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Metabolic syndromes

Estrogen-related receptor α (ERR α): A novel target in type 2 diabetes

Christoph Handschin^{1,*}, Vamsi K. Mootha²

¹Dana-Farber Cancer Institute and Department of Cell Biology, Harvard Medical School, One Jimmy Fund Way, Boston, MA 02115, USA

²Departments of Systems Biology and of Medicine, Harvard Medical School, Broad Institute of Harvard and MIT, Cambridge, MA 02139, USA

Recent studies have shown that reduced mitochondrial content and function in skeletal muscle are common features of type 2 diabetes. Here, we review the molecular mechanisms involved in the regulation of mitochondrial genes in skeletal muscle, focusing on a key transcriptional network consisting of ERR α and PGC-1 α . We describe how knowledge of this transcriptional circuit can be translated to the development of novel therapies for type 2 diabetes.

Introduction

Type 2 diabetes is a complex disease that stems from an interaction of environmental and genetic factors. Hallmarks of the disease are insulin resistance in skeletal muscle, liver and fat, combined with relative insulin insufficiency due to a decline in β -cell function. Moreover, intracellular triglyceride accumulation in muscle and liver has also been associated with the disease [1].

Recently, genome-wide expression analysis revealed that mitochondrial oxidative phosphorylation (OXPHOS) genes exhibit reduced expression in pre-diabetic and diabetic individuals when compared to healthy controls [2,3], and that these genes are downstream of the transcriptional co-activator PGC-1 α [2]. These genes also show reduced expression in the healthy individuals with a family history of diabetes [2,3]. Consistent with these findings, several reports have shown that diabetics as well as individuals with a family history of diabetes have reduced OXPHOS capacity in muscle [4]. At

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present, whether reduced OXPHOS gene expression is simply a correlate of diabetes or actually causal in this common disorder is not known.

Together, these recent findings motivate the tantalizing hypothesis that drugs that boost OXPHOS capacity in muscle might improve diabetes. Accordingly, it has long been known that aerobic exercise, which is one of the best non-pharmacologic interventions for ameliorating diabetes, increases mitochondrial content and promotes OXPHOS gene expression. Although attractive, these studies did not provide a druggable target for modulating mitochondrial OXPHOS capacity. Recently, we discovered that the nuclear receptor ERR α is recruited by PGC-1 α to regulate the OXPHOS transcriptional program that is altered in diabetic muscle [5]. Knowledge of this transcriptional circuit provides a new opportunity to modulate the mitochondrion for treating diabetes (Table 1).

Strategies for targeting ERR α and PGC-1 α to promote OXPHOS

ERR α is a member of the nuclear receptor superfamily. Nuclear receptors are modular proteins with distinct DNA-binding, activation and ligand-binding domains. The tertiary structure of the ligand-binding domain often permits binding of full and partial agonists, antagonists and inverse agonists. These proteins are located either in the cytoplasm or the nucleus and thus, their ligands are often small and lipophilic. Nuclear receptors are attractive drug targets because of these special properties [6].

*Corresponding author: C. Handschin (christoph_handschin@dfci.harvard.edu)

Table 1. Different approaches to improve mitochondrial function in type 2 diabetes

| | Pros | Cons | Relevant patents | Refs |
|--|--|---|--|-----------|
| ERRα agonists | Nuclear receptor: good drug target | Tissue selectivity; feasibility of designing an agonist | WO 00/47735, WO 05/003766 | [17] |
| PGC-1α activators | Signaling pathways and proteins modulating PGC-1 α function in skeletal muscle are well described | Tissue selectivity | WO 02/062297, WO 00/32215, WO 01/90356, WO 01/35096 | [40,43] |
| Modulation of ERRα-PGC-1α binding | Specific targeting of protein-protein interaction might circumvent adverse effects in other tissues | Feasibility of targeting a protein-protein interaction | WO 00/47735, WO 02/062297, WO 00/32215, WO 01/90356, WO 01/35096 | [5,11,38] |

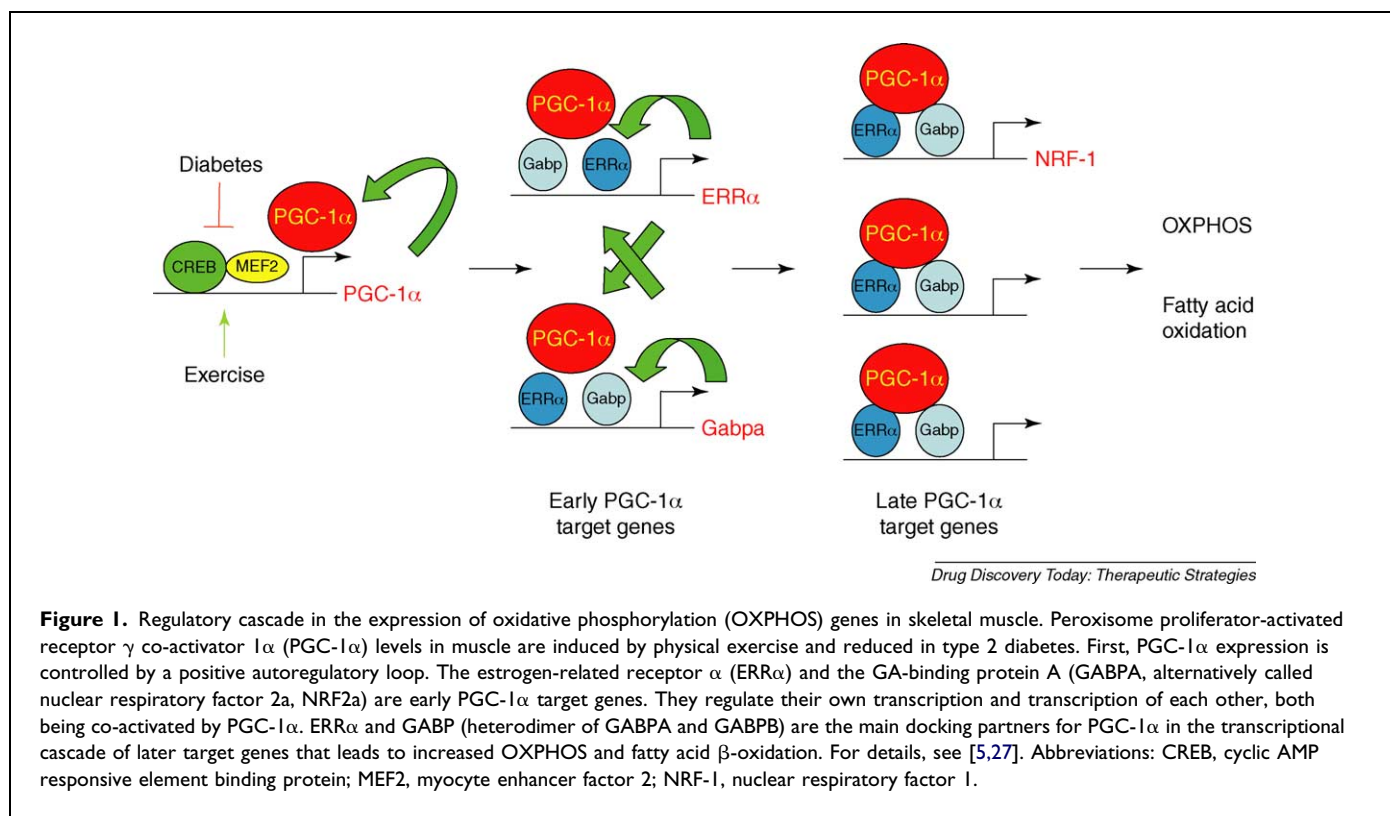
^a Abbreviations: ERR α , estrogen-related receptor α ; PGC-1 α , peroxisome proliferator-activated receptor γ co-activator 1 α .

ERR α binds to an individual or repeats of extended half-sites (usually six to nine basepairs long) in the promoter of target genes, either as a monomer or as a homodimer, respectively [7,8]. ERR α is thought to be involved in bone formation, aromatase and lactoferrin expression in estrogen-responsive tissues as well as mitochondrial fatty acid β -oxidation in skeletal muscle and the heart [7,8]. Relatively little was known about the roles for ERR α (NR3B1) or its two closely related family members ERR β (NR3B2) or ERR γ (NR3B3) *in vivo*.

Recently, the discovery of the interaction between ERR α and the transcriptional co-activator PGC-1 α led to a breakthrough in understanding the function of ERR α [5,9–11]. PGC-1 α is a key regulator of mitochondrial biogenesis and oxidative metabolism in different tissues [12]. An unbiased,

global screen revealed that PGC-1 α regulates many mitochondrial OXPHOS genes via its interaction with ERR α and the GA-binding protein A (GABPA, alternatively called nuclear respiratory factor 2a or NRF-2a), as depicted in Fig. 1 [5]. Binding sites for ERR α in the promoter of PGC-1 α target genes are the highest scoring motifs on day 1, day 2 and day 3 after adenoviral PGC-1 α infection of mouse myotubes as found by motifADE, a computer algorithm that combined gene expression data with promoter analysis [5]. Among the genes regulated by PGC-1 α and ERR α are those found to be decreased in skeletal muscle of type 2 diabetic patients [2,3].

Less is known about the role for GABPA in this process; this review will thus focus on the physiological significance of the interaction between PGC-1 α and ERR α . In the next few



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sections, we discuss strategies for promoting mitochondrial biogenesis and OXPHOS activity through targeting ERR α alone, PGC-1 α alone, or through promoting interactions between both proteins.

Direct targeting of ERR α

ERR α is a very early PGC-1 α target gene and thus a major regulator of OXPHOS and fatty acid oxidation gene expression. In cultured myotubes, adenoviral infection with PGC-1 α elevates ERR α expression on day 1 post infection [5]. Moreover, ERR α binding motifs are located in the promoter regions of early and late PGC-1 α target genes, including ERR α itself and GABPA [5]. Although additional transcription factors downstream of ERR α could also be considered as targets for modulating mitochondrial OXPHOS, these factors alone will probably not be sufficient in stimulating the entire transcriptional program involved in mitochondrial biogenesis. Those include the nuclear respiratory factor 1 (NRF-1), the nuclear respiratory factor 2 (which is the GABPA/B heterodimer) involved in mitochondrial biogenesis [5,13] or the peroxisome proliferator-activated receptor α (PPAR α , NR1C1), which is a target of fibrates and regulates mitochondrial fatty acid β -oxidation [14].

ERR α controls its own transcription by an autoregulatory loop [5,15]. Interestingly, ERR α binding sites in the ERR α promoter are polymorphic in their copy number [15]. Increased number of ERR α binding motifs results in elevated activation of ERR α transcription by ERR α and PGC-1 α . It remains to be shown whether this copy number polymorphism confers risk to the development of type 2 diabetes. Thus, as a nuclear receptor, targeting of ERR α with small molecules is an attractive strategy to increase mitochondrial OXPHOS function in diabetic patients. In principle, such a small molecule can activate the double-positive feedback loop between GABPA and ERR α shown in Fig. 1, hence stimulating the entire transcriptional cascade involved in mitochondrial biogenesis. Moreover, because ERR α is involved in the regulation of fatty acid β -oxidation, activating ERR α can ameliorate the lipid accumulation in skeletal muscle, which is believed to contribute to insulin resistance.

Caveat

Transcriptional activity of ERR α is dependent on cellular context [16]. Under some circumstances, the ability of ERR α to drive transcription of target genes is very low whereas in other cells, this receptor has high constitutive activity. Thus, cell-dependent transcriptional activity could reflect the presence of context-specific transcriptional co-activators, signaling cascades or endogenous ligands. The crystal structure of the ERR α ligand-binding domain together with a co-activator peptide derived from PGC-1 α revealed a transcriptionally active conformation even in the absence of a ligand [17]. In addition, the ligand-binding pocket of ERR α is very small

in comparison to other nuclear receptors [17]. Because of the steric limitations and the conformation of the ligand-binding domain, it is not clear whether it is possible to further activate ERR α with synthetic agonists. However, it is encouraging that several synthetic compounds have been found to repress the activity of ERR α , indicating that, in principle, this receptor can be pharmacologically targeted.

The physiological role of ERR α is not restricted to its metabolic functions in skeletal muscle. Although activation of ERR α in skeletal muscle can ameliorate diabetes and can improve osteoporosis in bone [18], it might have undesirable consequences in mammary tissue, because ERR α is a biomarker for poor outcome in human breast cancer [19]. Paradoxically, ERR α knockout animals are lean and resistant to a high fat diet [20], in contrast to what was expected from the data linking ERR α to OXPHOS and fatty acid oxidation. Because of the tight functional interaction between ERR α and PGC-1 α and the complex expression pattern of ERR α in the central nervous system, it is conceivable that the ERR α $-/-$ mice have a similar brain phenotype as observed in the lean, hyperactive PGC-1 α knockouts [21]. Another explanation for the lean phenotype is reduced apolipoprotein expression in the intestine and a subsequent defect in fat absorption in the ERR α knockout mice [22]. In this case, selective inhibition of ERR α in the intestine, where ERR α is highly expressed, might be an interesting approach in both obesity and diabetes. Future work should thus aim at providing a more comprehensive understanding of the physiological role of ERR α in different tissues and how those could be specifically targeted by pharmacological means.

Increasing PGC-1 α activity

The transcriptional co-activator PGC-1 α is a master regulator of mitochondrial biogenesis and oxidative metabolism [12]. Moreover, PGC-1 α increases expression of the insulin-sensitive glucose transporter GLUT4 and promotes muscle fiber-type switching from type 2b toward the more oxidative type 2a and type 1 muscle fibers [23,24]. Expression of PGC-1 α is decreased in skeletal muscle of type 2 diabetic patients concomitant with the observed defects in mitochondrial function [2,3]; thus, increasing PGC-1 α activity could potentially counter the deleterious effects observed in diabetes. Intriguingly, exercise combined with changes in lifestyle is one of the most potent interventions for the prevention and treatment of type 2 diabetes [25]. It is thought that many of the beneficial effects of physical activity are due to induction of PGC-1 α levels by exercise.

PGC-1 α activity is regulated at multiple levels: first, because the half-life of the PGC-1 α protein is relatively short [26], its levels are rapidly adjusted by transcriptional control. Exercise-induced calcium signaling potently induces PGC-1 α transcription in skeletal muscle [27,28]. Modulation of this pathway or of the transcription factors involved (calcium/

calmodulin-dependent protein kinase IV, calcineurin A, myocyte enhancer factor 2) can elevate PGC-1 α levels. Second, post-translational modifications can both stabilize the PGC-1 α protein as well as control its interaction with inhibitory (p160 myb binding protein, histone deacetylase 5) and activating protein complexes (histone acetyltransferases, the TRAP/mediator complex and sirtuin 1/SIRT1) [26,28–32]. As a transcriptional co-activator, PGC-1 α has neither a DNA-binding domain nor a ligand-binding domain. Moreover, it is not known to have enzymatic activity, making it difficult to target pharmacologically. These obstacles can be overcome by modulating the activity of PGC-1 α binding partners, for example, by using histone deacetylase inhibitors. Finally, it might be possible to target the upstream signaling pathways that result in PGC-1 α phosphorylation and deacetylation and subsequent change in activity [26,29].

Caveat

PGC-1 α is expressed in a variety of different tissues. Although increasing adaptive thermogenesis in brown fat or OXPHOS capacity in muscle via PGC-1 α could help obese and diabetic individuals, increasing PGC-1 α activity in all tissues of type 2 diabetic patients could have untoward side effects. For example, PGC-1 α is a strong regulator of hepatic gluconeogenesis and accordingly, PGC-1 α levels are elevated in the liver of animal models of type 1 and type 2 diabetes [33]. Similarly, PGC-1 α inhibits insulin secretion in pancreatic β -cells [34] and thus PGC-1 α activity in these two tissues should be reduced in diabetes. In the heart, PGC-1 α is involved in the switch in fuel utilization during development [35] and can also play a role in mediating cardiomyopathy and heart failure, although this is currently still under debate [35,36]. By contrast, PGC-1 α and its target genes are reduced in different animal models and patients with heart failure and this dysregulation might contribute to the pathological remodeling in cardiac muscle [35,36]. The function of PGC-1 α in other tissues (e.g. kidney, brain) has yet to be more thoroughly explored before a conclusive statement can be given about the effect of PGC-1 α modulation in those tissues. Hence, direct targeting of PGC-1 α could have numerous undesired side effects in other tissues.

Targeting the ERR α –PGC-1 α interaction

Perhaps the most promising and most specific strategy to boost OXPHOS would involve targeting the PGC-1 α /ERR α interaction (Fig. 1). Some of the known synthetic inhibitors of nuclear receptors work by interfering with the binding of co-activators, for example, toxaphene and chlordane reduce binding of the glucocorticoid receptor-interacting protein 1 (GRIP1) [37]. Recently, the inverse agonist XCT790 was shown to reduce the interaction between ERR α and PGC-1 α [5,38]. By inhibiting PGC-1 α binding to ERR α with XCT790, skeletal muscle cellular respiration and expression

of OXPHOS genes were reduced [5]. This ERR α inverse agonist thus elicited a ‘diabetic’ phenotype in these cells. Other PGC-1 α target genes were unaffected by treatment with XCT790 in muscle and in liver, respectively. Importantly, XCT790 did *not* inhibit PGC-1 α -driven hepatic gluconeogenic gene expression [5]. Therefore, in principle, synthetic compounds that *enhance* PGC-1 α -ERR α interactions ought to selectively improve the aberrant OXPHOS gene expression in skeletal muscle whereas not modulating ERR α -independent functions of PGC-1 α or PGC-1 α -independent functions of ERR α . Hence, this strategy might confer the needed specificity to avoid the deleterious effects of modulating these proteins in other tissues, which, as discussed previously, could exacerbate diabetes.

Caveat

ERR α has so far only been targeted with inhibitory synthetic compounds. It is unclear whether the PGC-1 α -ERR α binding can be *promoted* because PGC-1 α might not require a conformational change in the ERR α structure for optimal binding. In that case, PGC-1 α -dependent ERR α activity might be exclusively regulated by relative levels of PGC-1 α in a specific tissue and context. Compounds that mimic PGC-1 α binding to ERR α could circumvent that scenario.

Conclusions

At present, a wealth of clinical and basic biological studies support the notion that inherited or acquired variation in mitochondria can contribute to the development of type 2 diabetes (summarized in [4]). First, genome-wide expression analyses have suggested that the muscle of diabetics, as well as pre-diabetics and individuals with a family history of diabetes, have reduced expression of mitochondrial OXPHOS genes. Second, functional studies have shown that diabetics and pre-diabetics have lower ATP production capacity in muscle. Third, functional and histological studies of skeletal muscle mitochondria from diabetic patients have revealed smaller mitochondria with reduced enzymatic capacities than those in healthy volunteers. Fourth, there appears to be reduced oxidative phosphorylation activity in elderly, insulin-resistant individuals as compared to a younger control group. Moreover, a Gly482Ser single nucleotide polymorphism in the PGC-1 α gene was found to be associated with type 2 diabetes in some populations [39] as well as with cardiovascular adaptation following physical exercise [40]. Thus, reduced OXPHOS and PGC-1 α levels might be causally linked to the development of the disease.

ERR α and PGC-1 α each are members of a small family of related genes. Whereas expression of ERR β in postnatal development is restricted and only low levels are detected in liver, stomach, skeletal muscle, heart and kidney, ERR γ is widely expressed in adult tissues [7,8]. ERR γ is co-activated by PGC-1 α and thus could have similar importance as a drug target.

Links

- <http://www.niddk.nih.gov> (National Institute of Diabetes and Digestive and Kidney Diseases)
- <http://www.cdc.gov/diabetes> (Center for Disease Control Diabetes Public Health Resource)
- <http://www.diabetes.org> (American Diabetes Association)

Unfortunately, ERR γ ligand-binding domain crystal structures revealed a ligand-independent active conformation [41]. Therefore, finding ligands for ERR γ suffers from the same limitations as with ERR α . PGC-1 β has a similar expression pattern as PGC-1 α [12]. These two proteins have distinct as well as overlapping functions, both being strong activators of mitochondrial biogenesis and oxidative metabolism. In addition, like PGC-1 α , PGC-1 β levels are reduced in skeletal muscle of pre-diabetic and diabetic patients [3]. Thus, the potential of PGC-1 β for the treatment of type 2 diabetes remains to be investigated. Probably less interesting in this regard, the PGC-1-related co-activator (PRC) is expressed ubiquitously and is not subject to the same regulatory mechanisms as PGC-1 α and PGC-1 β [12].

Mitochondrial biogenesis and oxidative metabolism are fundamental processes resident in virtually all cells; therefore, therapeutic strategies involving this organelle must consider tissue-specific differences in mitochondria [42]. Similarly, tissue-selective targeting the ERR α -PGC-1 α axis in skeletal muscle is an attractive approach to treat the mitochondrial dysfunctions that have been associated with type 2 diabetes with the caveats in other tissues as described above [4,40,43].

Worldwide, type 2 diabetes is on a steep rise as a result of an aging population as well as by obesity and a sedentary lifestyle [1]. Diabetes and related disorders are the fifth leading cause of death in the United States. This not only has implications for affected patients, but also places a tremendous financial burden on the healthcare system. At present, only a handful of drugs in combination with diet and exercise, are useful in delaying the onset of diabetes and its complications.

Related articles

- Taylor, R. (2004) Causation of type 2 diabetes – the Gordian knot unravels. *N. Engl. J. Med.* 350, 639–641
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- Houten, S.M. and Auwerx, J. (2004) PGC-1 α : turbocharging mitochondria. *Cell* 119, 5–7
- Attie, A.D. and Kendziora, C.M. (2003) PGC-1 α at the crossroads of type 2 diabetes. *Nat. Genet.* 34, 244–245
- Lowell, B.B. and Shulman, G.I. (2005) Mitochondrial dysfunction and type 2 diabetes. *Science* 307, 384–387

Recent discoveries suggest that the mitochondrion can be central in the pathogenesis of type 2 diabetes; these studies motivate the idea that targeting this organelle can ameliorate diabetes. Augmenting mitochondrial mass and function via pharmacologic manipulation of ERR α /PGC-1 α might represent a fundamentally new approach to treating and preventing this growing epidemic. It might even be possible that this pathway has broader implication in the metabolic syndrome; however, association of the ERR α -specified PGC-1 α target gene expression with cardiovascular disease or stroke remains to be shown.

Outstanding issues

- Is it possible to design ERR α agonists?
- Can the ERR α -PGC-1 α protein-protein interaction be enhanced with synthetic compounds?
- What are the roles for other ERR (ERR β , ERR γ) and PGC-1 (PGC-1 β , PRC) family members?
- What are the potential side effects (in other tissues) that would arise from the various proposed strategies affect?

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References

- 1 Brower, V. (2004) Like a snake in the grass. *EMBO Rep.* 5, 555–558
- 2 Mootha, V.K. *et al.* (2003) PGC-1 α -responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat. Genet.* 34, 267–273
- 3 Patti, M.E. *et al.* (2003) Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. *Proc. Natl. Acad. Sci. USA* 100, 8466–8471
- 4 Lowell, B.B. and Shulman, G.I. (2005) Mitochondrial dysfunction and type 2 diabetes. *Science* 307, 384–387
- 5 Mootha, V.K. *et al.* (2004) Erralpha and Gabpa/b specify PGC-1 α -dependent oxidative phosphorylation gene expression that is altered in diabetic muscle. *Proc. Natl. Acad. Sci. USA* 101, 6570–6575
- 6 Gronemeyer, H. *et al.* (2004) Principles for modulation of the nuclear receptor superfamily. *Nat. Rev. Drug Discov.* 3, 950–964
- 7 Horard, B. and Vanacker, J.M. (2003) Estrogen receptor-related receptors: orphan receptors desperately seeking a ligand. *J. Mol. Endocrinol.* 31, 349–357
- 8 Giguère, V. (2002) To ERR in the estrogen pathway. *Trends Endocrinol. Metab.* 13, 220–225
- 9 Schreiber, S.N. *et al.* (2003) The transcriptional coactivator PGC-1 regulates the expression and activity of the orphan nuclear receptor estrogen-related receptor alpha (ERR α). *J. Biol. Chem.* 278, 9013–9018
- 10 Huss, J.M. *et al.* (2002) Peroxisome proliferator-activated receptor coactivator-1 α (PGC-1 α) coactivates the cardiac-enriched nuclear receptors estrogen-related receptor- α and - γ . Identification of novel leucine-rich interaction motif within PGC-1 α . *J. Biol. Chem.* 277, 40265–40274

- 11 Schreiber, S.N. *et al.* (2004) The estrogen-related receptor alpha (ERRalpha) functions in PPARgamma coactivator 1alpha (PGC-1alpha)-induced mitochondrial biogenesis. *Proc. Natl. Acad. Sci. USA* 101, 6472–6477
- 12 Puigserver, P. and Spiegelman, B.M. (2003) Peroxisome proliferator-activated receptor-gamma coactivator 1alpha (PGC-1alpha): transcriptional coactivator and metabolic regulator. *Endocr. Rev.* 24, 78–90
- 13 Wu, Z. *et al.* (1999) Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* 98, 115–124
- 14 Huss, J.M. *et al.* (2004) 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, 9079–9091
- 15 Laganier, J. *et al.* (2004) 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, 18504–18510
- 16 Vanacker, J.M. *et al.* (1999) Transcriptional activities of the orphan nuclear receptor ERR alpha (estrogen receptor-related receptor-alpha). *Mol. Endocrinol.* 13, 764–773
- 17 Kallen, J. *et al.* (2004) 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, 49330–49337
- 18 Bonnelye, E. *et al.* (2002) Estrogen receptor-related receptor alpha impinges on the estrogen axis in bone: potential function in osteoporosis. *Endocrinology* 143, 3658–3670
- 19 Ariazi, E.A. *et al.* (2002) Estrogen-related receptor alpha and estrogen-related receptor gamma associate with unfavorable and favorable biomarkers, respectively, in human breast cancer. *Cancer Res.* 62, 6510–6518
- 20 Luo, J. *et al.* (2003) Reduced fat mass in mice lacking orphan nuclear receptor estrogen-related receptor alpha. *Mol. Cell Biol.* 23, 7947–7956
- 21 Lin, J. *et al.* (2004) Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. *Cell* 119, 121–135
- 22 Carrier, J.C. *et al.* (2004) Estrogen-related receptor alpha (ERRalpha) is a transcriptional regulator of apolipoprotein A-IV and controls lipid handling in the intestine. *J. Biol. Chem.* 279, 52052–52058
- 23 Michael, L.F. *et al.* (2001) Restoration of insulin-sensitive glucose transporter (GLUT4) gene expression in muscle cells by the transcriptional coactivator PGC-1. *Proc. Natl. Acad. Sci. USA* 98, 3820–3825
- 24 Lin, J. *et al.* (2002) Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature* 418, 797–801
- 25 Knowler, W.C. *et al.* (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346, 393–403
- 26 Puigserver, P. *et al.* (2001) Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. *Mol. Cell* 8, 971–982
- 27 Handschin, C. *et al.* (2003) An autoregulatory loop controls peroxisome proliferator-activated receptor gamma coactivator 1alpha expression in muscle. *Proc. Natl. Acad. Sci. USA* 100, 7111–7116
- 28 Czubryt, M.P. *et al.* (2003) Regulation of peroxisome proliferator-activated receptor gamma coactivator 1alpha (PGC-1alpha) and mitochondrial function by MEF2 and HDAC5. *Proc. Natl. Acad. Sci. USA* 100, 1711–1716
- 29 Fan, M. *et al.* (2004) Suppression of mitochondrial respiration through recruitment of p160 myb binding protein to PGC-1alpha: modulation by p38 MAPK. *Genes Dev.* 18, 278–289
- 30 Puigserver, P. *et al.* (1999) Activation of PPARgamma coactivator-1 through transcription factor docking. *Science* 286, 1368–1371
- 31 Wallberg, A.E. *et al.* (2003) Coordination of p300-mediated chromatin remodeling and TRAP/mediator function through coactivator PGC-1alpha. *Mol. Cell* 12, 1137–1149
- 32 Rodgers, J.T. *et al.* (2005) Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature* 434, 113–118
- 33 Yoon, J.C. *et al.* (2001) Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1. *Nature* 413, 131–138
- 34 Yoon, J.C. *et al.* (2003) Suppression of beta cell energy metabolism and insulin release by PGC-1alpha. *Dev. Cell* 5, 73–83
- 35 Huss, J.M. and Kelly, D.P. (2004) Nuclear receptor signaling and cardiac energetics. *Circ. Res.* 95, 568–578
- 36 Arany, Z. *et al.* (2005) Transcriptional coactivator PGC-1alpha controls the energy state and contractile function of cardiac muscle. *Cell Metab.* 1, 259–271
- 37 Yang, C. and Chen, S. (1999) Two organochlorine pesticides, toxaphene and chlordane, are antagonists for estrogen-related receptor alpha-1 orphan receptor. *Cancer Res.* 59, 4519–4524
- 38 Willy, P.J. *et al.* (2004) Regulation of PPARgamma coactivator 1alpha (PGC-1alpha) signaling by an estrogen-related receptor alpha (ERRalpha) ligand. *Proc. Natl. Acad. Sci. USA* 101, 8912–8917
- 39 Ek, J. *et al.* (2001) Mutation analysis of peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1) and relationships of identified amino acid polymorphisms to type II diabetes mellitus. *Diabetologia* 44, 2220–2226
- 40 Shuldiner, A.R. and McLenithan, J.C. (2004) Genes and pathophysiology of type 2 diabetes: more than just the Randle cycle all over again. *J. Clin. Invest.* 114, 1414–1417
- 41 Greschik, H. *et al.* (2002) Structural and functional evidence for ligand-independent transcriptional activation by the estrogen-related receptor 3. *Mol. Cell* 9, 303–313
- 42 Mootha, V.K. *et al.* (2003) Integrated analysis of protein composition, tissue diversity, and gene regulation in mouse mitochondria. *Cell* 115, 629–640
- 43 Taylor, R. (2004) Causation of type 2 diabetes – the Gordian knot unravels. *N. Engl. J. Med.* 350, 639–641