Road to exercise mimetics: targeting nuclear receptors in skeletal muscle

Weiwei Fan[1], Annette R Atkins[1,2], Ruth T Yu[1], Michael Downes[1] and Ronald M Evans[1,2]

[1]Gene Expression Laboratory [2]Howard Hughes Medical Institute, Salk Institute for Biological Studies, La Jolla, California 92037, USA

Correspondence should be addressed to R M Evans
Email
evans@salk.edu

Abstract

Skeletal muscle is the largest organ in the human body and is the major site for energy expenditure. It exhibits remarkable plasticity in response to physiological stimuli such as exercise. Physical exercise remodels skeletal muscle and enhances its capability to burn calories, which has been shown to be beneficial for many clinical conditions including the metabolic syndrome and cancer. Nuclear receptors (NRs) comprise a class of transcription factors found only in metazoans that regulate major biological processes such as reproduction, development, and metabolism. Recent studies have demonstrated crucial roles for NRs and their co-regulators in the regulation of skeletal muscle energy metabolism and exercise-induced muscle remodeling. While nothing can fully replace exercise, development of exercise mimetics that enhance or even substitute for the beneficial effects of physical exercise would be of great benefit. The unique property of NRs that allows modulation by endogenous or synthetic ligands makes them bona fide therapeutic targets. In this review, we present an overview of the current understanding of the role of NRs and their co-regulators in skeletal muscle oxidative metabolism and summarize recent progress in the development of exercise mimetics that target NRs and their co-regulators.

Key Words
- exercise
- skeletal muscle
- nuclear receptors
- molecular endocrinology

Journal of Molecular Endocrinology
(2013) **51**, T87–T100

Journal of Molecular Endocrinology

Introduction

Exercise has been known for its health benefits since ancient times. It is now widely accepted that physical activity positively affects a variety of clinical conditions including obesity, type 2 diabetes, metabolic syndrome, neurodegenerative diseases, cardiovascular diseases, and cancer (Perseghin *et al*. 1996, Grazina & Massano 2013, Lemanne *et al*. 2013, Mellett & Bousquet 2013). On the other hand, physical inactivity has major negative influences on these disease conditions (Hu *et al*. 2004).

How exactly exercise exerts its beneficial effects is not fully understood; however, skeletal muscle is believed to play a vital role (Hamilton & Booth 2000). As the largest organ in the human body, skeletal muscle comprises ~40% of total body mass and accounts for ~30% of whole-body energy metabolism during rest (Zurlo *et al*. 1990). Upon insulin stimulation, skeletal muscle can be responsible for ~85% of total glucose disposal (Defronzo *et al*. 1981). During peak activity, whole-body energy metabolism can be increased by up to 20-fold, ~90% of which is contributed by skeletal muscle (Zurlo *et al*. 1990). Hence, muscle is the major site of calorie burning of energy substrates such as glucose and free fatty acids. Exercise training remodels skeletal muscle to more efficiently clear these substrates, the excess levels of which negatively affect many tissues.

In mammals, skeletal muscle is a mosaic of heterogeneous myofibers with diverse structural and functional properties (Schiaffino & Reggiani 2011). Based on the expression patterns of different myosin heavy chain (MYH) isoforms, which coincide with various biochemical

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd.
This paper is one of nine papers that form part of the 25th anniversary special issue of *Journal of Molecular Endocrinology*. The Guest Editor for this section was Ronald M Evans, Investigator, Howard Hughes Medical Institute and Professor, Salk Institute for Biological Studies, La Jolla, CA, USA. He was not involved in the handling of this paper, on which he is listed as an author

characteristics, myofibers can be classified into four major groups: slow-twitch type I and fast-twitch types IIa, IIx/d, and IIb. Type I and IIa fibers are red in appearance due to their high myoglobin content. They are rich in mitochondria and predominantly powered by complete oxidation of glucose and fatty acids. These oxidative fibers are also dense with vasculature and resistant to fatigue. By contrast, the glycolytic type IIx/d and IIb fibers are generally white in color, have less myoglobin content and mitochondria, mainly rely on glycolysis for energy production, have less vasculature, and fatigue rapidly (Schiaffino & Reggiani 2011). In humans, fiber-type composition is strongly associated with metabolic health, with more glycolytic fibers being seen in obese and type 2 diabetic patients (Hickey *et al*. 1995).

It has been well documented that skeletal muscle undergoes a series of physiological and biochemical adaptations upon exercise training (Hamilton & Booth 2000), of which the most intriguing is fiber-type transformation. Many human and animal studies have clearly demonstrated that prolonged exercise induces the glycolytic type IIb and IIx/d fibers to transform to the more oxidative type IIa fibers (Gollnick *et al*. 1973, Foster *et al*. 1978, Wu *et al*. 2001). Although some professional athletes have an increased proportion of type I fibers (Gollnick *et al*. 1972), it remains unclear whether exercise training can switch type II fibers completely to type I. While exercise has a positive effect on the glycolytic-to-oxidative fiber-type transformation, physical inactivity and obesity usually have the opposite effect and lead to the reverse transformation (Bergouignan *et al*. 2011). During fiber-type transformation, not only is the expression of MYH isoforms switched, but other fiber-type-specific properties, such as mitochondrial density, oxidative phosphorylation (OXPHOS) activity, vasculature, and fatigue resistance, are also changed accordingly (Yan *et al*. 2011).

Skeletal muscle adaptation during exercise involves numerous transcriptional and epigenetic changes, which are regulated by multiple signaling pathways (Bassel-Duby & Olson 2006, Barrès *et al*. 2012). In addition to the widely known calcineurin/NFAT and HDAC/MEF pathways, it has recently been shown that nuclear receptors (NRs) and their co-regulatory factors also play important roles in skeletal muscle adaptation.

NRs are ligand-modulated transcription factors that respond to a variety of hydrophobic molecules including hormones, lipids, steroids, retinoids, and xenobiotics. All NRs share similar modular domains, including a highly conserved DNA-binding domain (DBD), a ligand-binding domain (LBD), variable N- and C-terminal domains, and a hinge domain between the DBD and LBD (Mangelsdorf *et al*. 1995). The DBD is characterized by a zinc finger motif that recognizes the hormone response element on target chromatin and the LBD by a hydrophobic ligand-binding pocket. Upon ligand binding, NRs undergo conformational changes, which alter their interactions with other proteins and trigger epigenetic chromatin changes and downstream transcriptional regulation (Wurtz *et al*. 1996).

A major goal of exercise science is to find substitutes for physical exercise that achieve its beneficial effects in people unable to exercise. The ability of NRs to sense and respond to small-molecule ligands makes them ideal pharmacological targets. This review focuses on the roles of NRs and their co-regulatory factors in the regulation of skeletal muscle functions, including fiber-type determination, mitochondrial biogenesis, vasculature development, and fatigue resistance, with the goal of shedding some light on the development of the 'exercise in a pill'.

The peroxisome proliferator-activated receptor subfamily

The peroxisome proliferator-activated receptor (PPAR) subfamily of NRs is composed of three members: PPARα, PPARδ (also referred to as PPARβ), and PPARγ. PPARα was the first PPAR identified during a screen for the molecular target of fibrates, a class of cholesterol-lowering compounds that increase hepatic fatty acid oxidation and peroxisome proliferation (hence the name) (Issemann & Green 1990). Based on sequence homology, PPARδ and PPARγ, which do not induce peroxisome proliferation, were later cloned from mouse tissue (Zhu *et al*. 1993, Kliewer *et al*. 1994).

PPARs are predominantly localized in the nucleus. They form heterodimers with retinoid X receptors (RXRs) and can be activated by both PPAR ligands and RXR ligands. In the absence of a ligand, the PPAR/RXR heterodimers bind to PPAR response elements (PPREs) in association with transcriptional co-repressors such as nuclear receptor co-repressor (NCoR) and SMRT. Ligand binding leads to a conformational change and recruitment of co-activators such as PPARγ co-activator 1α and PPARγ co-activator 1β (PGC1α and PGC1β) to replace the co-repressors, resulting in the activation of downstream target gene expression. PPARs play essential roles in the regulation of lipid metabolism. They sense and respond to free fatty acids and their derivatives to regulate genes involved at almost all levels of lipid metabolism, including lipid import/export, synthesis, storage, breakdown, and oxidation (Evans *et al*. 2004). Although the PPAR

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

subfamily shares certain common target genes, PPARα and PPARδ are typically involved in the regulation of lipid catabolism and oxidation, while PPARγ is responsible for adipogenesis and lipid synthesis. All the three PPARs are expressed in skeletal muscle (Muoio *et al*. 2002, Amin *et al*. 2010), and over the last decade, both gain-of-function and loss-of-function studies have contributed significantly to our understanding of their roles in muscle.

PPARδ is the most abundant PPAR in skeletal muscle (Muoio *et al*. 2002, Amin *et al*. 2010) and plays important roles in the regulation of fiber-type determination, mitochondrial function, lipid metabolism, and fatigue resistance (Fig. 1). It is expressed relatively highly in oxidative fibers compared to glycolytic fibers. Exercise, in both acute and prolonged forms (Luquet *et al*. 2003, Watt *et al*. 2004), induces the expression of *Pparδ* (*Ppard*) in skeletal muscle. Similar to exercise, fasting also triggers a fuel-source switch in skeletal muscle from glucose to fatty acid utilization. Consistently, 6–48 h of fasting dramatically increases the expression of *Pparδ* in skeletal muscle (de Lange *et al*. 2006).

Two independent studies have shown that the overexpression of *Pparδ* in skeletal muscle induces a glycolytic-to-oxidative fiber-type transformation (Luquet *et al*. 2003, Wang *et al*. 2004). Mice overexpressing WT *Pparδ* have more oxidative fibers, higher OXPHOS enzyme activities, and more uncoupling proteins (UCPs). These transgenic mice also have reduced fat content with smaller adipocyte size, similar to what is observed in exercised animals (Luquet *et al*. 2003). Mice expressing a constitutively active form of *Pparδ* were nicknamed 'marathon mice' as they can run for up to twice the distance of their WT littermates. They have more type I and less type II fibers, have increased mitochondrial biogenesis and uncoupling, are resistant to diet-induced obesity, and have improved glucose tolerance (Wang *et al*. 2004). Conversely, conditional knockout of *Pparδ* in skeletal muscle leads to an oxidative-to-glycolytic fiber-type switch. The knockout muscle has lower expression of genes involved in fatty acid catabolism and oxidation, as well as reduced OXPHOS activities (Schuler *et al*. 2006). Upon a high-fat diet challenge, the mutant mice gain more weight mainly due to increased fat content and are more susceptible to developing insulin resistance and glucose intolerance (Schuler *et al*. 2006). Therefore, *Pparδ* appears to be necessary for the maintenance of oxidative

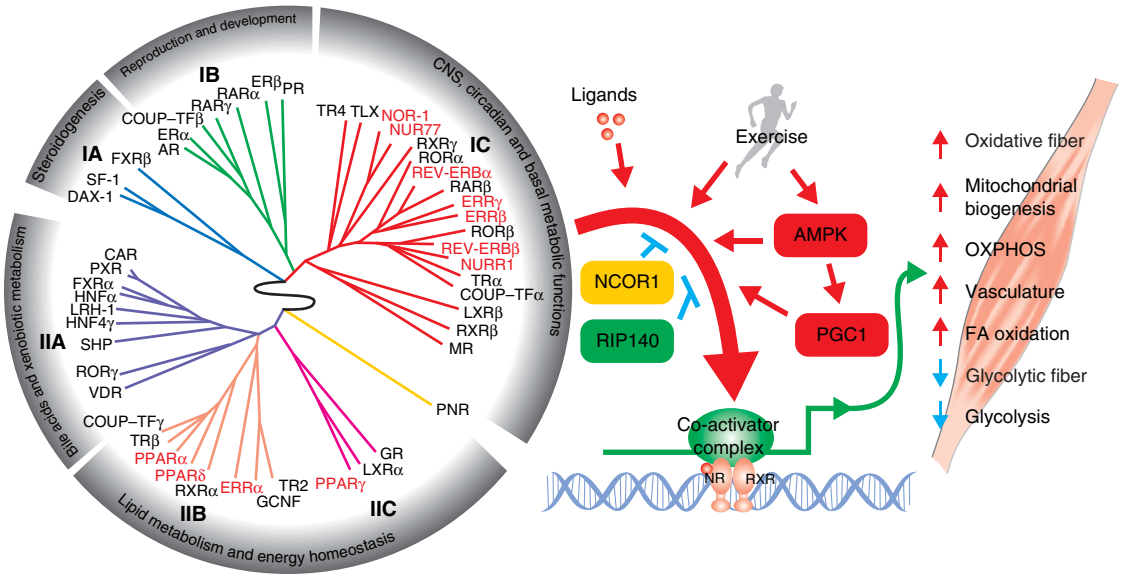

Figure 1

NR regulation of energy metabolism and remodeling in skeletal muscle. The NR ring of physiology is shown on the left (Bookout *et al*. 2006). It clusters 49 mouse NRs into six groups based on their tissue distribution patterns. The NRs that have been found to play crucial roles in skeletal muscle function (highlighted in red/bold) are clustered mainly in two groups: group IC, the members of which are selectively expressed in highly metabolic tissues and are involved in CNS, circadian, and basal metabolic functions, including NOR1, NUR77, NURR1, ERRβ, ERRγ, REV-ERBα, and REV-ERBβ, and groups IIB and IIC, the members of which are broadly expressed and are linked to lipid metabolism and energy homeostasis, including PPARα, PPARδ, PPARγ, and ERRα. These NRs work in concert with exercise and co-regulators to regulate many aspects of skeletal muscle physiology. Synthetic ligands targeting NRs and their co-regulators can enhance or replace the physiological benefits induced by exercise, which is of great value to public health.

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

fibers and their oxidative functions in skeletal muscle. However, it remains to be demonstrated whether *Pparδ* is required for exercise-induced muscle remodeling.

Pparα (*Ppara*) is abundantly expressed in tissues with high fatty acid catabolism, such as liver and heart (Fig. 1; Braissant *et al*. 1996), where it is activated by free fatty acids and promotes fatty acid oxidation (Kersten *et al*. 1999). *Pparα* is also expressed at significant levels in skeletal muscle. Both *Pparα* and *Pparδ* regulate fatty acid catabolism and share common target genes. Similar to *Pparδ*, the overexpression of *Pparα* in skeletal muscle also induces the expression of genes involved in fatty acid catabolism, tricarboxylic acid (TCA) cycle, and mitochondrial OXPHOS. As a result, fatty acid oxidation is increased in the transgenic muscle and the mice are resistant to diet-induced obesity (Finck *et al*. 2005). However, the transgenic mice are more prone to developing insulin resistance and glucose intolerance due to the reduced expression of genes involved in glucose uptake and glycolysis (Finck *et al*. 2005). Thus, although *Pparα* has a positive role in the regulation of fatty acid oxidation in skeletal muscle, its activity needs to be finely regulated to balance glucose and fatty acid metabolism.

In addition to their different roles in metabolic regulation, *Pparα* also functions distinctly from *Pparδ* in fiber-type determination. In contrast to *Pparδ*, the overexpression of *Pparα* in skeletal muscle does not increase endurance but rather reduces it by more than 50% (Gan *et al*. 2011). Consistently, an oxidative-to-glycolytic fiber-type switch is found in these mice, as shown by the expression of MYH genes, metachromatic ATPase staining, and MYH immunohistochemistry staining (Gan *et al*. 2013). The opposing functions of PPARα and PPARδ in the induction of glycolytic and oxidative fiber-type transformations respectively seem to be mediated by a miRNA network involving two specific miRNAs, *miR-208b* and *miR-499* (Gan *et al*. 2013), which play important roles in fiber-type determination by activating the oxidative and repressing the glycolytic myofiber gene program (van Rooij *et al*. 2009). In contrast to the overexpression model, knockout of *Pparα* in skeletal muscle induces a glycolytic-to-oxidative fiber-type switch (Gan *et al*. 2013). Therefore, endogenous PPARα counteracts PPARδ to maintain a proper fiber-type composition in skeletal muscle.

Pparγ (*Pparg*) is expressed most highly in adipose tissues, where it plays an essential role in adipogenesis and whole-body lipid homeostasis (Fig. 1). Its ablation in adipose tissues leads to severe lipodystrophy and elevated levels of blood triglycerides and free fatty acids. The knockout mice are more susceptible to diet-induced insulin resistance. However, treatment with thiazolidinediones (TZDs), a class of PPARγ-specific ligands, can still improve insulin sensitivity in these knockout mice, suggesting that PPARγ in non-adipose tissues also contributes to its regulation of lipid homeostasis and insulin sensitivity (He *et al*. 2003). The strongest evidence showing a positive role for muscle PPARγ in metabolic regulation comes from the generation of a mouse model with *Pparγ* specifically deleted in skeletal muscle (Hevener *et al*. 2003). These knockout mice develop glucose intolerance and insulin resistance. Moreover, they are less responsive to TZD-induced skeletal muscle insulin sensitization, while the effects of TZDs in the liver and adipose tissues remain unaffected (Hevener *et al*. 2003). A similar study seems to have drawn a different conclusion, showing that the knockout mice only have mild insulin resistance and respond normally to TZD treatment (Norris *et al*. 2003). However, the two studies were carried out in mice with different genetic backgrounds, one being a pure C57BL/6J background (Hevener *et al*. 2003) and the other a mixed 129/sv, C57BL/6, and FVB background, which might account for the different phenotypes observed. In addition to the knockout models, the overexpression of *Pparγ* in skeletal muscle also demonstrates its importance in metabolic regulation (Amin *et al*. 2010). These transgenic mice are protected from diet-induced insulin resistance and glucose intolerance. Interestingly, these mice produce significant amounts of adiponectin in skeletal muscle, despite their reduced intramuscular adiposity. Furthermore, the activation of AMP-activated protein kinase (AMPK), a known adiponectin target, in the transgenic muscle suggests that the increased adiponectin functions locally. Similar to *Pparδ*, the overexpression of *Pparγ* induces a glycolytic-to-oxidative fiber-type switch and an increase in mitochondrial gene expression, which may be a secondary effect from the activated AMPK pathway (Amin *et al*. 2010). Therefore, PPARγ is required in skeletal muscle for glucose and lipid homeostasis. In addition, its role in the generation of muscle adiponectin provides another layer of metabolism regulation.

The estrogen-related receptor subfamily

The estrogen-related receptor (ERR) subfamily includes three members: ERRα, ERRβ, and ERRγ. ERRα was the first to be identified based on its high sequence homology with the estrogen receptor α (ERα; Giguère *et al*. 1988). ERRβ was cloned in the same study using *Errα* (*Esrra*) cDNA as a probe (Giguère *et al*. 1988). Last but not least, ERRγ was discovered in three independent studies using different

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

strategies (Eudy *et al*. 1998, Hong *et al*. 1999, Heard *et al*. 2000). Although all the three ERRs share high structural similarities with ERs at both the DNA and protein levels, they are distinct from ERs in both their functions and their regulation of target gene transcription (Eichner & Giguere 2011).

All the three ERRs are believed to be constitutively active and, to date, no natural ligand(s) has been identified (Eichner & Giguere 2011). Instead, the transcriptional activities of ERRs are regulated by a number of co-regulatory factors, the most studied of which include the steroid receptor co-activators (SRC1, SRC2, and SRC3; Hong *et al*. 1999, Xie *et al*. 1999, Zhang & Teng 2000), the PGC1α and PGCβ (Huss *et al*. 2002, Kamei *et al*. 2003), and the NR co-repressors RIP140 (receptor-interacting protein 140) and NCoR1 (Sanyal *et al*. 2004, Pérez-Schindler *et al*. 2012).

Extensive studies in the past decade have clearly established a central role of ERRs in the regulation of energy metabolism (Eichner & Giguere 2011), which is further supported by their tissue expression patterns. *Errα* is the most abundant of the three. It is ubiquitously expressed but peaks in tissues with high energy needs including brain, heart, muscle, and kidney (Fig. 1; Giguère *et al*. 1988, Bookout *et al*. 2006). *Errβ* (*Esrrb*) and *Errγ* (*Esrrg*) have similar tissue distribution patterns. Both are selectively expressed in metabolically active tissues such as retina, spinal cord, heart, muscle, and kidney, with *Errγ* generally being expressed at a higher level (Fig. 1; Bookout *et al*. 2006). All the three ERRs are highly expressed in skeletal muscle, and their roles in the regulation of muscle energy metabolism have been explored in both gain-of-function and loss-of-function studies (Luo *et al*. 1997, 2003, Huss *et al*. 2004, Wende *et al*. 2005, Alaynick *et al*. 2007, Chinsomboon *et al*. 2009, Rangwala *et al*. 2010, Narkar *et al*. 2011, Gan *et al*. 2013, Matsakas *et al*. 2013).

Studies of ERRα in skeletal muscle have mainly focused on its synergistic interaction with PGC1α in target gene regulation. No phenotypic change in skeletal muscle is observed after whole-body *Errα* ablation, possibly due to a compensatory induction of *Pgc1α* (*Ppargc1a*; Luo *et al*. 2003, Huss *et al*. 2004). ERRα seems to play a role in the regulation of fatty acid metabolism and fuel selection in skeletal muscle as its overexpression induces the expression of *Pparα*, a key regulator of fatty acid metabolism, and *Pdk4*, the mitochondrial gate keeper for pyruvate oxidation. The overexpression of its co-activator PGC1α can further enhance the expression of these genes (Huss *et al*. 2004, Wende *et al*. 2005). Such regulation is mediated by the direct binding of ERRα to the ERR response element (ERRE) on the promoters of *Pparα* and *Pdk4* (Huss *et al*. 2004, Wende *et al*. 2005). In addition, ERRα also regulates myocyte differentiation. The overexpression of *Errα* in C2C12 myoblasts accelerates myotube formation, while *Errα*-null primary myocytes show delayed myogenesis and mitochondrial dysfunction (Murray & Huss 2011). Although *ERRα* positively regulates lipid metabolism and mitochondrial OXPHOS in cooperation with PGC1α in heart and brown adipose tissue (Dufour *et al*. 2007, Villena *et al*. 2007), its physiological function in skeletal muscle remains to be elucidated.

Similar to ERRα, ERRγ also plays an important role in the regulation of energy metabolism. *Errγ*-null mice die within the first week of life, possibly from heart failure due to disrupted mitochondrial energy production (Alaynick *et al*. 2007). The importance of ERRγ in energy metabolism is also indicated by its distribution in skeletal muscle, where it is exclusively expressed in oxidative muscles such as soleus and red gastrocnemius but not in glycolytic muscles such as white gastrocnemius or quadriceps (Narkar *et al*. 2011). Transgenic mice with muscle-specific overexpression of *Errγ* have a remarkable conversion of glycolytic to oxidative fibers, with all white muscles appearing red (Narkar *et al*. 2011). The transgenic mice are fatigue resistant and can run about twice the distance of the controls. They also have a higher energy expenditure rate and a lower respiratory exchange ratio (RER), indicating a fuel preference for fatty acids. Both mitochondrial biogenesis and vascularization are induced. Gene expression analysis has further revealed a gene signature change from glycolytic to oxidative muscles, including the induction of genes involved in lipid metabolism, TCA cycle, angiogenesis, and mitochondrial OXPHOS (Rangwala *et al*. 2010, Narkar *et al*. 2011). In addition, the overexpression of ERRγ also alleviates the symptoms of Duchenne muscular dystrophy and promotes muscle recovery from ischemic damage (Matsakas *et al*. 2012, 2013). Therefore, genetic activation of ERRγ can induce an exercise-like phenotype in skeletal muscle with positive impacts on muscle diseases. However, its endogenous roles in the regulation of skeletal muscle function and exercise-induced muscle remodeling remain to be demonstrated.

Unlike ERRα and ERRγ, little is known about whether and how ERRβ regulates energy metabolism. Loss-of-function studies have demonstrated the crucial roles of ERRβ in placental development (Luo *et al*. 1997), germ cell development (Mitsunaga *et al*. 2004), inner ear development (Chen & Nathans 2007), and retinal photoreceptor survival (Onishi *et al*. 2010). In skeletal muscle, it has been briefly shown that both ERRβ and ERRγ are required to

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

maintain type I muscle fibers in the oxidative/glycolytic mixed muscle gastrocnemius but not in the mostly oxidative muscle soleus (Gan *et al*. 2013). However, the extent of functional redundancy between ERRβ and ERRγ in skeletal muscle is unclear, and more work is needed to fully understand the role of ERRβ in the regulation of energy metabolism and skeletal muscle function.

The NR4A subfamily

The NR4A subfamily of NRs consists of three closely related members: NR4A1 (NUR77), NR4A2 (NURR1), and NR4A3 (NOR1). Similar to ERRs, the NR4As are also orphan receptors that do not bind to any natural agonist (Pearen & Muscat 2010). They are constitutively active and their transcriptional activities appear to be primarily regulated by their abundance and post-translational modifications (Chao *et al*. 2012).

Based on their tissue expression patterns, the NR4As are clustered in the same group as ERRβ and ERRγ; they are preferentially expressed in tissues with high energy needs such as brain, muscle, and brown adipose tissue (Fig. 1; Bookout *et al*. 2006). While little is known about the function of NURR1 in skeletal muscle, both NUR77 and NOR1 have been clearly shown to play important roles in the regulation of skeletal muscle metabolism (Maxwell *et al*. 2005, Chao *et al*. 2007, 2012, Pearen *et al*. 2008, 2012).

In skeletal muscle, *Nur77* is selectively expressed in glycolytic vs oxidative muscles, suggesting a positive role in the regulation of glucose metabolism (Chao *et al*. 2007). The expression of NUR77 can be significantly induced by β-adrenergic signaling from the sympathetic nervous system to regulate muscle energy metabolism (Maxwell *et al*. 2005). Contrarily, skeletal muscle denervation reduces the expression of NUR77, as well as a subset of glucose metabolism genes, which is restored by the ectopic expression of *Nur77* in denervated muscle (Chao *et al*. 2007). The importance of NUR77 in the regulation of glucose metabolism can be further demonstrated by the overexpression of *Nur77* in C2C12 cells, which not only induces glucose metabolism genes but also enhances cellular glucose transport (Chao *et al*. 2007). Despite its role in the regulation of glucose metabolism, muscle-specific overexpression of *Nur77* induces an oxidative fiber-type switch, similar to *Pparδ* and *Errγ* (Chao *et al*. 2012). The transgenic muscle has typical characteristics of oxidative fibers such as increased fatty acid oxidation, higher mitochondrial OXPHOS activity, and fatigue resistance. However, the level of glycogen, which is usually high in glycolytic fibers and low in oxidative fibers, is increased in the *Nur77* transgenic muscle, suggesting a different working model for its fiber-type determination compared with PPARδ and ERRγ. More detailed analysis of fiber-type composition, endurance performance, and gene expression profiling will be required to understand the mechanism of muscle remodeling induced by NUR77. In addition, the endogenous role of NUR77 in the β-adrenergic signaling cascade remains to be elucidated.

Similar to *Nur77*, *Nor1* is also induced by β-adrenergic signaling in skeletal muscle (Pearen *et al*. 2008). However, NOR1 seems to participate more in the regulation of fatty acid metabolism rather than in that of glucose. Knockdown of *NOR1* in C2C12 cells reduces fatty acid oxidation and mitochondrial OXPHOS, but induces glycolysis (Pearen *et al*. 2008). The overexpression of an active form of *Nor1* in skeletal muscle leads to a fiber-type switch from glycolytic to oxidative fibers (Pearen *et al*. 2012). The transgenic mice have increased running endurance, improved insulin sensitivity and glucose tolerance, and higher energy expenditure. Both myoglobin expression and mitochondrial activity are induced in the transgenic muscle. The fiber-type switch phenotype seems to be dependent on muscle groups, with overall more type IIa and IIx fibers but less type I and IIb fibers. This intermediate oxidative fiber-type switch might be due to the enhanced HDAC5 activity, which has been shown to promote oxidative fiber formation (Potthoff *et al*. 2007). However, the direct targets of NOR1 remain to be identified. It is also not clear how NOR1 activates HDAC5 and whether or not other pathways are involved in the fiber-type conversion induced by NOR1.

The REV-ERB subfamily

There are two members in the REV-ERB subfamily of NRs: REV-ERBα and REV-ERBβ. REV-ERBs were originally discovered as orphan receptors (Miyajima *et al*. 1989), but were later 'adopted' by the identification of heme as their physiological ligand (Raghuram *et al*. 2007). Upon heme binding, REV-ERBs recruit co-repressors such as NCoR1 and repress target gene expression (Raghuram *et al*. 2007, Yin *et al*. 2007). REV-ERBs are active components of the circadian clock (Preitner *et al*. 2002, Bass 2012), and recent studies have also linked their functions to metabolic regulation in adipose tissues, liver, and muscle (Yang *et al*. 2006, Kumar *et al*. 2010, Cho *et al*. 2012, Woldt *et al*. 2013). Anatomical profiling of NRs clusters REV-ERBs in the same group as ERRβ, ERRγ, NUR77, and NOR1, all of

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

which are preferentially expressed in metabolically active tissues (Fig. 1; Bookout *et al*. 2006). This further indicates an active role of REV-ERBs in the regulation of energy metabolism.

While little is known about the function of REV-ERBβ in skeletal muscle, REV-ERBα has recently been shown to positively regulate energy metabolism and mitochondrial OXPHOS function in muscle (Woldt *et al*. 2013). *Rev-erbα* (*Nr1d1*) is expressed at higher levels in oxidative muscles than in glycolytic muscles and exercise can further induce its expression (Woldt *et al*. 2013). The importance of REV-ERBα in skeletal muscle has been demonstrated in *Rev-erbα*-null mice. These mice have reduced voluntary wheel-running activity, diminished endurance exercise performance, and lower energy expenditure during exercise. The knockout muscle has decreased mitochondrial density, reduced OXPHOS activity, and downregulated fatty acid metabolism genes (Woldt *et al*. 2013). On the other hand, the overexpression of *Rev-erbα* in C2C12 cells increases mitochondrial biogenesis and OXPHOS activity, accompanied by the induction of fatty acid metabolism genes. The *in vivo* overexpression of *Rev-erbα* in muscle via adeno-associated viral (AAV) infection also induces mitochondrial OXPHOS activity. These physiological changes seem to be mediated by the AMPK–Sirt1–PGC1α signaling pathway, which is downregulated in the knockout muscle but upregulated in *Rev-erbα*-overexpressing muscle cells. In addition to its roles in the regulation of mitochondrial biogenesis and OXPHOS activity, muscle REV-ERBα is also involved in the modulation of mitochondrial autophagy (mitophagy, Woldt *et al*. 2013). Mitophagy is induced in *Rev-erbα*-knockout muscle but suppressed in overexpressing C2C12 cells. REV-ERBα seems to directly bind to and repress genes in multiple steps of mitophagy, including the mitophagy regulator *Park2*, the autophagosome initiation factor *Ulk1*, the autophagosome elongation factors *Atg5* and *Bnip3*, and the lysosomal enzymes *Ctsl* and *Atpase6v1b2*. Therefore, REV-ERBα increases mitochondria number by both inducing mitochondrial biogenesis through the AMPK–Sirt1 pathway and reducing mitochondrial turnover by inhibiting mitophagy. However, it is not clear how AMPK is activated by the overexpression of *Rev-erbα* since the level of ATP is much lower in *Rev-erbα*-knockout muscle (Woldt *et al*. 2013), which is usually associated with AMPK activation. Also, the inhibition of mitophagy might be deleterious in the long term due to the diminished clearance of dysfunctional mitochondria (Narendra *et al*. 2008, Jin & Youle 2012).

NR co-regulatory factors

The functions of NRs are finely modulated by associated co-activators and co-repressors. The abundance of these co-regulators and their post-translational modifications are regulated in response to a variety of physiological stimuli such as exercise and fasting, which then induce conformational changes in the NR–chromatin complexes and regulate their transcriptional activities. Recent studies have demonstrated important roles for NR co-regulators in energy metabolism and fiber-type determination in skeletal muscle.

PPARγ co-activator 1

The PGC1α and PGC1β are probably the best-known and most studied NR co-regulators implicated in energy metabolism. Both are highly expressed in metabolically active tissues such as brain, heart, muscle, and brown adipose tissue, where they serve as co-activators for a number of transcription factors involved in the regulation of energy metabolism, including the PPAR and ERR NRs, and the nuclear respiratory factors 1 and 2 (NRF1 and NRF2/GABPA).

PGC1α was first identified as a cold-inducible thermogenic factor in brown adipose tissue (Puigserver *et al*. 1998). In skeletal muscle, *Pgc1α* is predominantly expressed in oxidative muscles such as soleus (Wu *et al*. 1999). The expression of *Pgc1α* can be induced by exercise or cold exposure in skeletal muscle (Puigserver *et al*. 1998, Baar *et al*. 2002, Russell *et al*. 2003). In addition to expression level, its co-transcriptional activity can also be modulated by a variety of post-translational modifications such as phosphorylation (Puigserver *et al*. 2001, Jäger *et al*. 2007), acetylation (Rodgers *et al*. 2005), and methylation (Teyssier *et al*. 2005). When overexpressed in C2C12 muscle cells, *Pgc1α* stimulates mitochondrial biogenesis by upregulating the mitochondrial transcription factor A (*Tfam*) as well as the mitochondrial regulators *Nrf1* and *Nrf2* (*Nfe2l2*). It can further function as a co-activator for NRF1 and NRF2 in the upregulation of the expression of mitochondrial genes. In addition to mitochondrial biogenesis, *Pgc1α* also stimulates mitochondrial uncoupling by upregulating the mitochondrial *Ucp2*, to further enhance mitochondrial energy expenditure (Wu *et al*. 1999). *In vivo* ectopic expression of *Pgc1α* in skeletal muscle not only induces mitochondrial biogenesis and OXPHOS activity but also switches type IIb and IIx/d glycolytic fibers to type I and IIa oxidative fibers (Lin *et al*. 2002*b*). As a result, the transgenic mice have improved endurance running performance

Journal of Molecular Endocrinology

Published by Bioscientifica Ltd

(Calvo *et al*. 2008). Loss-of-function studies, both whole-body and muscle-specific, have shown that *Pgc1α* is required for proper mitochondrial OXPHOS and energy metabolism in skeletal muscle (Leone *et al*. 2005, Handschin *et al*. 2007). However, fiber-type composition and exercise-induced fiber-type switches are not affected by the knockout of *Pgc1α* (Geng *et al*. 2010). On top of that, a recent study has shown that muscle mitochondrial biogenesis can still be induced by exercise without *Pgc1α* (Rowe *et al*. 2012), suggesting an alternate signaling pathway in remodeling skeletal muscle upon exercise induction.

PGC1β was identified by its high homology with PGC1α (Kressler *et al*. 2002, Lin *et al*. 2002*a*). It is also highly involved in the regulation of mitochondrial function and energy metabolism (Kamei *et al*. 2003). *In vitro* overexpression of *Pgc1β* (*Ppargc1b*) in muscle cells has effects similar to that of *Pgc1α* in terms of promoting mitochondrial biogenesis and oxidative fiber-type transformation (Mortensen *et al*. 2006). Similarly, the overexpression of *Pgc1β* in skeletal muscle stimulates mitochondrial OXPHOS and fatty acid oxidation, along with oxidative fiber-type transformation (Arany *et al*. 2007). However, instead of a switch toward the most oxidative type I and IIa fibers as seen in the PGC1α model, PGC1β induces a more intermediate switch toward type IIx/d fibers (Arany *et al*. 2007), suggesting a different working mechanism. Whole-body or muscle-specific knockout of *Pgc1β* causes reduced mitochondrial OXPHOS function in skeletal muscle but does not change fiber-type composition (Lelliott *et al*. 2006, Sonoda *et al*. 2007, Zechner *et al*. 2010). It would be expected that PGC1α and PGC1β compensate for each other when one is absent. This is true for their contributions to the regulation of mitochondrial function. Double-knockout mice lacking *Pgc1α* and *Pgc1β* in skeletal muscle have significantly lower mitochondrial OXPHOS activity compared with the single-knockout mice. However, the fiber-type composition of the double-knockout mice is not different from that of the WT controls (Zechner *et al*. 2010). Therefore, PGC1α and PGC1β are necessary for mitochondrial OXPHOS function in skeletal muscle, but appear dispensable for oxidative fiber-type determination.

Receptor-interacting protein 140

In addition to the co-activators of NRs, their co-repressors also contribute to the regulation of energy metabolism in skeletal muscle, one of which is the RIP140. It was originally identified as a co-regulatory factor for the ERs (Cavaillès *et al*. 1995). RIP140 (NRIP) is highly expressed in metabolic tissues such as fat and muscle (Leonardsson *et al*. 2004). In skeletal muscle, it is selectively expressed in glycolytic vs oxidative muscles (Seth *et al*. 2007), indicating a repressive role in the regulation of oxidative metabolism. *Rip140*-null mice exhibit ~70% reduction in total fat content, mainly due to increased fatty acid oxidation and mitochondrial energy consumption in muscle and white adipose tissue (Leonardsson *et al*. 2004). The knockout mice exhibit ~25% increase in whole-body energy expenditure and a lower RER, suggesting a shift toward fat utilization as energy source. In primarily glycolytic muscles where *Rip140* is endogenously expressed, loss of *Rip140* induces an oxidative fiber-type switch toward type IIa and IIx/d fibers, as well as increases in myoglobin content and mitochondrial biogenesis. Gene expression profiling further reveals significant induction of genes involved in fatty acid oxidation and mitochondrial OXPHOS in the knockout muscle (Seth *et al*. 2007). On the contrary, ectopic expression of *Rip140* in oxidative muscles causes a reduction of oxidative fibers and myoglobin content. However, the exercise-induced fiber-type conversion is still retained in these transgenic mice (Seth *et al*. 2007). A subset of oxidative genes repressed by RIP140 are known targets of PPARs and ERRs and can be co-activated by PGC1α, including *Mcad (Cdh15)*, *Cidea*, *Cpt1b*, and *Fabp3* (Christian *et al*. 2006, Hallberg *et al*. 2008). Additionally, RIP140 is recruited to either known or predicted PPREs and ERREs at the promoters of these genes (Seth *et al*. 2007). Hence, RIP140 and PGC1 could work in a yin–yang fashion in the regulation of the transcriptional activity of NRs such as PPARs and ERRs.

Nuclear receptor co-repressor 1

The NCoR1 was first identified as a ligand-independent transcriptional co-repressor for thyroid hormone receptor and retinoic acid receptor (Hörlein *et al*. 1995). It is ubiquitously expressed and is required for normal embryonic development (Jepsen *et al*. 2000). In skeletal muscle, NCoR1 is expressed at similar levels in oxidative and glycolytic muscles (Schuler *et al*. 1999). However, in conditions when fatty acid metabolism is stimulated, such as during fasting, high-fat diet challenge, and exercise, its expression in skeletal muscle is significantly reduced (Yamamoto *et al*. 2011, Pérez-Schindler *et al*. 2012), indicating that NCoR1 is involved in the repression of fatty acid metabolism. Muscle-specific deletion of *NCoR1* increases muscle mass and exercise endurance (Yamamoto *et al*. 2011). The *Ncor1*-null mice have higher locomotor

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

activity and whole-body energy expenditure. Similar to the overexpression of *Pgc1α* or deletion of *Rip140*, the knockout of *Ncor1* induces an oxidative fiber-type switch, associated with increased mitochondrial biogenesis and enhanced oxidative metabolism. In addition, there is a high overlap between the genes induced by the overexpression of *Pgc1α* and knockout of *Ncor1* or *Rip140* in skeletal muscle. Similar to RIP140, NCoR1 functions through PPARs and ERRs in opposition to PGC1α. It is recruited to PPREs or ERREs at their target gene promoters to repress their transcriptional activity, which can be antagonized by PGC1α (Christian *et al*. 2006, Pérez-Schindler *et al*. 2012). Thus, the three co-regulatory factors work cooperatively with PPARs and ERRs in the regulation of skeletal muscle adaptation and energy metabolism. However, the abundance of NCoR1 and PGC1α, but not of RIP140, fluctuates in response to exercise, suggesting that they both play an important role in the exertion of exercise-induced muscle remodeling (Frier *et al*. 2011).

AMP-activated protein kinase

The AMPK is a central mediator of metabolism that functions by sensing and regulating cellular energy supplies. It is activated when energy levels are low to restore energy balance by promoting catabolism and inhibiting anabolism (Hardie 2007). In skeletal muscle, the activity of AMPK is significantly higher in oxidative vs glycolytic muscles, indicating its contribution to the maintenance of the basal oxidative metabolism (Narkar *et al*. 2011). This is further confirmed by the *in vivo* overexpression of an inactive form of AMPK in skeletal muscle, which dramatically reduces endurance exercise capacity and induces insulin resistance and glucose intolerance (Fujii *et al*. 2007, 2008). In addition to the basal oxidative metabolism, the activation of AMPK is also required for exercise-induced mitochondrial biogenesis via PGC1α (Zong *et al*. 2002, Jäger *et al*. 2007), in which AMPK is activated by exercise and directly phosphorylates PGC1α and upregulates its co-transcriptional activity (Jäger *et al*. 2007, Narkar *et al*. 2008). In some NR genetic models where oxidative fiber-type conversion is induced, such as the muscle-specific overexpression of *Pparδ*, *Pparγ*, *Errγ*, or *Rev-erbα*, AMPK activity is also significantly increased (Narkar *et al*. 2008, 2011, Amin *et al*. 2010, Woldt *et al*. 2013). Furthermore, direct interaction between AMPK and PPARδ has been observed to synergistically activate target genes involved in oxidative metabolism (Narkar *et al*. 2008, Gan *et al*. 2011). Thus, although AMPK is not a canonical NR co-regulator, it interacts with NRs and is highly involved in their regulation of energy metabolism (Fan *et al*. 2011).

Road to exercise mimetics

A common feature of NRs and AMPK is that their activities can be modulated by small-molecule ligands, which makes them ideal pharmacological targets. Toward this end, a number of synthetic ligands have been developed for NRs including the ones described above. Some of these ligands have already been shown to promote skeletal muscle oxidative metabolism, including the PPARδ agonist GW501516 (Narkar *et al*. 2008), ERRβ/γ agonist GSK4716 (Rangwala *et al*. 2010), and REV-ERBα/β agonists SR9009 and SR9011 (Woldt *et al*. 2013).

GW501516 was originally developed as a potent and selective PPARδ agonist (Oliver *et al*. 2001). Its activation of PPARδ in cultured C2C12 muscle cells induces the expression of genes involved in fatty acid catabolism, mitochondrial OXPHOS, and cholesterol efflux (Dressel *et al*. 2003). GW501516 also works *in vivo* to enhance oxidative metabolism in skeletal muscle. Oral doses of 5 mg/kg per day for 4 weeks have been shown to significantly upregulate oxidative genes such as *Ucp3, Pdk4*, and *Cpt1a*, similar to that seen with the muscle-specific overexpression of *Pparδ* (Luquet *et al*. 2003, Wang *et al*. 2004, Narkar *et al*. 2008). The ligand activation of PPARδ alone does not stimulate any oxidative fiber-type switch or mitochondrial biogenesis in skeletal muscle, which is different from the muscle overexpression model. However, when co-administered with exercise training, GW501516 treatment increases the proportion of type I oxidative fibers by ∼38% and mitochondrial biogenesis by ∼50%, while training alone has little effect. In addition, the pairing of GW501516 treatment with exercise training has been shown to dramatically increase endurance running performance compared with GW501516 treatment or training alone. Gene expression profiling has revealed a unique oxidative gene signature, which is also found in the *Pparδ* transgenic muscle but not during either GW501516 treatment or training alone (Wang *et al*. 2004, Narkar *et al*. 2008). Thus, *in vivo* activation of PPARδ by oral administration of GW501516 enhances the effect of exercise training.

GSK4716 was identified as a specific agonist for ERRβ and ERRγ, without any crossover activity with the ERs (Zuercher *et al*. 2005). It seems to have good potential for promoting oxidative metabolism in skeletal muscle. In primary mouse myotubes, treatment with GSK4716 leads

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

to the upregulation of all the three *Err* genes and their co-activators *Pgc1α* and *Pgc1β*. Additionally, it induces the expression of genes involved in fatty acid oxidation, TCA cycle, and mitochondrial OXPHOS, such as *Cpt1b, Idh3*, and *Atp5b*. It also stimulates mitochondrial biogenesis as both the mitochondrial citrate synthase activity and the amount of cytochrome c are increased (Rangwala *et al*. 2010). However, no *in vivo* trial has been reported and more functional studies will be needed to fully assess its effect in skeletal muscle.

The synthetic REV-ERB agonists SR9009 and SR9011 have been developed recently (Solt *et al*. 2012). Treatment with SR9009 or SR9011 increases the transcriptional repression of REV-ERBs on their target genes. *In vivo*, a single injection of SR9009 or SR9011 has been shown to result in the induction of genes involved in glycolysis, fatty acid catabolism, and mitochondrial OXPHOS, including *Hk1, Pkm2, Pgc1α, Cpt1b, Fatp1*, and *Ucp3*. Mice treated with SR9011 for 12 days have increased energy expenditure with no change in RER, indicating that the oxidation of both fatty acids and glucose is induced. Additionally, 30 days of treatment with SR9009 has been found to significantly increase mouse running endurance. In C2C12 myotubes, treatment with SR9009 or SR9011 has been reported to increase mitochondria number (Woldt *et al*. 2013). While the effects of these agonists on skeletal muscle seem promising, questions regarding the requirement for skeletal muscle REV-ERBs and how REV-ERBs activate energy metabolism genes remain to be answered.

In addition to the NR ligands, the AMPK activator AICAR also works as an exercise mimetic (Narkar *et al*. 2008). AICAR treatment for 4 weeks increases mouse energy expenditure and enhances running endurance by ~40%. It induces the expression of a number of genes linked to oxidative metabolism, including *Scd1, Pdk4, Fasn, Lipe*, and *Dgat*, most of which are also induced by the overexpression of *Pparδ* in skeletal muscle (Wang *et al*. 2004). The stimulation of oxidative genes by AICAR seems to be dependent on PPARδ as AICAR fails to induce these genes in *Pparδ*-null muscle cells. In addition, when administered together, AICAR and GW501516 synergistically activate PPARδ target genes such as *Ucp3, Pdk4*, and *Lpl* (Narkar *et al*. 2008). Therefore, the activation of AMPK by its activator AICAR induces an oxidative gene signature change mediated by PPARδ, which causes skeletal muscle remodeling and enhances endurance. However, the mechanism as to how AMPK synergistically activates PPARδ target genes remains to be elucidated.

Conclusions

Studies over the past decade have made it clear that NRs and their co-regulators are key regulatory components of energy metabolism and exercise-induced remodeling in skeletal muscle. Synthetic ligands targeting NRs and their co-regulators, including GW501516, AICAR, GSK4716, and SR9009/9011, have been developed and proven to be effective in enhancing or mimicking exercise effects. To date, many issues remain with the current generation of exercise mimetics, such as toxicity, side effects, and high dosage, which prevent their immediate clinical applications. However, with advances in our understanding of the molecular mechanism by which NRs regulate skeletal muscle physiology, we are optimistic that the next generation of exercise mimetics is not far away.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Funding

This work was supported by US National Institutes of Health grant numbers (DK057978, DK090962, HL088093, HL105278, CA014195, and ES010337), the Glenn Foundation for Medical Research, the Leona M and Harry B Helmsley Charitable Trust, Ipsen/Biomeasure, and the Ellison Medical Foundation.

Acknowledgements

The authors thank L Ong and C Brondos for administrative assistance. RM Evans is an Investigator of the Howard Hughes Medical Institute at the Salk Institute and March of Dimes Chair in Molecular and Developmental Biology.

References

Alaynick WA, Kondo RP, Xie W, He W, Dufour CR, Downes M, Jonker JW, Giles W, Naviaux RK, Giguère V *et al*. 2007 ERRγ directs and maintains the transition to oxidative metabolism in the postnatal heart. *Cell Metabolism* **6** 13–24. (doi:10.1016/j.cmet.2007.06.007)

Amin RH, Mathews ST, Camp HS, Ding L & Leff T 2010 Selective activation of PPARγ in skeletal muscle induces endogenous production of adiponectin and protects mice from diet-induced insulin resistance. *American Journal of Physiology. Endocrinology and Metabolism* **298** E28–E37. (doi:10.1152/ajpendo.00446.2009)

Arany Z, Lebrasseur N, Morris C, Smith E, Yang W, Ma Y, Chin S & Spiegelman BM 2007 The transcriptional coactivator PGC-1β drives the formation of oxidative type IIX fibers in skeletal muscle. *Cell Metabolism* **5** 35–46. (doi:10.1016/j.cmet.2006.12.003)

Baar K, Wende AR, Jones TE, Marison M, Nolte LA, Chen M, Kelly DP & Holloszy JO 2002 Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1. *FASEB Journal* **16** 1879–1886. (doi:10.1096/fj.02-0367com)

Barrès R, Yan J, Egan B, Treebak JT, Rasmussen M, Fritz T, Caidahl K, Krook A & O'Gorman DJ 2012 Acute exercise remodels promoter methylation in

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

human skeletal muscle. *Cell Metabolism* **15** 405–411. (doi:10.1016/j.cmet.2012.01.001)

Bass J 2012 Circadian topology of metabolism. *Nature* **491** 348–356. (doi:10.1038/nature11704)

Bassel-Duby R & Olson EN 2006 Signaling pathways in skeletal muscle remodeling. *Annual Review of Biochemistry* **75** 19–37. (doi:10.1146/annurev.biochem.75.103004.142622)

Bergouignan A, Rudwill F, Simon C & Blanc S 2011 Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies. *Journal of Applied Physiology* **111** 1201–1210. (doi:10.1152/japplphysiol.00698.2011)

Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM & Mangelsdorf DJ 2006 Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* **126** 789–799. (doi:10.1016/j.cell.2006.06.049)

Braissant O, Foufelle F, Scotto C, Dauça M & Wahli W 1996 Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-α, -β, and -γ in the adult rat. *Endocrinology* **137** 354–366. (doi:10.1210/en.137.1.354)

Calvo JA, Daniels TG, Wang X, Paul A, Lin J, Spiegelman BM, Stevenson SC & Rangwala SM 2008 Muscle-specific expression of PPARγ coactivator-1α improves exercise performance and increases peak oxygen uptake. *Journal of Applied Physiology* **104** 1304–1312. (doi:10.1152/japplphysiol.01231.2007)

Cavaillès V, Dauvois S, L'Horset F, Lopez G, Hoare S, Kushner PJ & Parker MG 1995 Nuclear factor Rip140 modulates transcriptional activation by the estrogen-receptor. *EMBO Journal* **14** 3741–3751.

Chao LC, Zhang Z, Pei L, Saito T, Tontonoz P & Pilch PF 2007 Nur77 coordinately regulates expression of genes linked to glucose metabolism in skeletal muscle. *Molecular Endocrinology* **21** 2152–2163. (doi:10.1210/me.2007-0169)

Chao LC, Wroblewski K, Ilkayeva OR, Stevens RD, Bain J, Meyer GA, Schenk S, Martinez L, Vergnes L, Narkar VA *et al.* 2012 Skeletal muscle Nur77 expression enhances oxidative metabolism and substrate utilization. *Journal of Lipid Research* **53** 2610–2619. (doi:10.1194/jlr.M029355)

Chen J & Nathans J 2007 Estrogen-related receptor β/NR3B2 controls epithelial cell fate and endolymph production by the stria vascularis. *Developmental Cell* **13** 325–337. (doi:10.1016/j.devcel.2007.07.011)

Chinsomboon J, Ruas J, Gupta RK, Thom R, Shoag J, Rowe GC, Sawada N, Raghuram S & Arany Z 2009 The transcriptional coactivator PGC-1α mediates exercise-induced angiogenesis in skeletal muscle. *PNAS* **106** 21401–21406. (doi:10.1073/pnas.0909131106)

Cho H, Zhao X, Hatori M, Yu RT, Barish GD, Lam MT, Chong LW, DiTacchio L, Atkins AR, Glass CK *et al.* 2012 Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. *Nature* **485** 123–127. (doi:10.1038/nature11048)

Christian M, White R & Parker MG 2006 Metabolic regulation by the nuclear receptor corepressor RIP140. *Trends in Endocrinology and Metabolism* **17** 243–250. (doi:10.1016/j.tem.2006.06.008)

DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J & Felber JP 1981 The effect of insulin on the disposal of intravenous glucose – results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes* **30** 1000–1007. (doi:10.2337/diab.30.12.1000)

Dressel U, Allen TL, Pippal JB, Rohde PR, Lau P & Muscat GE 2003 The peroxisome proliferator-activated receptor β/δ agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. *Molecular Endocrinology* **17** 2477–2493. (doi:10.1210/me.2003-0151)

Dufour CR, Wilson BJ, Huss JM, Kelly DP, Alaynick WA, Downes M, Evans RM, Blanchette M & Giguère V 2007 Genome-wide orchestration of cardiac functions by the orphan nuclear receptors ERRα and γ. *Cell Metabolism* **5** 345–356. (doi:10.1016/j.cmet.2007.03.007)

Eichner LJ & Giguere V 2011 Estrogen related receptors (ERRs): a new dawn in transcriptional control of mitochondrial gene networks. *Mitochondrion* **11** 544–552. (doi:10.1016/j.mito.2011.03.121)

Eudy JD, Yao S, Weston MD, Ma-Edmonds M, Talmadge CB, Cheng JJ, Kimberling WJ & Sumegi J 1998 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** 382–384. (doi:10.1006/geno.1998.5345)

Evans RM, Barish GD & Wang YX 2004 PPARs and the complex journey to obesity. *Nature Medicine* **10** 355–361. (doi:10.1038/nm1025)

Fan W, Downes M, Atkins A, Yu R & Evans RM 2011 Nuclear receptors and AMPK: resetting metabolism. *Cold Spring Harbor Symposia on Quantitative Biology* **76** 17–22. (doi:10.1101/sqb.2012.76.010470)

Finck BN, Bernal-Mizrachi C, Han DH, Coleman T, Sambandam N, LaRiviere LL, Holloszy JO, Semenkovich CF & Kelly DP 2005 A potential link between muscle peroxisome proliferator-activated receptor-α signaling and obesity-related diabetes. *Cell Metabolism* **1** 133–144. (doi:10.1016/j.cmet.2005.01.006)

Foster C, Costill DL, Daniels JT & Fink WJ 1978 Skeletal muscle enzyme activity, fiber composition and VO2 max in relation to distance running performance. *European Journal of Applied Physiology and Occupational Physiology* **39** 73–80. (doi:10.1007/BF00421711)

Frier BC, Hancock CR, Little JP, Fillmore N, Bliss TA, Thomson DM, Wan Z & Wright DC 2011 Reductions in RIP140 are not required for exercise- and AICAR-mediated increases in skeletal muscle mitochondrial content. *Journal of Applied Physiology* **111** 688–695. (doi:10.1152/japplphysiol.00279.2011)

Fujii N, Seifert MM, Kane EM, Peter LE, Ho RC, Winstead S, Hirshman MF & Goodyear LJ 2007 Role of AMP-activated protein kinase in exercise capacity, whole body glucose homeostasis, and glucose transport in skeletal muscle – insight from analysis of a transgenic mouse model. *Diabetes Research and Clinical Practice* **77** S92–S98. (doi:10.1016/j.diabres.2007.01.040)

Fujii N, Ho RC, Manabe Y, Jessen N, Toyoda T, Holland WL, Summers SA, Hirshman MF & Goodyear LJ 2008 Ablation of AMP-activated protein kinase α2 activity exacerbates insulin resistance induced by high-fat feeding of mice. *Diabetes* **57** 2958–2966. (doi:10.2337/db07-1187)

Gan Z, Burkart-Hartman EM, Han DH, Finck B, Leone TC, Smith EY, Ayala JE, Holloszy J & Kelly DP 2011 The nuclear receptor PPARβ/δ programs muscle glucose metabolism in cooperation with AMPK and MEF2. *Genes and Development* **25** 2619–2630. (doi:10.1101/gad.178434.111)

Gan Z, Rumsey J, Hazen BC, Lai L, Leone TC, Vega RB, Xie H, Conley KE, Auwerx J, Smith SR *et al.* 2013 Nuclear receptor/microRNA circuitry links muscle fiber type to energy metabolism. *Journal of Clinical Investigation* **123** 2564–2575. (doi:10.1172/JCI67652)

Geng T, Li P, Okutsu M, Yin X, Kwek J, Zhang M & Yan Z 2010 PGC-1α plays a functional role in exercise-induced mitochondrial biogenesis and angiogenesis but not fiber-type transformation in mouse skeletal muscle. *American Journal of Physiology. Cell Physiology* **298** C572–C579. (doi:10.1152/ajpcell.00481.2009)

Giguère V, Yang N, Segui P & Evans RM 1988 Identification of a new class of steroid hormone receptors. *Nature* **331** 91–94. (doi:10.1038/331091a0)

Gollnick PD, Armstrong RB, Saubert CW IV, Piehl K & Saltin B 1972 Enzyme-activity and fiber composition in skeletal-muscle of untrained and trained men. *Journal of Applied Physiology* **33** 312–319.

Gollnick PD, Armstrong RB, Saltin B, Saubert CW IV, Sembrowich WL & Shepherd RE 1973 Effect of training on enzyme activity and fiber composition of human skeletal muscle. *Journal of Applied Physiology* **34** 107–111.

Grazina R & Massano J 2013 Physical exercise and Parkinson's disease: influence on symptoms, disease course and prevention. *Reviews in the Neurosciences* **24** 139–152. (doi:10.1515/revneuro-2012-0087)

Hallberg M, Morganstein DL, Kiskinis E, Shah K, Kralli A, Dilworth SM, White R, Parker MG & Christian M 2008 A functional interaction between RIP140 and PGC-1α regulates the expression of the lipid droplet protein CIDEA. *Molecular and Cellular Biology* **28** 6785–6795. (doi:10.1128/MCB.00504-08)

Hamilton MT & Booth WF 2000 Booth skeletal muscle adaptation to exercise: a century of progress. *Journal of Applied Physiology* **88** 327–331.

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

Handschin C, Choi CS, Chin S, Kim S, Kawamori D, Kurpad AJ, Neubauer N, Hu J, Mootha VK, Kim YB *et al*. 2007 Abnormal glucose homeostasis in skeletal muscle-specific PGC-1α knockout mice reveals skeletal muscle-pancreatic β cell crosstalk. *Journal of Clinical Investigation* **117** 3463–3474. (doi:10.1172/JCI31785)

Hardie DG 2007 AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. *Nature Reviews. Molecular Cell Biology* **8** 774–785. (doi:10.1038/nrm2249)

He W, Barak Y, Hevener A, Olson P, Liao D, Le J, Nelson M, Ong E, Olefsky JM & Evans RM 2003 Adipose-specific peroxisome proliferator-activated receptor γ knockout causes insulin resistance in fat and liver but not in muscle. *PNAS* **100** 15712–15717. (doi:10.1073/pnas.2536828100)

Heard DJ, Norby PL, Holloway J & Vissing H 2000 Human ERRγ, 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. *Molecular Endocrinology* **14** 382–392. (doi:10.1210/me.14.3.382)

Hevener AL, He W, Barak Y, Le J, Bandyopadhyay G, Olson P, Wilkes J, Evans RM & Olefsky J 2003 Muscle-specific Pparg deletion causes insulin resistance. *Nature Medicine* **9** 1491–1497. (doi:10.1038/nm956)

Hickey MS, Carey JO, Azevedo JL, Houmard JA, Pories WJ, Israel RG & Dohm GL 1995 Skeletal muscle fiber composition is related to adiposity and *in vitro* glucose transport rate in humans. *American Journal of Physiology* **268** E453–E457.

Hong H, Yang L & Stallcup MR 1999 Hormone-independent transcriptional activation and coactivator binding by novel orphan nuclear receptor ERR3. *Journal of Biological Chemistry* **274** 22618–22626. (doi:10.1074/jbc.274.32.22618)

Hörlein AJ, Näär AM, Heinzel T, Torchia J, Gloss B, Kurokawa R, Ryan A, Kamei Y, Söderström M, Glass CK *et al*. 1995 Ligand-independent repression by the thyroid-hormone receptor-mediated by a nuclear receptor co-repressor. *Nature* **377** 397–404. (doi:10.1038/377397a0)

Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA & Manson JE 2004 Adiposity as compared with physical activity in predicting mortality among women. *New England Journal of Medicine* **351** 2694–2703. (doi:10.1056/NEJMoa042135)

Huss JM, Kopp RP & Kelly DP 2002 Peroxisome proliferator-activated receptor coactivator-1α (PGC-1α) coactivates the cardiac-enriched nuclear receptors estrogen-related receptor-α and -γ – identification of novel leucine-rich interaction motif within PGC-1α. *Journal of Biological Chemistry* **277** 40265–40274. (doi:10.1074/jbc.M206324200)

Huss JM, Torra IP, Staels B, Giguère V & Kelly DP 2004 Estrogen-related receptor α directs peroxisome proliferator-activated receptor at signaling in the transcriptional control of energy metabolism in cardiac and skeletal muscle. *Molecular and Cellular Biology* **24** 9079–9091. (doi:10.1128/MCB.24.20.9079-9091.2004)

Issemann I & Green S 1990 Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* **347** 645–650. (doi:10.1038/347645a0)

Jäger S, Handschin C, St-Pierre J & Spiegelman BM 2007 AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1α. *PNAS* **104** 12017–12022. (doi:10.1073/pnas.0705070104)

Jepsen K, Hermanson O, Onami TM, Gleiberman AS, Lunyak V, McEvilly RJ, Kurokawa R, Kumar V, Liu F, Seto E *et al*. 2000 Combinatorial roles of the nuclear receptor corepressor in transcription and development. *Cell* **102** 753–763. (doi:10.1016/S0092-8674(00)00064-7)

Jin SM & Youle RJ 2012 PINK1-and Parkin-mediated mitophagy at a glance. *Journal of Cell Science* **125** 795–799. (doi:10.1242/jcs.093849)

Kamei Y, Ohizumi H, Fujitani Y, Nemoto T, Tanaka T, Takahashi N, Kawada T, Miyoshi M, Ezaki O & Kakizuka A 2003 PPARγ coactivator 1β/ERR ligand 1 is an ERR protein ligand, whose expression induces a high-energy expenditure and antagonizes obesity. *PNAS* **100** 12378–12383. (doi:10.1073/pnas.2135217100)

Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B & Wahli W 1999 Peroxisome proliferator-activated receptor α mediates the adaptive response to fasting. *Journal of Clinical Investigation* **103** 1489–1498. (doi:10.1172/JCI6223)

Kliewer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K & Evans RM 1994 Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. *PNAS* **91** 7355–7359. (doi:10.1073/pnas.91.15.7355)

Kressler D, Schreiber SN, Knutti D & Kralli A 2002 The PGC-1-related protein PERC is a selective coactivator of estrogen receptor α. *Journal of Biological Chemistry* **277** 13918–13925. (doi:10.1074/jbc.M201134200)

Kumar N, Solt LA, Wang Y, Rogers PM, Bhattacharyya G, Kamenecka TM, Stayrook KR, Crumbley C, Floyd ZE, Gimble JM *et al*. 2010 Regulation of adipogenesis by natural and synthetic REV-ERB ligands. *Endocrinology* **151** 3015–3025. (doi:10.1210/en.2009-0800)

de Lange P, Farina P, Moreno M, Ragni M, Lombardi A, Silvestri E, Burrone L, Lanni A & Goglia F 2006 Sequential changes in the signal transduction responses of skeletal muscle following food deprivation. *FASEB Journal* **20** 2579–2581. (doi:10.1096/fj.06-6025fje)

Lelliott CJ, Medina-Gomez G, Petrovic N, Kis A, Feldmann HM, Bjursell M, Parker N, Curtis K, Campbell M, Hu P *et al*. 2006 Ablation of PGC-1β results in defective mitochondrial activity, thermogenesis, hepatic function, and cardiac performance. *PLoS Biology* **4** e369. (doi:10.1371/journal.pbio.0040369)

Lemanne D, Cassileth B & Gubili J 2013 The role of physical activity in cancer prevention, treatment, recovery, and survivorship. *Oncology* **27** 580–585.

Leonardsson G, Steel JH, Christian M, Pocock V, Milligan S, Bell J, So PW, Medina-Gomez G, Vidal-Puig A, White R *et al*. 2004 Nuclear receptor corepressor RIP140 regulates fat accumulation. *PNAS* **101** 8437–8442. (doi:10.1073/pnas.0401013101)

Leone TC, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S, Courtois M, Wozniak DF, Sambandam N, Bernal-Mizrachi C *et al*. 2005 PGC-1α deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. *PLoS Biology* **3** e101. (doi:10.1371/journal.pbio.0030101)

Lin J, Puigserver P, Donovan J, Tarr P & Spiegelman BM 2002*a* Peroxisome proliferator-activated receptor γ coactivator 1β (PGC-1β), a novel PGC-1-related transcription coactivator associated with host cell factor. *Journal of Biological Chemistry* **277** 1645–1648. (doi:10.1074/jbc.C100631200)

Lin J, Wu H, Tarr PT, Zhang CY, Wu Z, Boss O, Michael LF, Puigserver P, Isotani E, Olson EN *et al*. 2002*b* Transcriptional co-activator PGC-1α drives the formation of slow-twitch muscle fibres. *Nature* **418** 797–801. (doi:10.1038/nature00904)

Luo J, Sladek R, Bader JA, Matthyssen A, Rossant J & Giguère V 1997 Placental abnormalities in mouse embryos lacking the orphan nuclear receptor ERR-β. *Nature* **388** 778–782. (doi:10.1038/42022)

Luo J, Sladek R, Carrier J, Bader JA, Richard D & Giguère V 2003 Reduced fat mass in mice lacking orphan nuclear receptor estrogen-related receptor α. *Molecular and Cellular Biology* **23** 7947–7956. (doi:10.1128/MCB.23.22.7947-7956.2003)

Luquet S, Lopez-Soriano J, Holst D, Fredenrich A, Melki J, Rassoulzadegan M & Grimaldi PA 2003 Peroxisome proliferator-activated receptor δ controls muscle development and oxidative capability. *FASEB Journal* **17** 2299–2301.

Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P *et al*. 1995 The nuclear receptor superfamily: the second decade. *Cell* **83** 835–839. (doi:10.1016/0092-8674(95)90199-X)

Matsakas A, Yadav V, Lorca S, Evans RM & Narkar VA 2012 Revascularization of ischemic skeletal muscle by estrogen-related receptor-γ. *Circulation Research* **110** 1087–1096. (doi:10.1161/CIRCRESAHA.112.266478)

Matsakas A, Yadav V, Lorca S & Narkar V 2013 Muscle ERRγ mitigates Duchenne muscular dystrophy via metabolic and angiogenic reprogramming. *FASEB Journal* **27** 4004–4016. (doi:10.1096/fj.13-228296)

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

Maxwell MA, Cleasby ME, Harding A, Stark A, Cooney GJ & Muscat GE 2005 Nur77 regulates lipolysis in skeletal muscle cells – evidence for cross-talk between the β-adrenergic and an orphan nuclear hormone receptor pathway. *Journal of Biological Chemistry* **280** 12573–12584. (doi:10.1074/jbc.M409580200)

Mellett LH & Bousquet G 2013 Cardiology patient page. Heart-healthy exercise. *Circulation* **127** e571–e572. (doi:10.1161/CIRCULATIONAHA.112.000880)

Mitsunaga K, Araki K, Mizusaki H, Morohashi K, Haruna K, Nakagata N, Giguère V, Yamamura K & Abe K 2004 Loss of PGC-specific expression of the orphan nuclear receptor ERR-β results in reduction of germ cell number in mouse embryos. *Mechanisms of Development* **121** 237–246. (doi:10.1016/j.mod.2004.01.006)

Miyajima N, Horiuchi R, Shibuya Y, Fukushige S, Matsubara K, Toyoshima K & Yamamoto T 1989 Two erbA homologs encoding proteins with different T3 binding capacities are transcribed from opposite DNA strands of the same genetic locus. *Cell* **57** 31–39. (doi:10.1016/0092-8674(89)90169-4)

Mortensen OH, Frandsen L, Schjerling P, Nishimura E & Grunnet N 2006 PGC-1α and PGC-1β have both similar and distinct effects on myofiber switching toward an oxidative phenotype. *American Journal of Physiology. Endocrinology and Metabolism* **291** E807–E816. (doi:10.1152/ajpendo.00591.2005)

Muoio DM, MacLean PS, Lang DB, Li S, Houmard JA, Way JM, Winegar DA, Corton JC, Dohm GL & Kraus WE 2002 Fatty acid homeostasis and induction of lipid regulatory genes in skeletal muscles of peroxisome proliferator-activated receptor (PPAR) α knock-out mice. Evidence for compensatory regulation by PPARδ. *Journal of Biological Chemistry* **277** 26089–26097. (doi:10.1074/jbc.M203997200)

Murray J & Huss JM 2011 Estrogen-related receptor α regulates skeletal myocyte differentiation via modulation of the ERK MAP kinase pathway. *American Journal of Physiology. Cell Physiology* **301** C630–C645. (doi:10.1152/ajpcell.00033.2011)

Narendra D, Tanaka A, Suen DF & Youle RJ 2008 Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *Journal of Cell Biology* **183** 795–803. (doi:10.1083/jcb.200809125)

Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, Mihaylova MM, Nelson MC, Zou Y, Juguilon H *et al.* 2008 AMPK and PPARδ agonists are exercise mimetics. *Cell* **134** 405–415. (doi:10.1016/j.cell.2008.06.051)

Narkar VA, Fan W, Downes M, Yu RT, Jonker JW, Alaynick WA, Banayo E, Karunasiri MS, Lorca S & Evans RM 2011 Exercise and PGC-1α-independent synchronization of type I muscle metabolism and vasculature by ERRγ. *Cell Metabolism* **13** 283–293. (doi:10.1016/j.cmet.2011.01.019)

Norris AW, Chen L, Fisher SJ, Szanto I, Ristow M, Jozsi AC, Hirshman MF, Rosen ED, Goodyear LJ, Gonzalez FJ *et al.* 2003 Muscle-specific PPARγ-deficient mice develop increased adiposity and insulin resistance but respond to thiazolidinediones. *Journal of Clinical Investigation* **112** 608–618.

Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznaidman ML, Lambert MH *et al.* 2001 A selective peroxisome proliferator-activated receptor δ agonist promotes reverse cholesterol transport. *PNAS* **98** 5306–5311. (doi:10.1073/pnas.091021198)

Onishi A, Peng GH, Poth EM, Lee DA, Chen J, Alexis U, de Melo J, Chen S & Blackshaw S 2010 The orphan nuclear hormone receptor ERRβ controls rod photoreceptor survival. *PNAS* **107** 11579–11584. (doi:10.1073/pnas.1000102107)

Pearen MA & Muscat GEO 2010 Minireview: Nuclear hormone receptor 4A signaling: implications for metabolic disease. *Molecular Endocrinology* **24** 1891–1903. (doi:10.1210/me.2010-0015)

Pearen MA, Myers SA, Raichur S, Ryall JG, Lynch GS & Muscat GE 2008 The orphan nuclear receptor, NOR-1, a target of β-adrenergic signaling, regulates gene expression that controls oxidative metabolism in skeletal muscle. *Endocrinology* **149** 2853–2865. (doi:10.1210/en.2007-1202)

Pearen MA, Eriksson NA, Fitzsimmons RL, Goode JM, Martel N, Andrikopoulos S & Muscat GE 2012 The nuclear receptor, Nor-1, markedly increases type II oxidative muscle fibers and resistance to fatigue. *Molecular Endocrinology* **26** 372–384. (doi:10.1210/me.2011-1274)

Pérez-Schindler J, Summermatter S, Salatino S, Zorzato F, Beer M, Balwierz PJ, van Nimwegen E, Feige JN, Auwerx J & Handschin C 2012 The corepressor NCoR1 antagonizes PGC-1α and estrogen-related receptor α in the regulation of skeletal muscle function and oxidative metabolism. *Molecular and Cellular Biology* **32** 4913–4924. (doi:10.1128/MCB.00877-12)

Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K, Rothman DL & Shulman GI 1996 Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. *New England Journal of Medicine* **335** 1357–1362. (doi:10.1056/NEJM199610313351804)

Potthoff MJ, Wu H, Arnold MA, Shelton JM, Backs J, McAnally J, Richardson JA, Bassel-Duby R & Olson EN 2007 Histone deacetylase degradation and MEF2 activation promote the formation of slow-twitch myofibers. *Journal of Clinical Investigation* **117** 2459–2467. (doi:10.1172/JCI31960)

Preitner N, Damiola F, Lopez-Molina L, Zakany J, Duboule D, Albrecht U & Schibler U 2002 The orphan nuclear receptor REV-ERBα controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell* **110** 251–260. (doi:10.1016/S0092-8674(02)00825-5)

Puigserver P, Wu Z, Park CW, Graves R, Wright M & Spiegelman BM 1998 A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* **92** 829–839. (doi:10.1016/S0092-8674(00)81410-5)

Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY, Krauss S, Mootha VK, Lowell BB & Spiegelman BM 2001 Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARγ coactivator-1. *Molecular Cell* **8** 971–982. (doi:10.1016/S1097-2765(01)00390-2)

Raghuram S, Stayrook KR, Huang P, Rogers PM, Nosie AK, McClure DB, Burris LL, Khorasanizadeh S, Burris TP & Rastinejad F 2007 Identification of heme as the ligand for the orphan nuclear receptors REV-ERBα and REV-ERBβ. *Nature Structural & Molecular Biology* **14** 1207–1213. (doi:10.1038/nsmb1344)

Rangwala SM, Wang X, Calvo JA, Lindsley L, Zhang Y, Deyneko G, Beaulieu V, Gao J, Turner G & Markovits J 2010 Estrogen-related receptor γ is a key regulator of muscle mitochondrial activity and oxidative capacity. *Journal of Biological Chemistry* **285** 22619–22629. (doi:10.1074/jbc.M110.125401)

Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM & Puigserver P 2005 Nutrient control of glucose homeostasis through a complex of PGC-1α and SIRT1. *Nature* **434** 113–118. (doi:10.1038/nature03354)

van Rooij E, Quiat D, Johnson BA, Sutherland LB, Qi X, Richardson JA, Kelm RJ Jr & Olson EN 2009 A family of microRNAs encoded by myosin genes governs myosin expression and muscle performance. *Developmental Cell* **17** 662–673. (doi:10.1016/j.devcel.2009.10.013)

Rowe GC, El-Khoury R, Patten IS, Rustin P & Arany Z 2012 PGC-1α is dispensable for exercise-induced mitochondrial biogenesis in skeletal muscle. *PLoS ONE* **7** e41817. (doi:10.1371/journal.pone.0041817)

Russell AP, Feilchenfeldt J, Schreiber S, Praz M, Crettenand A, Gobelet C, Meier CA, Bell DR, Kralli A, Giacobino JP *et al.* 2003 Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-γ coactivator-1 and peroxisome proliferator-activated receptor-α in skeletal muscle. *Diabetes* **52** 2874–2881. (doi:10.2337/diabetes.52.12.2874)

Sanyal S, Matthews J, Bouton D, Kim HJ, Choi HS, Treuter E & Gustafsson JA 2004 Deoxyribonucleic acid response element-dependent regulation of transcription by orphan nuclear receptor estrogen receptor-related receptor γ. *Molecular Endocrinology* **18** 312–325. (doi:10.1210/me.2003-0165)

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd

Schiaffino S & Reggiani C 2011 Fiber types in mammalian skeletal muscles. *Physiological Reviews* **91** 1447–1531. (doi:10.1152/physrev.00031.2010)

Schuler MJ, Bühler S & Pette D 1999 Effects of contractile activity and hypothyroidism on nuclear hormone receptor mRNA isoforms in rat skeletal muscle. *European Journal of Biochemistry* **264** 982–988. (doi:10.1046/j.1432-1327.1999.00706.x)

Schuler M, Ali F, Chambon C, Duteil D, Bornert JM, Tardivel A, Desvergne B, Wahli W, Chambon P & Metzger D 2006 PGC1α expression is controlled in skeletal muscles by PPARβ, whose ablation results in fiber-type switching, obesity, and type 2 diabetes. *Cell Metabolism* **4** 407–414. (doi:10.1016/j.cmet.2006.10.003)

Seth A, Steel JH, Nichol D, Pocock V, Kumaran MK, Fritah A, Mobberley M, Ryder TA, Rowlerson A, Scott J *et al.* 2007 The transcriptional corepressor RIP140 regulates oxidative metabolism in skeletal muscle. *Cell Metabolism* **6** 236–245. (doi:10.1016/j.cmet.2007.08.004)

Solt LA, Wang Y, Banerjee S, Hughes T, Kojetin DJ, Lundasen T, Shin Y, Liu J, Cameron MD, Noel R *et al.* 2012 Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. *Nature* **485** 62–68. (doi:10.1038/nature11030)

Sonoda J, Mehl IR, Chong LW, Nofsinger RR & Evans RM 2007 PGC-1β controls mitochondrial metabolism to modulate circadian activity, adaptive thermogenesis, and hepatic steatosis. *PNAS* **104** 5223–5228. (doi:10.1073/pnas.0611623104)

Teyssier C, Ma H, Emter R, Kralli A & Stallcup MR 2005 Activation of nuclear receptor coactivator PGC-1α by arginine methylation. *Genes and Development* **19** 1466–1473. (doi:10.1101/gad.1295005)

Villena JA, Hock MB, Chang WY, Barcas JE, Giguère V & Kralli A 2007 Orphan nuclear receptor estrogen-related receptor α is essential for adaptive thermogenesis. *PNAS* **104** 1418–1423. (doi:10.1073/pnas.0607696104)

Wang YX, Zhang CL, Yu RT, Cho HK, Nelson MC, Bayuga-Ocampo CR, Ham J, Kang H & Evans RM 2004 Regulation of muscle fiber type and running endurance by PPARδ. *PLoS Biology* **2** e294. (doi:10.1371/journal.pbio.0020294)

Watt MJ, Southgate RJ, Holmes AG & Febbraio MA 2004 Suppression of plasma free fatty acids upregulates peroxisome proliferator-activated receptor (PPAR) α and δ and PPAR coactivator 1α in human skeletal muscle, but not lipid regulatory genes. *Journal of Molecular Endocrinology* **33** 533–544. (doi:10.1677/jme.1.01499)

Wende AR, Huss JM, Schaeffer PJ, Giguère V & Kelly DP 2005 PGC-1α coactivates PDK4 gene expression via the orphan nuclear receptor ERRα: a mechanism for transcriptional control of muscle glucose metabolism. *Molecular and Cellular Biology* **25** 10684–10694. (doi:10.1128/MCB.25.24.10684-10694.2005)

Woldt E, Sebti Y, Solt LA, Duhem C, Lancel S, Eeckhoute J, Hesselink MK, Paquet C, Delhaye S, Shin Y *et al.* 2013 Rev-erb-α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. *Nature Medicine* **19** 1039–1046. (doi:10.1038/nm.3213)

Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, Troy A, Cinti S, Lowell B, Scarpulla RC *et al.* 1999 Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* **98** 115–124. (doi:10.1016/S0092-8674(00)80611-X)

Wu H, Rothermel B, Kanatous S, Rosenberg P, Naya FJ, Shelton JM, Hutcheson KA, DiMaio JM, Olson EN, Bassel-Duby R *et al.* 2001 Activation of MEF2 by muscle activity is mediated through a calcineurin-dependent pathway. *EMBO Journal* **20** 6414–6423. (doi:10.1093/emboj/20.22.6414)

Wurtz JM, Bourguet W, Renaud JP, Vivat V, Chambon P, Moras D & Gronemeyer H 1996 A canonical structure for the ligand-binding domain of nuclear receptors. *Nature Structural Biology* **3** 87–94. (doi:10.1038/nsb0196-87)

Xie W, Hong H, Yang NN, Lin RJ, Simon CM, Stallcup MR & Evans RM 1999 Constitutive activation of transcription and binding of coactivator by estrogen-related receptors 1 and 2. *Molecular Endocrinology* **13** 2151–2162. (doi:10.1210/me.13.12.2151)

Yamamoto H, Williams EG, Mouchiroud L, Cantó C, Fan W, Downes M, Héligon C, Barish GD, Desvergne B, Evans RM *et al.* 2011 NCoR1 is a conserved physiological modulator of muscle mass and oxidative function. *Cell* **147** 827–839. (doi:10.1016/j.cell.2011.10.017)

Yan Z, Okutsu M, Akhtar YN & Lira VA 2011 Regulation of exercise-induced fiber type transformation, mitochondrial biogenesis, and angiogenesis in skeletal muscle. *Journal of Applied Physiology* **110** 264–274. (doi:10.1152/japplphysiol.00993.2010)

Yang X, Downes M, Yu RT, Bookout AL, He W, Straume M, Mangelsdorf DJ & Evans RM 2006 Nuclear receptor expression links the circadian clock to metabolism. *Cell* **126** 801–810. (doi:10.1016/j.cell.2006.06.050)

Yin L, Wu N, Curtin JC, Qatanani M, Szwergold NR, Reid RA, Waitt GM, Parks DJ, Pearce KH, Wisely GB *et al.* 2007 Rev-erbα, a heme sensor that coordinates metabolic and circadian pathways. *Science* **318** 1786–1789. (doi:10.1126/science.1150179)

Zechner C, Lai L, Zechner JF, Geng T, Yan Z, Rumsey JW, Collia D, Chen Z, Wozniak DF, Leone TC *et al.* 2010 Total skeletal muscle PGC-1 deficiency uncouples mitochondrial derangements from fiber type determination and insulin sensitivity. *Cell Metabolism* **12** 633–642. (doi:10.1016/j.cmet.2010.11.008)

Zhang ZP & Teng CT 2000 Estrogen receptor-related receptor α1 interacts with coactivator and constitutively activates the estrogen response elements of the human lactoferrin gene. *Journal of Biological Chemistry* **275** 20837–20846. (doi:10.1074/jbc.M001880200)

Zhu Y, Alvares K, Huang Q, Rao MS & Reddy JK 1993 Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver. *Journal of Biological Chemistry* **268** 26817–26820.

Zong H, Ren JM, Young LH, Pypaert M, Mu J, Birnbaum MJ & Shulman GI 2002 AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. *PNAS* **99** 15983–15987. (doi:10.1073/pnas.252625599)

Zuercher WJ, Gaillard S, Orband-Miller LA, Chao EY, Shearer BG, Jones DG, Miller AB, Collins JL, McDonnell DP & Willson TM 2005 Identification and structure–activity relationship of phenolic acyl hydrazones as selective agonists for the estrogen-related orphan nuclear receptors ERRβ and ERRγ. *Journal of Medicinal Chemistry* **48** 3107–3109. (doi:10.1021/jm050161j)

Zurlo F, Larson K, Bogardus C & Ravussin E 1990 Skeletal-muscle metabolism is a major determinant of resting energy-expenditure. *Journal of Clinical Investigation* **86** 1423–1427. (doi:10.1172/JCI114857)

Received in final form 31 October 2013
Accepted 1 November 2013

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0258

Published by Bioscientifica Ltd