs with improved selectivity for the orphan ERRgamma, Bioorg. Med. Chem. Lett. 16 (2006) 821–824.
[36] P. Coward, D. Lee, M.V. Hull, J.M. Lehmann, 4-Hydroxytamoxifen binds to and deactivates the estrogen-related receptor gamma, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 8880–8884.
[37] W.J. Zuercher, S. Gaillard, L.A. Orband-Miller, E.Y. Chao, B.G. Shearer, D.G. Jones, A.B. Miller, J.L. Collins, D.P. McDonnell, T.M. Willson, Identification and structure–activity relationship of phenolic acyl hydrazones as selective agonists for the estrogen-related orphan nuclear receptors ERRbeta and ERRgamma, J. Med. Chem. 48 (2005) 3107–3109.
[38] D.D. Yu, B.M. Forman, Identification of an agonist ligand for estrogen-related receptors ERRbeta/gamma, Bioorg. Med. Chem. Lett. 15 (2005) 1311–1313.
[39] M.C. Abad, H. Askari, J. O'Neill, A.L. Klinger, C. Milligan, F. Lewandowski, B. Springer, J. Spurlino, D. Rentzeperis, Structural determination of estrogen-related receptor gamma in the presence of phenol derivative compounds, J. Steroid Biochem. Mol. Biol. 108 (2008) 44–54.
[40] S. Takayanagi, T. Tokunaga, X. Liu, H. Okada, A. Matsushima, Y. Shimohigashi, Endocrine disruptor bisphenol A strongly binds to human estrogen-related receptor gamma (ERRgamma) with high constitutive activity, Toxicol. Lett. 167 (2006) 95–105.
[41] M. Tohme, S.M. Prud'homme, A. Boulahtouf, E. Samarut, F. Brunet, L. Bernard, W. Bourguet, Y. Gibert, P. Balaguer, V. Laudet, Estrogen-related receptor gamma is an in vivo receptor of bisphenol A, FASEB J. 28 (2014) 3124–3133.
[42] X. Liu, A. Matsushima, M. Nakamura, T. Costa, T. Nose, Y. Shimohigashi, Fine spatial assembly for construction of the phenol-binding pocket to capture bisphenol A in the human nuclear receptor estrogen-related receptor gamma, J. Biochem. 151 (2012) 403–415.
[43] H. Okada, T. Tokunaga, X. Liu, S. Takayanagi, A. Matsushima, Y. Shimohigashi, Direct evidence revealing structural elements essential for the high binding ability of

bisphenol A to human estrogen-related receptor-gamma, Environ. Health Perspect. 116 (2008) 32–38.
[44] D.K. Kim, G.T. Gang, D. Ryu, M. Koh, Y.N. Kim, S.S. Kim, J. Park, Y.H. Kim, T. Sim, I.K. Lee, C.S. Choi, S.B. Park, C.H. Lee, S.H. Koo, H.S. Choi, Inverse agonist of nuclear receptor ERRgamma mediates antidiabetic effect through inhibition of hepatic gluconeogenesis, Diabetes 62 (2013) 3093–3102.
[45] G. Deblois, G. Chahrour, M.C. Perry, G. Sylvain-Drolet, W.J. Muller, V. Giguere, Transcriptional control of the ERBB2 amplicon by ERRalpha and PGC-1beta promotes mammary gland tumorigenesis, Cancer Res. 70 (2010) 10277–10287.
[46] G. Deblois, V. Giguere, Nuclear receptor location analyses in mammalian genomes: from gene regulation to regulatory networks, Mol. Endocrinol. 22 (2008) 1999–2011.
[47] G. Deblois, J.A. Hall, M.C. Perry, J. Laganiere, M. Ghahremani, M. Park, M. Hallett, V. Giguere, Genome-wide identification of direct target genes implicates estrogen-related receptor alpha as a determinant of breast cancer heterogeneity, Cancer Res. 69 (2009) 6149–6157.
[48] G. Deblois, V. Giguere, Functional and physiological genomics of estrogen-related receptors (ERRs) in health and disease, Biochim. Biophys. Acta 1812 (2011) 1032–1040.
[49] C.R. Dufour, B.J. Wilson, J.M. Huss, D.P. Kelly, W.A. Alaynick, M. Downes, R.M. Evans, M. Blanchette, V. Giguere, Genome-wide orchestration of cardiac functions by the orphan nuclear receptors ERRalpha and gamma, Cell Metab. 5 (2007) 345–356.
[50] J.M. Huss, I.P. Torra, B. Staels, V. Giguere, D.P. Kelly, Estrogen-related receptor alpha directs peroxisome proliferator-activated receptor alpha signaling in the transcriptional control of energy metabolism in cardiac and skeletal muscle, Mol. Cell. Biol. 24 (2004) 9079–9091.
[51] J.M. Huss, K. Imahashi, C.R. Dufour, C.J. Weinheimer, M. Courtois, A. Kovacs, V. Giguere, E. Murphy, D.P. Kelly, The nuclear receptor ERRalpha is required for the bioenergetic and functional adaptation to cardiac pressure overload, Cell Metab. 6 (2007) 25–37.
[52] A. Charest-Marcotte, C.R. Dufour, B.J. Wilson, A.M. Tremblay, L.J. Eichner, D.H. Arlow, V.K. Mootha, V. Giguere, The homeobox protein Prox1 is a negative modulator of ERR{alpha}/PGC-1{alpha} bioenergetic functions, Genes Dev. 24 (2010) 537–542.
[53] W.A. Alaynick, R.P. Kondo, W. Xie, W. He, C.R. Dufour, M. Downes, J.W. Jonker, W. Giles, R.K. Naviaux, V. Giguere, R.M. Evans, ERRgamma directs and maintains the transition to oxidative metabolism in the postnatal heart, Cell Metab. 6 (2007) 13–24.
[54] A.M. Tremblay, C.R. Dufour, M. Ghahremani, T.L. Reudelhuber, V. Giguere, Physiological genomics identifies estrogen-related receptor alpha as a regulator of renal sodium and potassium homeostasis and the renin–angiotensin pathway, Mol. Endocrinol. 24 (2010) 22–32.
[55] B.N. Finck, D.P. Kelly, PGC-1 coactivators: inducible regulators of energy metabolism in health and disease, J. Clin. Invest. 116 (2006) 615–622.
[56] R.C. Scarpulla, Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network, Biochim. Biophys. Acta 1813 (2011) 1269–1278.
[57] Y. Kamei, H. Ohizumi, Y. Fujitani, T. Nemoto, T. Tanaka, N. Takahashi, T. Kawada, M. Miyoshi, O. Ezaki, A. Kakizuka, PPARgamma coactivator 1beta/ERR ligand 1 is an ERR protein ligand, whose expression induces a high-energy expenditure and antagonizes obesity, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 12378–12383.
[58] J.M. Huss, R.P. Kopp, D.P. Kelly, Peroxisome proliferator-activated receptor coactivator-1alpha (PGC-1alpha) coactivates the cardiac-enriched nuclear receptors estrogen-related receptor-alpha and -gamma. Identification of novel leucine-rich interaction motif within PGC-1alpha, J. Biol. Chem. 277 (2002) 40265–40274.
[59] S.N. Schreiber, D. Knutti, K. Brogli, T. Uhlmann, A. Kralli, The transcriptional coactivator PGC-1 regulates the expression and activity of the orphan nuclear receptor estrogen-related receptor alpha (ERRalpha), J. Biol. Chem. 278 (2003) 9013–9018.
[60] R. Sladek, J.A. Bader, V. Giguere, The orphan nuclear receptor estrogen-related receptor alpha is a transcriptional regulator of the human medium-chain acyl coenzyme A dehydrogenase gene, Mol. Cell. Biol. 17 (1997) 5400–5409.
[61] R.B. Vega, D.P. Kelly, A role for estrogen-related receptor alpha in the control of mitochondrial fatty acid beta-oxidation during brown adipocyte differentiation, J. Biol. Chem. 272 (1997) 31693–31699.
[62] J. Lin, C. Handschin, B.M. Spiegelman, Metabolic control through the PGC-1 family of transcription coactivators, Cell Metab. 1 (2005) 361–370.
[63] D. Zhou, S. Chen, PNRC2 is a 16 kDa coactivator that interacts with nuclear receptors through an SH3-binding motif, Nucleic Acids Res. 29 (2001) 3939–3948.
[64] V.K. Mootha, C. Handschin, D. Arlow, X. Xie, J.St. Pierre, S. Sihag, W. Yang, D. Altshuler, P. Puigserver, N. Patterson, P.J. Willy, I.G. Schulman, R.A. Heyman, E.S. Lander, B.M. Spiegelman, Errα and Gabpa/b specify PGC-1α-dependent oxidative phosphorylation gene expression that is altered in diabetic muscle, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 6570–6575.
[65] S.N. Schreiber, R. Emter, M.B. Hock, D. Knutti, J. Cardenas, M. Podvinec, E.J. Oakeley, A. Kralli, The estrogen-related receptor alpha (ERRalpha) functions in PPARgamma coactivator 1alpha (PGC-1alpha)-induced mitochondrial biogenesis, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 6472–6477.
[66] J. Laganiere, G.B. Tremblay, C.R. Dufour, S. Giroux, F. Rousseau, V. Giguere, A polymorphic autoregulatory hormone response element in the human estrogen-related receptor alpha (ERRalpha) promoter dictates peroxisome proliferator-activated receptor gamma coactivator-1alpha control of ERRalpha expression, J. Biol. Chem. 279 (2004) 18504–18510.
[67] Z. Arany, N. Lebrasseur, C. Morris, E. Smith, W. Yang, Y. Ma, S. Chin, B.M. Spiegelman, The transcriptional coactivator PGC-1beta drives the formation of oxidative type IIX fibers in skeletal muscle, Cell Metab. 5 (2007) 35–46.
[68] L. Wang, J. Liu, P. Saha, J. Huang, L. Chan, B. Spiegelman, D.D. Moore, The orphan nuclear receptor SHP regulates PGC-1alpha expression and energy production in brown adipocytes, Cell Metab. 2 (2005) 227–238.
[69] A. Fritah, M. Christian, M.G. Parker, The metabolic coregulator RIP140: an update, Am. J. Physiol. Endocrinol. Metab. 299 (2010) E335–E340.
[70] A. Castet, A. Herledan, S. Bonnet, S. Jalaguier, J.M. Vanacker, V. Cavailles, Receptor-interacting protein 140 differentially regulates estrogen receptor-related receptor transactivation depending on target genes, Mol. Endocrinol. 20 (2006) 1035–1047.
[71] A.M. Powelka, A. Seth, J.V. Virbasius, E. Kiskinis, S.M. Nicoloro, A. Guilherme, X. Tang, J. Straubhaar, A.D. Cherniack, M.G. Parker, M.P. Czech, Suppression of oxidative metabolism and mitochondrial biogenesis by the transcriptional corepressor RIP140 in mouse adipocytes, J. Clin. Invest. 116 (2006) 125–136.
[72] J. Luo, R. Sladek, J. Carrier, J.-A. Bader, D. Richard, V. Giguere, Reduced fat mass in mice lacking orphan nuclear receptor estrogen-related receptor {alpha}, Mol. Cell. Biol. 23 (2003) 7947–7956.
[73] A. Seth, J.H. Steel, D. Nichol, V. Pocock, M.K. Kumaran, A. Fritah, M. Mobberley, T.A. Ryder, A. Rowlerson, J. Scott, M. Poutanen, R. White, M. Parker, The transcriptional corepressor RIP140 regulates oxidative metabolism in skeletal muscle, Cell Metab. 6 (2007) 236–245.
[74] A. Fritah, J.H. Steel, D. Nichol, N. Parker, S. Williams, A. Price, L. Strauss, T.A. Ryder, M.A. Mobberley, M. Poutanen, M. Parker, R. White, Elevated expression of the metabolic regulator receptor-interacting protein 140 results in cardiac hypertrophy and impaired cardiac function, Cardiovasc. Res. 86 (2010) 443–451.
[75] P. Webb, C.M. Anderson, C. Valentine, P. Nguyen, A. Marimuthu, B.L. West, J.D. Baxter, P.J. Kushner, The nuclear receptor corepressor (N-CoR) contains three isoleucine motifs (I/LXXII) that serve as receptor interaction domains (IDs), Mol. Endocrinol. 14 (2000) 1976–1985.
[76] H.G. Yoon, D.W. Chan, Z.Q. Huang, J. Li, J.D. Fondell, J. Qin, J. Wong, Purification and functional characterization of the human N-CoR complex: the roles of HDAC3, TBL1 and TBLR1, EMBO J. 22 (2003) 1336–1346.
[77] H. Yamamoto, E.G. Williams, L. Mouchiroud, C. Canto, W. Fan, M. Downes, C. Heligon, G.D. Barish, B. Desvergne, R.M. Evans, K. Schoonjans, J. Auwerx, NCoR1 is a conserved physiological modulator of muscle mass and oxidative function, Cell 147 (2011) 827–839.
[78] J. Perez-Schindler, S. Summermatter, S. Salatino, F. Zorzato, M. Beer, P.J. Balwierz, E. van Nimwegen, J.N. Feige, J. Auwerx, C. Handschin, The corepressor NCoR1 antagonizes PGC-1alpha and estrogen-related receptor alpha in the regulation of skeletal muscle function and oxidative metabolism, Mol. Cell. Biol. 32 (2012) 4913–4924.
[79] A.L. Bookout, Y. Jeong, M. Downes, R.T. Yu, R.M. Evans, D.J. Mangelsdorf, Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network, Cell 126 (2006) 789–799.
[80] E. Bonnelye, J.M. Vanacker, N. Spruyt, S. Alric, B. Fournier, X. Desbiens, V. Laudet, Expression of the estrogen-related receptor 1 (ERR-1) orphan receptor during mouse development, Mech. Dev. 65 (1997) 71–85.
[81] S.M. Rangwala, X. Wang, J.A. Calvo, L. Lindsley, Y. Zhang, G. Deyneko, V. Beaulieu, J. Gao, G. Turner, J. Markovits, Estrogen-related receptor gamma is a key regulator of muscle mitochondrial activity and oxidative capacity, J. Biol. Chem. 285 (2010) 22619–22629.
[82] A.R. Wende, J.M. Huss, P.J. Schaeffer, V. Giguere, D.P. Kelly, PGC-1alpha coactivates PDK4 gene expression via the orphan nuclear receptor ERRalpha: a mechanism for transcriptional control of muscle glucose metabolism, Mol. Cell. Biol. 25 (2005) 10684–10694.
[83] R. Cartoni, B. Leger, M.B. Hock, M. Praz, A. Crettenand, S. Pich, J.L. Ziltener, F. Luthi, O. Deriaz, A. Zorzano, C. Gobelet, A. Kralli, A.P. Russell, Mitofusins 1/2 and ERRalpha expression are increased in human skeletal muscle after physical exercise, J. Physiol. 567 (2005) 349–358.
[84] Z. Arany, PGC-1 coactivators and skeletal muscle adaptations in health and disease, Curr. Opin. Genet. Dev. 18 (2008) 426–434.
[85] C. Canto, L.Q. Jiang, A.S. Deshmukh, C. Mataki, A. Coste, M. Lagouge, J.R. Zierath, J. Auwerx, Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle, Cell Metab. 11 (2010) 213–219.
[86] J.B. Barry, V. Giguere, Epidermal growth factor-induced signaling in breast cancer cells results in selective target gene activation by orphan nuclear receptor estrogen-related receptor alpha, Cancer Res. 65 (2005) 6120–6129.
[87] J. Chinsomboon, J. Ruas, R.K. Gupta, R. Thom, J. Shoag, G.C. Rowe, N. Sawada, S. Raghuram, Z. Arany, The transcriptional coactivator PGC-1alpha mediates exercise-induced angiogenesis in skeletal muscle, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 21401–21406.
[88] D. Liu, M.M. Hinshelwood, V. Giguere, C.R. Mendelson, Estrogen related receptor-alpha enhances surfactant protein-A gene expression in fetal lung type II cells, Endocrinology 147 (2006) 5187–5195.
[89] D.K. Kim, Y.H. Kim, D. Hynx, Y. Wang, K.J. Yang, D. Ryu, K.S. Kim, E.K. Yoo, J.S. Kim, S.H. Koo, I.K. Lee, H.Z. Chae, J. Park, C.H. Lee, S.B. Biddinger, B.A. Hemmings, H.S. Choi, PKB/Akt phosphorylation of ERRgamma contributes to insulin-mediated inhibition of hepatic gluconeogenesis, Diabetologia 57 (2014) 2576–2585.
[90] D.K. Kim, D. Ryu, M. Koh, M.W. Lee, D. Lim, M.J. Kim, Y.H. Kim, W.J. Cho, C.H. Lee, S.B. Park, S.H. Koo, H.S. Choi, Orphan nuclear receptor estrogen-related receptor gamma (ERRgamma) is key regulator of hepatic gluconeogenesis, J. Biol. Chem. 287 (2012) 21628–21639.
[91] D. Liu, Z. Zhang, C.T. Teng, Estrogen-related receptor-{gamma} and peroxisome proliferator-activated receptor-{gamma} coactivator-1{alpha} regulate estrogen-related receptor-{alpha} gene expression via a conserved multi-hormone response element, J. Mol. Endocrinol. 34 (2005) 473–487.
[92] K. Inoki, J. Kim, K.L. Guan, AMPK and mTOR in cellular energy homeostasis and drug targets, Annu. Rev. Pharmacol. Toxicol. 52 (2012) 381–400.

[93] R.J. Shaw, LKB1 and AMP-activated protein kinase control of mTOR signalling and growth, Acta Physiol. (Oxf.) 196 (2009) 65–80.
[94] C. Chaveroux, L.J. Eichner, C.R. Dufour, A. Shatnawi, A. Khoutorsky, G. Bourque, N. Sonenberg, V. Giguere, Molecular and genetic crosstalks between mTOR and ERRalpha are key determinants of rapamycin-induced nonalcoholic fatty liver, Cell Metab. 17 (2013) 586–598.
[95] J.T. Cunningham, J.T. Rodgers, D.H. Arlow, F. Vazquez, V.K. Mootha, P. Puigserver, mTOR controls mitochondrial oxidative function through a YY1-PGC-1alpha transcriptional complex, Nature 450 (2007) 736–740.
[96] T. Kaneko, T. Watanabe, M. Oishi, Effect of mitochondrial protein synthesis inhibitors on erythroid differentiation of mouse erythroleukemia (Friend) cells, Mol. Cell. Biol. 8 (1988) 3311–3315.
[97] C.D. Moyes, O.A. Mathieu-Costello, N. Tsuchiya, C. Filburn, R.G. Hansford, Mitochondrial biogenesis during cellular differentiation, Am. J. Physiol. Cell Physiol. 272 (1997) C1345–C1351.
[98] J.L. Vayssiere, L. Cordeau-Lossouarn, J.C. Larcher, M. Basseville, F. Gros, B. Croizat, Participation of the mitochondrial genome in the differentiation of neuroblastoma cells, In Vitro Cell. Dev. Biol. 28A (1992) 763–772.
[99] B. Feng, J. Jiang, P. Kraus, J.H. Ng, J.C. Heng, Y.S. Chan, L.P. Yaw, W. Zhang, Y.H. Loh, J. Han, V.B. Vega, V. Cacheux-Rataboul, B. Lim, T. Lufkin, H.H. Ng, Reprogramming of fibroblasts into induced pluripotent stem cells with orphan nuclear receptor Esrrb, Nat. Cell Biol. 11 (2009) 197–203.
[100] J. Luo, R. Sladek, J.A. Bader, A. Matthyssen, J. Rossant, V. Giguere, Placental abnormalities in mouse embryos lacking the orphan nuclear receptor ERR-beta, Nature 388 (1997) 778–782.
[101] H. Ogawa, N. Shindo, T. Kumagai, Y. Usami, M. Shikanai, K. Jonwn, A. Fukuda, M. Kawahara, Y. Sotomaru, S. Tanaka, T. Arima, T. Kono, Developmental ability of trophoblast stem cells in uniparental mouse embryos, Placenta 30 (2009) 448–456.
[102] I. Chambers, S.R. Tomlinson, The transcriptional foundation of pluripotency, Development 136 (2009) 2311–2322.
[103] X. Chen, H. Xu, P. Yuan, F. Fang, M. Huss, V.B. Vega, E. Wong, Y.L. Orlov, W. Zhang, J. Jiang, Y.H. Loh, H.C. Yeo, Z.X. Yeo, V. Narang, K.R. Govindarajan, B. Leong, A. Shahab, Y. Ruan, G. Bourque, W.K. Sung, N.D. Clarke, C.L. Wei, H.H. Ng, Integration of external signaling pathways with the core transcriptional network in embryonic stem cells, Cell 133 (2008) 1106–1117.
[104] N. Ivanova, R. Dobrin, R. Lu, I. Kotenko, J. Levorse, C. DeCoste, X. Schafer, Y. Lun, I.R. Lemischka, Dissecting self-renewal in stem cells with RNA interference, Nature 442 (2006) 533–538.
[105] C.Q. Xie, Y. Jeong, M. Fu, A.L. Bookout, M.T. Garcia-Barrio, T. Sun, B.H. Kim, Y. Xie, S. Root, J. Zhang, R.H. Xu, Y.E. Chen, D.J. Mangelsdorf, Expression profiling of nuclear receptors in human and mouse embryonic stem cells, Mol. Endocrinol. 23 (2009) 724–733.
[106] N. Festuccia, R. Osorno, F. Halbritter, V. Karwacki-Neisius, P. Navarro, D. Colby, F. Wong, A. Yates, S.R. Tomlinson, I. Chambers, Esrrb is a direct Nanog target gene that can substitute for Nanog function in pluripotent cells, Cell Stem Cell 11 (2012) 477–490.
[107] A. Gagliardi, N.P. Mullin, Z. Ying Tan, D. Colby, A.I. Kousa, F. Halbritter, J.T. Weiss, A. Felker, K. Bezstarosti, R. Favaro, J. Demmers, S.K. Nicolis, S.R. Tomlinson, R.A. Poot, I. Chambers, A direct physical interaction between Nanog and Sox2 regulates embryonic stem cell self-renewal, EMBO J. 32 (2013) 2231–2247.
[108] J. Liang, M. Wan, Y. Zhang, P. Gu, H. Xin, S.Y. Jung, J. Qin, J. Wong, A.J. Cooney, D. Liu, Z. Songyang, Nanog and Oct4 associate with unique transcriptional repression complexes in embryonic stem cells, Nat. Cell Biol. 10 (2008) 731–739.
[109] K. Uranishi, T. Akagi, C. Sun, H. Koide, T. Yokota, Dax1 associates with Esrrb and regulates its function in embryonic stem cells, Mol. Cell. Biol. 33 (2013) 2056–2066.
[110] D.L. van den Berg, W. Zhang, A. Yates, E. Engelen, K. Takacs, K. Bezstarosti, J. Demmers, I. Chambers, R.A. Poot, Estrogen-related receptor beta interacts with Oct4 to positively regulate Nanog gene expression, Mol. Cell. Biol. 28 (2008) 5986–5995.
[111] X. Zhang, J. Zhang, T. Wang, M.A. Esteban, D. Pei, Esrrb activates Oct4 transcription and sustains self-renewal and pluripotency in embryonic stem cells, J. Biol. Chem. 283 (2008) 35825–35833.
[112] M. Percharde, F. Lavial, J.H. Ng, V. Kumar, R.A. Tomaz, N. Martin, J.C. Yeo, J. Gil, S. Prabhakar, H.H. Ng, M.G. Parker, V. Azuara, Ncoa3 functions as an essential Esrrb coactivator to sustain embryonic stem cell self-renewal and reprogramming, Genes Dev. 26 (2012) 2286–2298.
[113] S. van der Laan, E. Golfetto, J.M. Vanacker, D. Maiorano, Cell cycle-dependent expression of Dub3, Nanog and the p160 family of nuclear receptor coactivators (NCoAs) in mouse embryonic stem cells, PLoS One 9 (2014) e93663.
[114] S. van der Laan, N. Tsanov, C. Crozet, D. Maiorano, High Dub3 expression in mouse ESCs couples the G1/S checkpoint to pluripotency, Mol. Cell 52 (2013) 366–379.
[115] W. Korohoda, Z. Pietrzkowski, K. Reiss, Chloramphenicol, an inhibitor of mitochondrial protein synthesis, inhibits myoblast fusion and myotube differentiation, Folia Histochem. Cytobiol. 31 (1993) 9–13.
[116] J. Murray, J.M. Huss, Estrogen-related receptor alpha regulates skeletal myocyte differentiation via modulation of the ERK MAP kinase pathway, Am. J. Physiol. Cell Physiol. 301 (2011) C630–C645.
[117] J. Murray, J. Auwerx, J.M. Huss, Impaired myogenesis in estrogen-related receptor gamma (ERRgamma)-deficient skeletal myocytes due to oxidative stress, FASEB J. 27 (2013) 135–150.
[118] S.C. Wang, S. Myers, C. Dooms, R. Capon, G.E. Muscat, An ERRbeta/gamma agonist modulates GRalpha expression, and glucocorticoid responsive gene expression in skeletal muscle cells, Mol. Cell. Endocrinol. 315 (2010) 146–152.
[119] E. Bonnelye, J.E. Aubin, An energetic orphan in an endocrine tissue: a revised perspective of the function of estrogen receptor-related receptor alpha in bone and cartilage, J. Bone Miner. Res. 28 (2013) 225–233.
[120] E. Bonnelye, L. Merdad, V. Kung, J.E. Aubin, The orphan nuclear estrogen receptor-related receptor alpha (ERRalpha) is expressed throughout osteoblast differentiation and regulates bone formation in vitro, J. Cell Biol. 153 (2001) 971–984.
[121] A.M. Rajalin, H. Pollock, P. Aarnisalo, ERRalpha regulates osteoblastic and adipogenic differentiation of mouse bone marrow mesenchymal stem cells, Biochem. Biophys. Res. Commun. 396 (2010) 477–482.
[122] J.M. Vanacker, C. Delmarre, X. Guo, V. Laudet, Activation of the osteopontin promoter by the orphan nuclear receptor estrogen receptor related alpha, Cell Growth Differ. 9 (1998) 1007–1014.
[123] R.A. Zirngibl, J.S. Chan, J.E. Aubin, Estrogen receptor-related receptor alpha (ERRalpha) regulates osteopontin expression through a non-canonical ERRalpha response element in a cell context-dependent manner, J. Mol. Endocrinol. 40 (2008) 61–73.
[124] I. Delhon, S. Gutzwiller, F. Morvan, S. Rangwala, L. Wyder, G. Evans, A. Studer, M. Kneissel, B. Fournier, Absence of estrogen receptor-related-alpha increases osteoblastic differentiation and cancellous bone mineral density, Endocrinology 150 (2009) 4463–4472.
[125] B.C. Jeong, Y.S. Lee, Y.Y. Park, I.H. Bae, D.K. Kim, S.H. Koo, H.R. Choi, S.H. Kim, R.T. Franceschi, J.T. Koh, H.S. Choi, The orphan nuclear receptor estrogen receptor-related receptor gamma negatively regulates BMP2-induced osteoblast differentiation and bone formation, J. Biol. Chem. 284 (2009) 14211–14218.
[126] M. Gallet, S. Saidi, E. Hay, J. Photsavang, C. Marty, J. Sailland, J. Carnesecchi, V. Tribollet, B. Barenton, C. Forcet, M.C. Birling, T. Sorg, O. Chassande, M. Cohen-Solal, J.M. Vanacker, Repression of osteoblast maturation by ERRalpha accounts for bone loss induced by estrogen deficiency, PLoS One 8 (2013) e54837.
[127] C. Teyssier, M. Gallet, B. Rabier, L. Monfoulet, J. Dine, C. Macari, J. Espallergues, B. Horard, V. Giguere, M. Cohen-Solal, O. Chassande, J.M. Vanacker, Absence of ERRalpha in female mice confers resistance to bone loss induced by age or estrogen-deficiency, PLoS One 4 (2009) e7942.
[128] K.A. Ishii, T. Fumoto, K. Iwai, S. Takeshita, M. Ito, N. Shimohata, H. Aburatani, S. Taketani, C.J. Lelliott, A. Vidal-Puig, K. Ikeda, Coordination of PGC-1beta and iron uptake in mitochondrial biogenesis and osteoclast activation, Nat. Med. 15 (2009) 259–266.
[129] W. Wei, X. Wang, M. Yang, L.C. Smith, P.C. Dechow, J. Sonoda, R.M. Evans, Y. Wan, PGC1beta mediates PPARgamma activation of osteoclastogenesis and rosiglitazone-induced bone loss, Cell Metab. 11 (2010) 503–516.
[130] M. Gallet, J.M. Vanacker, ERR receptors as potential targets in osteoporosis, Trends Endocrinol. Metab. 21 (2010) 637–641.
[131] C.R. Dufour, M.P. Levasseur, N.H. Pham, L.J. Eichner, B.J. Wilson, A. Charest-Marcotte, D. Duguay, J.F. Poirier-Heon, N. Cermakian, V. Giguere, Genomic convergence among ERRalpha, PROX1, and BMAL1 in the control of metabolic clock outputs, PLoS Genet. 7 (2011) e1002143.
[132] J.C. Carrier, G. Deblois, C. Champigny, E. Levy, V. Giguere, Estrogen-related receptor alpha (ERRalpha) is a transcriptional regulator of apolipoprotein A-IV and controls lipid handling in the intestine, J. Biol. Chem. 279 (2004) 52052–52058.
[133] M.L. Gantner, B.C. Hazen, J. Conkright, A. Kralli, GADD45gamma regulates the thermogenic capacity of brown adipose tissue, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 11870–11875.
[134] J.A. Villena, M.B. Hock, W.Y. Chang, J.E. Barcas, V. Giguere, A. Kralli, Orphan nuclear receptor estrogen-related receptor alpha is essential for adaptive thermogenesis, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 1418–1423.
[135] M.S. Byerly, M. Al Salayta, R.D. Swanson, K. Kwon, J.M. Peterson, Z. Wei, S. Aja, T.H. Moran, S. Blackshaw, G.W. Wong, Estrogen-related receptor beta deletion modulates whole-body energy balance via estrogen-related receptor gamma and attenuates neuropeptide Y gene expression, Eur. J. Neurosci. 37 (2013) 1033–1047.
[136] M.S. Byerly, R.D. Swanson, G.W. Wong, S. Blackshaw, Estrogen-related receptor beta deficiency alters body composition and response to restraint stress, BMC Physiol. 13 (2013) 10.
[137] J. Sonoda, J. Laganiere, I.R. Mehl, G.D. Barish, L.W. Chong, X. Li, I.E. Scheffler, D.C. Mock, A.R. Bataille, F. Robert, C.H. Lee, V. Giguere, R.M. Evans, Nuclear receptor ERR alpha and coactivator PGC-1 beta are effectors of IFN-gamma-induced host defense, Genes Dev. 21 (2007) 1909–1920.
[138] S.M. Rangwala, X. Li, L. Lindsley, X. Wang, S. Shaughnessy, T.G. Daniels, J. Szustakowski, N.R. Nirmala, Z. Wu, S.C. Stevenson, Estrogen-related receptor [alpha] is essential for the expression of antioxidant protection genes and mitochondrial function, Biochem. Biophys. Res. Commun. 357 (2007) 231–236.
[139] D.K. Kim, J.H. Jeong, J.M. Lee, K.S. Kim, S.H. Park, Y.D. Kim, M. Koh, M. Shin, Y.S. Jung, H.S. Kim, T.H. Lee, B.C. Oh, J.I. Kim, H.T. Park, W.I. Jeong, C.H. Lee, S.B. Park, J.J. Min, S.I. Jung, S.Y. Choi, H.E. Choy, H.S. Choi, Inverse agonist of estrogen-related receptor gamma controls Salmonella typhimurium infection by modulating host iron homeostasis, Nat. Med. 20 (2014) 419–424.
[140] E. Nemeth, T. Ganz, Regulation of iron metabolism by hepcidin, Annu. Rev. Nutr. 26 (2006) 323–342.
[141] R.D. Michalek, V.A. Gerriets, A.G. Nichols, M. Inoue, D. Kazmin, C.Y. Chang, M.A. Dwyer, E.R. Nelson, K.N. Pollizzi, O. Ilkayeva, V. Giguere, W.J. Zuercher, J.D. Powell, M.L. Shinohara, D.P. McDonnell, J.C. Rathmell, Estrogen-related receptor-alpha is a metabolic regulator of effector T-cell activation and differentiation, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 18348–18353.
[142] W.A. Alaynick, J.M. Way, S.A. Wilson, W.G. Benson, L. Pei, M. Downes, R. Yu, J.W. Jonker, J.A. Holt, D.K. Rajpal, H. Li, J. Stuart, R. McPherson, K.S. Remlinger, C.Y. Chang, D.P. McDonnell, R.M. Evans, A.N. Billin, ERRgamma regulates cardiac, gastric, and renal potassium homeostasis, Mol. Endocrinol. 24 (2010) 299–309.
[143] Q. Liang, L.J. De Windt, S.A. Witt, T.R. Kimball, B.E. Markham, J.D. Molkentin, The transcription factors GATA4 and GATA6 regulate cardiomyocyte hypertrophy in vitro and in vivo, J. Biol. Chem. 276 (2001) 30245–30253.

[144] D.H. Kwon, G.H. Eom, H.J. Kee, Y.S. Nam, Y.K. Cho, D.K. Kim, J.Y. Koo, H.S. Kim, K.I. Nam, K.K. Kim, I.K. Lee, S.B. Park, H.S. Choi, H. Kook, Estrogen-related receptor gamma induces cardiac hypertrophy by activating GATA4, J. Mol. Cell. Cardiol. 65 (2013) 88–97.
[145] M.S. Mitra, J.D. Schilling, X. Wang, P.Y. Jay, J.M. Huss, X. Su, B.N. Finck, Cardiac lipin 1 expression is regulated by the peroxisome proliferator activated receptor gamma coactivator 1alpha/estrogen related receptor axis, J. Mol. Cell. Cardiol. 51 (2011) 120–128.
[146] Y. Wei, S. Peng, M. Wu, R. Sachidanandam, Z. Tu, S. Zhang, C. Falce, E.A. Sobie, D. Lebeche, Y. Zhao, Multifaceted roles of miR-1s in repressing the fetal gene program in the heart, Cell Res. 24 (2014) 278–292.
[147] J. Rhee, Y. Inoue, J.C. Yoon, P. Puigserver, M. Fan, F.J. Gonzalez, B.M. Spiegelman, Regulation of hepatic fasting response by PPARgamma coactivator-1alpha (PGC-1): requirement for hepatocyte nuclear factor 4alpha in gluconeogenesis, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 4012–4017.
[148] Z. Zhang, C.T. Teng, Interplay between estrogen-related receptor alpha (ERRalpha) and gamma (ERRgamma) on the regulation of ERRalpha gene expression, Mol. Cell. Endocrinol. 264 (2007) 128–141.
[149] B. Herzog, J. Cardenas, R.K. Hall, J.A. Villena, P.J. Budge, V. Giguere, D.K. Granner, A. Kralli, Estrogen-related receptor alpha is a repressor of phosphoenolpyruvate carboxykinase gene transcription, J. Biol. Chem. 281 (2006) 99–106.
[150] S. Gaillard, L.L. Grasfeder, C.L. Haeffele, E.K. Lobenhofer, T.M. Chu, R. Wolfinger, D. Kazmin, T.R. Koves, D.M. Muoio, C.Y. Chang, D.P. McDonnell, Receptor-selective coactivators as tools to define the biology of specific receptor-coactivator pairs, Mol. Cell 24 (2006) 797–803.
[151] H.S. Ranhotra, Up-regulation of orphan nuclear estrogen-related receptor alpha expression during long-term caloric restriction in mice, Mol. Cell. Biochem. 332 (2009) 59–65.
[152] L.L. Zhu, Y. Liu, A.F. Cui, D. Shao, J.C. Liang, X.J. Liu, Y. Chen, N. Gupta, F.D. Fang, Y.S. Chang, PGC-1alpha coactivates estrogen-related receptor-alpha to induce the expression of glucokinase, Am. J. Physiol. Endocrinol. Metab. 298 (2010) E1210–E1218.
[153] C. Handschin, J. Lin, J. Rhee, A.K. Peyer, S. Chin, P.H. Wu, U.A. Meyer, B.M. Spiegelman, Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha, Cell 122 (2005) 505–515.
[154] S. Herzig, F. Long, U.S. Jhala, S. Hedrick, R. Quinn, A. Bauer, D. Rudolph, G. Schutz, C. Yoon, P. Puigserver, B. Spiegelman, M. Montminy, CREB regulates hepatic gluconeogenesis through the coactivator PGC-1, Nature 413 (2001) 179–183.
[155] P. Puigserver, J. Rhee, J. Donovan, C.J. Walkey, J.C. Yoon, F. Oriente, Y. Kitamura, J. Altomonte, H. Dong, D. Accili, B.M. Spiegelman, Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1alpha interaction, Nature 423 (2003) 550–555.
[156] J.C. Yoon, P. Puigserver, G. Chen, J. Donovan, Z. Wu, J. Rhee, G. Adelmant, J. Stafford, C.R. Kahn, D.K. Granner, C.B. Newgard, B.M. Spiegelman, Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1, Nature 413 (2001) 131–138.
[157] S.F. Schmidt, S. Mandrup, Gene program-specific regulation of PGC-1{alpha} activity, Genes Dev. 25 (2011) 1453–1458.
[158] Y. Lustig, J.L. Ruas, J.L. Estall, J.C. Lo, S. Devarakonda, D. Laznik, J.H. Choi, H. Ono, J.V. Olsen, B.M. Spiegelman, Separation of the gluconeogenic and mitochondrial functions of PGC-1{alpha} through S6 kinase, Genes Dev. 25 (2011) 1232–1244.
[159] J.T. Rodgers, W. Haas, S.P. Gygi, P. Puigserver, Cdc2-like kinase 2 is an insulin-regulated suppressor of hepatic gluconeogenesis, Cell Metab. 11 (2010) 23–34.
[160] S. LaBarge, M. McDonald, L. Smith-Powell, J. Auwerx, J.M. Huss, Estrogen-related receptor-alpha (ERRalpha) deficiency in skeletal muscle impairs regeneration in response to injury, FASEB J. 28 (2014) 1082–1097.
[161] M.C. Perry, C.R. Dufour, I.S. Tam, W. B'Chir, V. Giguere, Estrogen-Related Receptor Alpha coordinates transcriptional programs essential for exercise tolerance and muscle fitness, Mol. Endocrinol. 28 (2014) 2060–2071.
[162] V.A. Narkar, W. Fan, M. Downes, R.T. Yu, J.W. Jonker, W.A. Alaynick, E. Banayo, M.S. Karunasiri, S. Lorca, R.M. Evans, Exercise and PGC-1alpha-independent synchronization of type I muscle metabolism and vasculature by ERRgamma, Cell Metab. 13 (2011) 283–293.
[163] A. Matsakas, V. Yadav, S. Lorca, R.M. Evans, V.A. Narkar, Revascularization of ischemic skeletal muscle by estrogen-related receptor-gamma, Circ. Res. 110 (2012) 1087–1096.
[164] S. Duguez, L. Feasson, C. Denis, D. Freyssenet, Mitochondrial biogenesis during skeletal muscle regeneration, Am. J. Physiol. Endocrinol. Metab. 282 (2002) E802–E809.
[165] E. Fink, D. Fortin, B. Serrurier, R. Ventura-Clapier, A.X. Bigard, Recovery of contractile and metabolic phenotypes in regenerating slow muscle after notexin-induced or crush injury, J. Muscle Res. Cell Motil. 24 (2003) 421–429.
[166] A. Wagatsuma, N. Kotake, K. Mabuchi, S. Yamada, Expression of nuclear-encoded genes involved in mitochondrial biogenesis and dynamics in experimentally denervated muscle, J. Physiol. Biochem. 67 (2011) 359–370.
[167] A. Wagatsuma, N. Kotake, S. Yamada, Muscle regeneration occurs to coincide with mitochondrial biogenesis, Mol. Cell. Biochem. 349 (2011) 139–147.
[168] C. Handschin, S. Chin, P. Li, F. Liu, E. Maratos-Flier, N.K. Lebrasseur, Z. Yan, B.M. Spiegelman, Skeletal muscle fiber-type switching, exercise intolerance, and myopathy in PGC-1alpha muscle-specific knock-out animals, J. Biol. Chem. 282 (2007) 30014–30021.
[169] K. Nakashima, Y. Yakabe, AMPK activation stimulates myofibrillar protein degradation and expression of atrophy-related ubiquitin ligases by increasing FOXO transcription factors in C2C12 myotubes, Biosci. Biotechnol. Biochem. 71 (2007) 1650–1656.
[170] N. Stupka, J.D. Schertzer, R. Bassel-Duby, E.N. Olson, G.S. Lynch, Calcineurin-A alpha activation enhances the structure and function of regenerating muscles after myotoxic injury, Am. J. Physiol. Regul. Integr. Comp. Physiol. 293 (2007) R686–R694.
[171] N. Stupka, J.D. Schertzer, R. Bassel-Duby, E.N. Olson, G.S. Lynch, Stimulation of calcineurin Aalpha activity attenuates muscle pathophysiology in mdx dystrophic mice, Am. J. Physiol. Regul. Integr. Comp. Physiol. 294 (2008) R983–R992.
[172] T. Wenz, S.G. Rossi, R.L. Rotundo, B.M. Spiegelman, C.T. Moraes, Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 20405–20410.
[173] D.R. Bolster, S.J. Crozier, S.R. Kimball, L.S. Jefferson, AMP-activated protein kinase suppresses protein synthesis in rat skeletal muscle through down-regulated mammalian target of rapamycin (mTOR) signaling, J. Biol. Chem. 277 (2002) 23977–23980.
[174] A.Y.M. Chan, C.-L.M. Soltys, M.E. Young, C.G. Proud, J.R.B. Dyck, Activation of AMP-activated protein kinase inhibits protein synthesis associated with hypertrophy in the cardiac myocyte, J. Biol. Chem. 279 (2004) 32771–32779.
[175] M. Fulco, Y. Cen, P. Zhao, E.P. Hoffman, M.W. McBurney, A.A. Sauve, V. Sartorelli, Glucose restriction inhibits skeletal myoblast differentiation by activating SIRT1 through AMPK-mediated regulation of Nampt, Dev. Cell 14 (2008) 661–673.
[176] R. Mounier, L. Lantier, J. Leclerc, A. Sotiropoulos, M. Pende, D. Daegelen, K. Sakamoto, M. Foretz, B. Viollet, Important role for AMPK{alpha}1 in limiting skeletal muscle cell hypertrophy, FASEB J. 23 (2009) 2264–2273.
[177] E.D. Abel, T. Doenst, Mitochondrial adaptations to physiological vs. pathological cardiac hypertrophy, Cardiovasc. Res. 90 (2011) 234–242.
[178] Y. Chen, Y. Wang, J. Chen, X. Chen, W. Cao, S. Chen, S. Xu, H. Huang, P. Liu, Roles of transcriptional corepressor RIP140 and coactivator PGC-1alpha in energy state of chronically infarcted rat hearts and mitochondrial function of cardiomyocytes, Mol. Cell. Endocrinol. 362 (2012) 11–18.
[179] J. Gomez-Arroyo, S. Mizuno, K. Szczepanek, B. Van Tassell, R. Natarajan, C.G. dos Remedios, J.I. Drake, L. Farkas, D. Kraskauskas, D.S. Wijesinghe, C.E. Chalfant, J. Bigbee, A. Abbate, E.J. Lesnefsky, H.J. Bogaard, N.F. Voelkel, Metabolic gene remodeling and mitochondrial dysfunction in failing right ventricular hypertrophy secondary to pulmonary arterial hypertension, Circ. Heart Fail. 6 (2013) 136–144.
[180] P.A. Watson, N. Birdsey, G.S. Huggins, E. Svensson, D. Heppe, L. Knaub, Cardiac-specific overexpression of dominant-negative CREB leads to increased mortality and mitochondrial dysfunction in female mice, Am. J. Physiol. Heart Circ. Physiol. 299 (2010) H2056–H2068.
[181] Z. Arany, M. Novikov, S. Chin, Y. Ma, A. Rosenzweig, B.M. Spiegelman, Transverse aortic constriction leads to accelerated heart failure in mice lacking PPAR-gamma coactivator 1alpha, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 10086–10091.
[182] C. Riehle, A.R. Wende, V.G. Zaha, K.M. Pires, B. Wayment, C. Olsen, H. Bugger, J. Buchanan, X. Wang, A.B. Moreira, T. Doenst, G. Medina-Gomez, S.E. Litwin, C.J. Lelliott, A. Vidal-Puig, E.D. Abel, PGC-1beta deficiency accelerates the transition to heart failure in pressure overload hypertrophy, Circ. Res. 109 (2011) 783–793.
[183] X. Hu, X. Xu, Z. Lu, P. Zhang, J. Fassett, Y. Zhang, Y. Xin, J.L. Hall, B. Viollet, R.J. Bache, Y. Huang, Y. Chen, AMP activated protein kinase-alpha2 regulates expression of estrogen-related receptor-alpha, a metabolic transcription factor related to heart failure development, Hypertension 58 (2011) 696–703.
[184] S. Sihag, S. Cresci, A.Y. Li, C.C. Sucharov, J.J. Lehman, PGC-1alpha and ERRalpha target gene downregulation is a signature of the failing human heart, J. Mol. Cell. Cardiol. 46 (2009) 201–212.
[185] P.A. Crawford, J.E. Schaffer, Metabolic stress in the myocardium: adaptations of gene expression, J. Mol. Cell. Cardiol. 55 (2013) 130–138.
[186] P. Gurha, T. Wang, A.H. Larimore, Y. Sassi, C. Abreu-Goodger, M.O. Ramirez, A.K. Reddy, S. Engelhardt, G.E. Taffet, X.H. Wehrens, M.L. Entman, A. Rodriguez, microRNA-22 promotes heart failure through coordinate suppression of PPAR/ERR-nuclear hormone receptor transcription, PLoS One 8 (2013) e75882.
[187] S. Oka, P. Zhai, R. Alcendor, J.Y. Park, B. Tian, J. Sadoshima, Suppression of ERR targets by a PPARalpha/Sirt1 complex in the failing heart, Cell Cycle 11 (2012) 856–864.
[188] X. Palomer, L. Salvado, E. Barroso, M. Vazquez-Carrera, An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy, Int. J. Cardiol. 168 (2013) 3160–3172.
[189] S. Cresci, J.M. Huss, A.L. Beitelshees, P.G. Jones, M.R. Minton, G.W. Dorn, D.P. Kelly, J.A. Spertus, H.L. McLeod, A PPARalpha promoter variant impairs ERR-dependent transactivation and decreases mortality after acute coronary ischemia in patients with diabetes, PLoS One 5 (2010) e12584.
[190] N.F. Mistry, S. Cresci, PPAR transcriptional activator complex polymorphisms and the promise of individualized therapy for heart failure, Heart Fail. Rev. 15 (2010) 197–207.
[191] D. Baron, A. Magot, G. Ramstein, M. Steenman, G. Fayet, C. Chevalier, P. Jourdon, R. Houlgatte, F. Savagner, Y. Pereon, Immune response and mitochondrial metabolism are commonly deregulated in DMD and aging skeletal muscle, PLoS One 6 (2011) e26952.
[192] A. Matsakas, V. Yadav, S. Lorca, V. Narkar, Muscle ERRgamma mitigates Duchenne muscular dystrophy via metabolic and angiogenic reprogramming, FASEB J. 27 (2013) 4004–4016.
[193] V.E. Jahnke, J.H. Van Der Meulen, H.K. Johnston, S. Ghimbovschi, T. Partridge, E.P. Hoffman, K. Nagaraju, Metabolic remodeling agents show beneficial effects in the dystrophin-deficient mdx mouse model, Skelet. Muscle 2 (2012) 16.
[194] V. Ljubicic, P. Miura, M. Burt, L. Boudreault, S. Khogali, J.A. Lunde, J.M. Renaud, B.J. Jasmin, Chronic AMPK activation evokes the slow, oxidative myogenic program and triggers beneficial adaptations in mdx mouse skeletal muscle, Hum. Mol. Genet. 20 (2011) 3478–3493.
[195] R.J. Patch, L.L. Searle, A.J. Kim, D. De, X. Zhu, H.B. Askari, J.C. O'Neill, M.C. Abad, D. Rentzeperis, J. Liu, M. Kemmerer, L. Lin, J. Kasturi, J.G. Geisler, J.M. Lenhard, M.R.

Player, M.D. Gaul, Identification of diaryl ether-based ligands for estrogen-related receptor alpha as potential antidiabetic agents, J. Med. Chem. 54 (2011) 788–808.
[196] S.M. Aatsinki, M. Buler, H. Salomaki, M. Koulu, P. Pavek, J. Hakkola, Metformin induces PGC-1alpha expression and selectively affects hepatic PGC-1alpha functions, Br. J. Pharmacol. 171 (2014) 2351–2363.
[197] D.K. Kim, J.R. Kim, M. Koh, Y.D. Kim, J.M. Lee, D. Chanda, S.B. Park, J.J. Min, C.H. Lee, T.S. Park, H.S. Choi, Estrogen-related receptor gamma (ERRgamma) is a novel transcriptional regulator of phosphatidic acid phosphatase, LIPIN1, and inhibits hepatic insulin signaling, J. Biol. Chem. 286 (2011) 38035–38042.
[198] J.K. Kim, J.J. Fillmore, M.J. Sunshine, B. Albrecht, T. Higashimori, D.W. Kim, Z.X. Liu, T.J. Soos, G.W. Cline, W.R. O'Brien, D.R. Littman, G.I. Shulman, PKC-theta knockout mice are protected from fat-induced insulin resistance, J. Clin. Invest. 114 (2004) 823–827.
[199] C. Schmitz-Peiffer, C.L. Browne, N.D. Oakes, A. Watkinson, D.J. Chisholm, E.W. Kraegen, T.J. Biden, Alterations in the expression and cellular localization of protein kinase C isozymes epsilon and theta are associated with insulin resistance in skeletal muscle of the high-fat-fed rat, Diabetes 46 (1997) 169–178.
[200] C. Yu, Y. Chen, G.W. Cline, D. Zhang, H. Zong, Y. Wang, R. Bergeron, J.K. Kim, S.W. Cushman, G.J. Cooney, B. Atcheson, M.F. White, E.W. Kraegen, G.I. Shulman, Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle, J. Biol. Chem. 277 (2002) 50230–50236.
[201] N. Lu, W. Wang, J. Liu, C.W. Wong, Protein kinase C epsilon affects mitochondrial function through estrogen-related receptor alpha, Cell. Signal. 23 (2011) 1473–1478.
[202] T.R. Koves, J.R. Ussher, R.C. Noland, D. Slentz, M. Mosedale, O. Ilkayeva, J. Bain, R. Stevens, J.R. Dyck, C.B. Newgard, G.D. Lopaschuk, D.M. Muoio, Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance, Cell Metab. 7 (2008) 45–56.
[203] D.M. Muoio, C.B. Newgard, Obesity-related derangements in metabolic regulation, Annu. Rev. Biochem. 75 (2006) 367–401.
[204] S.E. Seiler, O.J. Martin, R.C. Noland, D.H. Slentz, K.L. Debalsi, O.R. Ilkayeva, J. An, C.B. Newgard, T.R. Koves, D.M. Muoio, Obesity and lipid stress inhibit carnitine acetyltransferase activity, J. Lipid Res. 55 (2014) 635–644.
[205] V.K. Mootha, C.M. Lindgren, K.F. Eriksson, A. Subramanian, S. Sihag, J. Lehar, P. Puigserver, E. Carlsson, M. Ridderstrale, E. Laurila, N. Houstis, M.J. Daly, N. Patterson, J.P. Mesirov, T.R. Golub, P. Tamayo, B. Spiegelman, E.S. Lander, J.N. Hirschhorn, D. Altshuler, L.C. Groop, PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes, Nat. Genet. 34 (2003) 267–273.
[206] B.B. Lowell, G.I. Shulman, Mitochondrial dysfunction and type 2 diabetes, Science 307 (2005) 384–387.
[207] M.E. Patti, A.J. Butte, S. Crunkhorn, K. Cusi, R. Berria, S. Kashyap, Y. Miyazaki, I. Kohane, M. Costello, R. Saccone, E.J. Landaker, A.B. Goldfine, E. Mun, R. DeFronzo, J. Finlayson, C.R. Kahn, L.J. Mandarino, Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 8466–8471.
[208] F.G. Toledo, Mitochondrial involvement in skeletal muscle insulin resistance, Diabetes 63 (2014) 59–61.
[209] B. Egan, J.R. Zierath, Exercise metabolism and the molecular regulation of skeletal muscle adaptation, Cell Metab. 17 (2013) 162–184.
[210] N.K. LeBrasseur, K. Walsh, Z. Arany, Metabolic benefits of resistance training and fast glycolytic skeletal muscle, Am. J. Physiol. Endocrinol. Metab. 300 (2011) E3–E10.
[211] T.R. Koves, P. Li, J. An, T. Akimoto, D. Slentz, O. Ilkayeva, G.L. Dohm, Z. Yan, C.B. Newgard, D.M. Muoio, Peroxisome proliferator-activated receptor-gamma coactivator 1alpha-mediated metabolic remodeling of skeletal myocytes mimics exercise training and reverses lipid-induced mitochondrial inefficiency, J. Biol. Chem. 280 (2005) 33588–33598.
[212] L. Li, R. Pan, R. Li, B. Niemann, A.C. Aurich, Y. Chen, S. Rohrbach, Mitochondrial biogenesis and peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1alpha) deacetylation by physical activity: intact adipocytokine signaling is required, Diabetes 60 (2011) 157–167.
[213] K. Baar, A.R. Wende, T.E. Jones, M. Marison, L.A. Nolte, M. Chen, D.P. Kelly, J.O. Holloszy, Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1, FASEB J. 16 (2002) 1879–1886.
[214] V.A. Lira, C.R. Benton, Z. Yan, A. Bonen, PGC-1alpha regulation by exercise training and its influences on muscle function and insulin sensitivity, Am. J. Physiol. Endocrinol. Metab. 299 (2010) E145–E161.
[215] J. Lin, H. Wu, P.T. Tarr, C.Y. Zhang, Z. Wu, O. Boss, L.F. Michael, P. Puigserver, E. Isotani, E.N. Olson, B.B. Lowell, R. Bassel-Duby, B.M. Spiegelman, Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres, Nature 418 (2002) 797–801.
[216] S. Summermatter, G. Shui, D. Maag, G. Santos, M.R. Wenk, C. Handschin, PGC-1alpha improves glucose homeostasis in skeletal muscle in an activity-dependent manner, Diabetes 62 (2013) 85–95.
[217] V.A. Narkar, M. Downes, R.T. Yu, E. Embler, Y.X. Wang, E. Banayo, M.M. Mihaylova, M.C. Nelson, Y. Zou, H. Juguilon, H. Kang, R.J. Shaw, R.M. Evans, AMPK and PPARdelta agonists are exercise mimetics, Cell 134 (2008) 405–415.
[218] L.C. Chao, K. Wroblewski, O.R. Ilkayeva, R.D. Stevens, J. Bain, G.A. Meyer, S. Schenk, L. Martinez, L. Vergnes, V.A. Narkar, B.G. Drew, C. Hong, R. Boyadjian, A.L. Hevener, R.M. Evans, K. Reue, M.J. Spencer, C.B. Newgard, P. Tontonoz, Skeletal muscle Nur77 expression enhances oxidative metabolism and substrate utilization, J. Lipid Res. 53 (2012) 2610–2619.
[219] J. Perez-Schindler, K. Svensson, E. Vargas-Fernandez, G. Santos, W. Wahli, C. Handschin, The coactivator PGC-1alpha regulates skeletal muscle oxidative metabolism independently of the nuclear receptor PPARbeta/delta in sedentary mice fed a regular chow diet, Diabetologia 57 (2014) 2405–2412.