Road to exercise mimetics: targeting nuclear receptors in skeletal muscle

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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

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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

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: PPAR α , PPAR δ (also referred to as PPAR β), and PPAR γ . PPAR α 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, PPAR δ and PPAR γ , 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 PPAR γ co-activator 1 α and PPAR γ co-activator 1 β (PGC1 α and PGC1 β) 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

subfamily shares certain common target genes, PPAR α and PPAR δ are typically involved in the regulation of lipid catabolism and oxidation, while PPAR γ 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.

PPAR δ 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 *Ppar δ* (*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 *Ppar δ* in skeletal muscle (de Lange *et al.* 2006).

Two independent studies have shown that the overexpression of *Ppar δ* in skeletal muscle induces a

glycolytic-to-oxidative fiber-type transformation (Luquet *et al.* 2003, Wang *et al.* 2004). Mice overexpressing WT *Ppar δ* 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 *Ppar δ* 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 *Ppar δ* 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, *Ppar δ* 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, ERR1, ERR2, REV-ERB1, and

REV-ERB2, and groups IIB and IIC, the members of which are broadly expressed and are linked to lipid metabolism and energy homeostasis, including PPAR1, PPAR2, PPAR3, PPAR4, PPAR5, PPAR6, PPAR7, PPAR8, PPAR9, PPAR10, PPAR11, PPAR12, PPAR13, PPAR14, PPAR15, PPAR16, PPAR17, PPAR18, PPAR19, PPAR20, PPAR21, PPAR22, PPAR23, PPAR24, PPAR25, PPAR26, PPAR27, PPAR28, PPAR29, PPAR30, PPAR31, PPAR32, PPAR33, PPAR34, PPAR35, PPAR36, PPAR37, PPAR38, PPAR39, PPAR40, PPAR41, PPAR42, PPAR43, PPAR44, PPAR45, PPAR46, PPAR47, PPAR48, and PPAR49. 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.

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

Ppar α (*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). *Ppar α* is also expressed at significant levels in skeletal muscle. Both *Ppar α* and *Ppar δ* regulate fatty acid catabolism and share common target genes. Similar to *Ppar δ* , the overexpression of *Ppar α* 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 *Ppar α* 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, *Ppar α* also functions distinctly from *Ppar δ* in fiber-type determination. In contrast to *Ppar δ* , the overexpression of *Ppar α* 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 PPAR α and PPAR δ 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 *Ppar α* in skeletal muscle induces a glycolytic-to-oxidative fiber-type switch (Gan *et al.* 2013). Therefore, endogenous PPAR α counteracts PPAR δ to maintain a proper fiber-type composition in skeletal muscle.

Ppar γ (*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 PPAR γ -specific ligands, can still improve insulin sensitivity in these knockout mice, suggesting that PPAR γ 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 PPAR γ in metabolic regulation comes from the generation of a mouse model with *Ppar γ* 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 *Ppar γ* 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 *Ppar δ* , the overexpression of *Ppar γ* 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, PPAR γ 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: ERR α , ERR β , and ERR γ . ERR α was the first to be identified based on its high sequence homology with the estrogen receptor α (ER α ; Giguère *et al.* 1988). ERR β was cloned in the same study using *Err α* (*Esrra*) cDNA as a probe (Giguère *et al.* 1988). Last but not least, ERR γ was discovered in three independent studies using different

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 PGC1 α and PGC β (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. *Erra* 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). *Errb* (*Esrrb*) and *Errg* (*Esrrg*) have similar tissue distribution patterns. Both are selectively expressed in metabolically active tissues such as retina, spinal cord, heart, muscle, and kidney, with *Errg* 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 ERR α in skeletal muscle have mainly focused on its synergistic interaction with PGC1 α in target gene regulation. No phenotypic change in skeletal muscle is observed after whole-body *Erra* ablation, possibly due to a compensatory induction of *Pgc1a* (*Ppargc1a*; Luo *et al.* 2003, Huss *et al.* 2004). ERR α 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 *Ppara*, a key regulator of fatty acid metabolism, and *Pdk4*, the mitochondrial gate keeper for pyruvate oxidation. The overexpression of its co-activator PGC1 α 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 ERR α to the ERR response element (ERRE) on the promoters of *Ppara* and

Pdk4 (Huss *et al.* 2004, Wende *et al.* 2005). In addition, ERR α also regulates myocyte differentiation. The overexpression of *Erra* in C2C12 myoblasts accelerates myotube formation, while *Erra*-null primary myocytes show delayed myogenesis and mitochondrial dysfunction (Murray & Huss 2011). Although ERR α positively regulates lipid metabolism and mitochondrial OXPHOS in cooperation with PGC1 α 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 ERR α , ERR γ also plays an important role in the regulation of energy metabolism. *Errg*-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 ERR γ 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 *Errg* 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 ERR γ also alleviates the symptoms of Duchenne muscular dystrophy and promotes muscle recovery from ischemic damage (Matsakas *et al.* 2012, 2013). Therefore, genetic activation of ERR γ 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 ERR α and ERR γ , little is known about whether and how ERR β regulates energy metabolism. Loss-of-function studies have demonstrated the crucial roles of ERR β 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 ERR β and ERR γ are required to

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 ERR β and ERR γ in skeletal muscle is unclear, and more work is needed to fully understand the role of ERR β 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 ERR β and ERR γ ; 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 *Ppar δ* and *Err γ* (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 PPAR δ and ERR γ . 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. Knock-down 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-ERB α and REV-ERB β . 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 ERR β , ERR γ , NUR77, and NOR1, all of

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-ERB β in skeletal muscle, REV-ERB α has recently been shown to positively regulate energy metabolism and mitochondrial OXPHOS function in muscle (Woldt *et al.* 2013). *Rev-erb α* (*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-ERB α in skeletal muscle has been demonstrated in *Rev-erb α* -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-erb α* in C2C12 cells increases mitochondrial biogenesis and OXPHOS activity, accompanied by the induction of fatty acid metabolism genes. The *in vivo* overexpression of *Rev-erb α* in muscle via adeno-associated viral (AAV) infection also induces mitochondrial OXPHOS activity. These physiological changes seem to be mediated by the AMPK–Sirt1–PGC1 α signaling pathway, which is down-regulated in the knockout muscle but upregulated in *Rev-erb α* -overexpressing muscle cells. In addition to its roles in the regulation of mitochondrial biogenesis and OXPHOS activity, muscle REV-ERB α is also involved in the modulation of mitochondrial autophagy (mitophagy, Woldt *et al.* 2013). Mitophagy is induced in *Rev-erb α* -knockout muscle but suppressed in overexpressing C2C12 cells. REV-ERB α 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-ERB α 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-erb α* since the level of ATP is much lower in *Rev-erb α* -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.

PPAR γ co-activator 1

The PGC1 α and PGC1 β 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).

PGC1 α was first identified as a cold-inducible thermogenic factor in brown adipose tissue (Puigserver *et al.* 1998). In skeletal muscle, *Pgc1 α* is predominantly expressed in oxidative muscles such as soleus (Wu *et al.* 1999). The expression of *Pgc1 α* 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, *Pgc1 α* 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, *Pgc1 α* also stimulates mitochondrial uncoupling by upregulating the mitochondrial *Ucp2*, to further enhance mitochondrial energy expenditure (Wu *et al.* 1999). *In vivo* ectopic expression of *Pgc1 α* 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.* 2002b). As a result, the transgenic mice have improved endurance running performance

(Calvo *et al.* 2008). Loss-of-function studies, both whole-body and muscle-specific, have shown that *Pgc1 α* 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 *Pgc1 α* (Geng *et al.* 2010). On top of that, a recent study has shown that muscle mitochondrial biogenesis can still be induced by exercise without *Pgc1 α* (Rowe *et al.* 2012), suggesting an alternate signaling pathway in remodeling skeletal muscle upon exercise induction.

PGC1 β was identified by its high homology with PGC1 α (Kressler *et al.* 2002, Lin *et al.* 2002a). It is also highly involved in the regulation of mitochondrial function and energy metabolism (Kamei *et al.* 2003). *In vitro* overexpression of *Pgc1 β* (*Ppargc1b*) in muscle cells has effects similar to that of *Pgc1 α* in terms of promoting mitochondrial biogenesis and oxidative fiber-type transformation (Mortensen *et al.* 2006). Similarly, the overexpression of *Pgc1 β* 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 PGC1 α model, PGC1 β 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 *Pgc1 β* 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 PGC1 α and PGC1 β compensate for each other when one is absent. This is true for their contributions to the regulation of mitochondrial function. Double-knockout mice lacking *Pgc1 α* and *Pgc1 β* 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, PGC1 α and PGC1 β 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

(Cavallès *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 PGC1 α , 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

activity and whole-body energy expenditure. Similar to the overexpression of *Pgc1 α* 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 *Pgc1 α* and knockout of *Ncor1* or *Rip140* in skeletal muscle. Similar to RIP140, NCoR1 functions through PPARs and ERRs in opposition to PGC1 α . It is recruited to PPREs or ERREs at their target gene promoters to repress their transcriptional activity, which can be antagonized by PGC1 α (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 PGC1 α , 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 PGC1 α (Zong *et al.* 2002, Jäger *et al.* 2007), in which AMPK is activated by exercise and directly phosphorylates PGC1 α 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 *Ppar δ* , *Ppar γ* , *Err γ* , or *Rev-erb α* , 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 PPAR δ 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 PPAR δ agonist GW501516 (Narkar *et al.* 2008), ERR β / γ agonist GSK4716 (Rangwala *et al.* 2010), and REV-ERB α / β agonists SR9009 and SR9011 (Woldt *et al.* 2013).

GW501516 was originally developed as a potent and selective PPAR δ agonist (Oliver *et al.* 2001). Its activation of PPAR δ 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 *Ppar δ* (Luquet *et al.* 2003, Wang *et al.* 2004, Narkar *et al.* 2008). The ligand activation of PPAR δ 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 *Ppar δ* transgenic muscle but not during either GW501516 treatment or training alone (Wang *et al.* 2004, Narkar *et al.* 2008). Thus, *in vivo* activation of PPAR δ by oral administration of GW501516 enhances the effect of exercise training.

GSK4716 was identified as a specific agonist for ERR β and ERR γ , 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

to the upregulation of all the three *Err* genes and their co-activators *Pgc1 α* and *Pgc1 β* . 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*, *Pgc1 α* , *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 *Ppar δ* in skeletal muscle (Wang *et al.* 2004). The stimulation of oxidative genes by AICAR seems to be dependent on PPAR δ as AICAR fails to induce these genes in *Ppar δ* -null muscle cells. In addition, when administered together, AICAR and GW501516 synergistically activate PPAR δ 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 PPAR δ , which causes skeletal muscle remodeling and enhances endurance. However, the mechanism as to how AMPK synergistically activates PPAR δ 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.

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