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Metabolic syndromes

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

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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 ERRα and PGC-1α. We describe how knowledge of this transcriptional circuit can be translated to the development of novel therapies for type 2 diabetes.

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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-1α [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 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 ERRα is recruited by PGC-1α 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 ERRα and PGC-1α to promote OXPHOS

ERRα 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].

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

	Pros	Cons	Relevant patents	Refs
ERRα[a] agonists	Nuclear receptor: good drug target	Tissue selectivity; feasibility of designing an agonist	WO 00/47735, WO 05/003766	[17]
PGC-1α[a] activators	Signaling pathways and proteins modulating PGC-1α 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[a]–PGC-1α[a] 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: ERRα, estrogen-related receptor α; PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α.

ERRα 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]. ERRα 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 ERRα (NR3B1) or its two closely related family members ERRβ (NR3B2) or ERRγ (NR3B3) *in vivo*.

Recently, the discovery of the interaction between ERRα and the transcriptional co-activator PGC-1α led to a breakthrough in understanding the function of ERRα [5,9–11]. PGC-1α is a key regulator of mitochondrial biogenesis and oxidative metabolism in different tissues [12]. An unbiased, global screen revealed that PGC-1α regulates many mitochondrial OXPHOS genes via its interaction with ERRα 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 ERRα in the promoter of PGC-1α target genes are the highest scoring motifs on day 1, day 2 and day 3 after adenoviral PGC-1α 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-1α and ERRα 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-1α and ERRα. In the next few

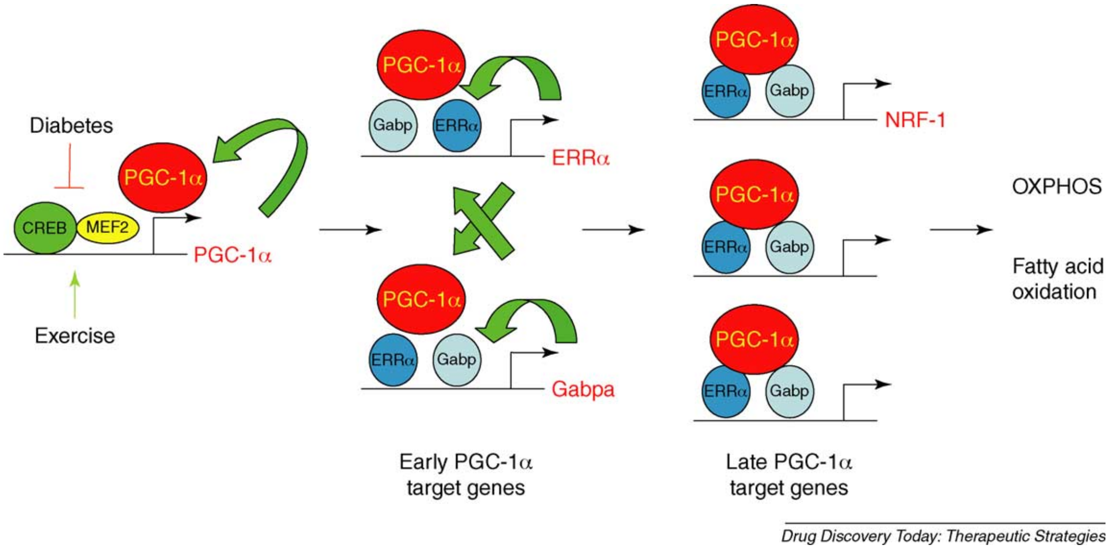

Figure 1. Regulatory cascade in the expression of oxidative phosphorylation (OXPHOS) genes in skeletal muscle. Peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) levels in muscle are induced by physical exercise and reduced in type 2 diabetes. First, PGC-1α expression is controlled by a positive autoregulatory loop. The estrogen-related receptor α (ERRα) and the GA-binding protein A (GABPA, alternatively called nuclear respiratory factor 2a, NRF2a) are early PGC-1α target genes. They regulate their own transcription and transcription of each other, both being co-activated by PGC-1α. ERRα and GABP (heterodimer of GABPA and GABPB) are the main docking partners for PGC-1α in the transcriptional cascade of later target genes that leads to increased OXPHOS and fatty acid β-oxidation. For details, see [5,27]. Abbreviations: CREB, cyclic AMP responsive element binding protein; MEF2, myocyte enhancer factor 2; NRF-1, nuclear respiratory factor 1.

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

Direct targeting of ERRα

ERRα is a very early PGC-1α target gene and thus a major regulator of OXPHOS and fatty acid oxidation gene expression. In cultured myotubes, adenoviral infection with PGC-1α elevates ERRα expression on day 1 post infection [5]. Moreover, ERRα binding motifs are located in the promoter regions of early and late PGC-1α target genes, including ERRα itself and GABPA [5]. Although additional transcription factors downstream of ERRα 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 (PPARα, NR1C1), which is a target of fibrate drugs and regulates mitochondrial fatty acid β-oxidation [14].

ERRα controls its own transcription by an autoregulatory loop [5,15]. Interestingly, ERRα binding sites in the ERRα promoter are polymorphic in their copy number [15]. Increased number of ERRα binding motifs results in elevated activation of ERRα transcription by ERRα and PGC-1α. 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 ERRα 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 ERRα shown in Fig. 1, hence stimulating the entire transcriptional cascade involved in mitochondrial biogenesis. Moreover, because ERRα is involved in the regulation of fatty acid β-oxidation, activating ERRα can ameliorate the lipid accumulation in skeletal muscle, which is believed to contribute to insulin resistance.

Caveat

Transcriptional activity of ERRα is dependent on cellular context [16]. Under some circumstances, the ability of ERRα 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 ERRα ligand-binding domain together with a co-activator peptide derived from PGC-1α revealed a transcriptionally active conformation even in the absence of a ligand [17]. In addition, the ligand-binding pocket of ERRα 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 ERRα with synthetic agonists. However, it is encouraging that several synthetic compounds have been found to repress the activity of ERRα, indicating that, in principle, this receptor can be pharmacologically targeted.

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

Increasing PGC-1α activity

The transcriptional co-activator PGC-1α is a master regulator of mitochondrial biogenesis and oxidative metabolism [12]. Moreover, PGC-1α 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-1α is decreased in skeletal muscle of type 2 diabetic patients concomitant with the observed defects in mitochondrial function [2,3]; thus, increasing PGC-1α 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-1α levels by exercise.

PGC-1α activity is regulated at multiple levels: first, because the half-life of the PGC-1α protein is relatively short [26], its levels are rapidly adjusted by transcriptional control. Exercise-induced calcium signaling potently induces PGC-1α 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-1α levels. Second, post-translational modifications can both stabilize the PGC-1α 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-1α 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-1α binding partners, for example, by using histone deacetylase inhibitors. Finally, it might be possible to target the upstream signaling pathways that result in PGC-1α phosphorylation and deacetylation and subsequent change in activity [26,29].

Caveat

PGC-1α is expressed in a variety of different tissues. Although increasing adaptive thermogenesis in brown fat or OXPHOS capacity in muscle via PGC-1α could help obese and diabetic individuals, increasing PGC-1α activity in all tissues of type 2 diabetic patients could have untoward side effects. For example, PGC-1α is a strong regulator of hepatic gluconeogenesis and accordingly, PGC-1α levels are elevated in the liver of animal models of type 1 and type 2 diabetes [33]. Similarly, PGC-1α inhibits insulin secretion in pancreatic β-cells [34] and thus PGC-1α activity in these two tissues should be reduced in diabetes. In the heart, PGC-1α 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-1α 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-1α 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-1α modulation in those tissues. Hence, direct targeting of PGC-1α could have numerous undesired side effects in other tissues.

Targeting the ERRα–PGC-1α interaction

Perhaps the most promising and most specific strategy to boost OXPHOS would involve targeting the PGC-1α/ERRα 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 ERRα and PGC-1α [5,38]. By inhibiting PGC-1α binding to ERRα with XCT790, skeletal muscle cellular respiration and expression of OXPHOS genes were reduced [5]. This ERRα inverse agonist thus elicited a 'diabetic' phenotype in these cells. Other PGC-1α target genes were unaffected by treatment with XCT790 in muscle and in liver, respectively. Importantly, XCT790 did *not* inhibit PGC-1α-driven hepatic gluconeogenic gene expression [5]. Therefore, in principle, synthetic compounds that *enhance* PGC-1α-ERRα interactions ought to selectively improve the aberrant OXPHOS gene expression in skeletal muscle whereas not modulating ERRα-independent functions of PGC-1α or PGC-1α-independent functions of ERRα. 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

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

ERRα and PGC-1α each are members of a small family of related genes. Whereas expression of ERRβ in postnatal development is restricted and only low levels are detected in liver, stomach, skeletal muscle, heart and kidney, ERRγ is widely expressed in adult tissues [7,8]. ERRγ is co-activated by PGC-1α 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, ERRγ ligand-binding domain crystal structures revealed a ligand-independent active conformation [41]. Therefore, finding ligands for ERRγ suffers from the same limitations as with ERRα. PGC-1β has a similar expression pattern as PGC-1α [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-1α, PGC-1β levels are reduced in skeletal muscle of pre-diabetic and diabetic patients [3]. Thus, the potential of PGC-1β 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-1α and PGC-1β [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 ERRα–PGC-1α 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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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 ERRα/PGC-1α 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 ERRα-specified PGC-1α target gene expression with cardiovascular disease or stroke remains to be shown.

Outstanding issues

- Is it possible to design ERRα agonists?
- Can the ERRα–PGC-1α protein–protein interaction be enhanced with synthetic compounds?
- What are the roles for other ERR (ERRβ, ERRγ) and PGC-1 (PGC-1β, 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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