Chapter 8

Transcription Factors Regulating Exercise Adaptation

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Skeletal muscle is an extremely flexible organ and adapts immediately to changes in use. The extent of adaptation depends on both the nature and the quantity of the demand placed on the muscle. While single bouts of exercise transiently alter gene expression, repeated bouts of exercise lead to a range of longer lasting adjustments. Endurance exercise builds the aerobic capacity, increasing the time over which the muscle can produce energy by oxidizing carbohydrate and lipid. On the other hand, resistance exercise increases the ability of the muscle to utilize glycolytic energy, thereby increasing the capability to produce power over a short length of time (Holloszy and Booth 1976). In response to exercise and contraction, skeletal muscle also becomes more sensitive to insulin. These changes are reversible, and thus the opposite effects occur in response to inactivity. Key questions include how these changes are initiated and coordinated at the level of gene transcription and whether there is a master signal activated by exercise. In this chapter we focus our attention on the transcription factors that regulate these processes.

With the advent of gene array technology, numerous studies were undertaken in an attempt to identify changes in mRNA following exercise training, and several candidate genes have been identified that appear to be involved in one or more exercise-induced adaptations (Mahoney and Tarnopolsky 2005; Teran-Garcia et al. 2005). Although gene array technology has been instrumental in mapping exercise-responsive genes, discovering the key transcription factors remains more challenging. Transcription factors can be regulated by at least three separate mechanisms. The first mechanism is increased expression. The second, which involves the physical location of the transcription factor within the cell, is usually controlled by changes in phosphorylation and can be affected by exercise without accompanying changes in mRNA expression. Thus phosphorylation and dephosphorylation can translocate the transcription factor to the nucleus, where it can bind target DNA sequences and direct transcription. Finally, the role of coactivators and corepressors is becoming increasingly appreciated. Interaction of transcription factors with coactivators may increase translocation to the nucleus or increase binding to the target promoter. Thus, in order to fully understand how transcription factors are regulated by exercise, we need to establish full proteomic activation profiles.

Activation of MAPK Signaling

Several MAPK proteins are activated in direct response to muscle contraction and exercise training (Long, Widegren, and Zierath 2004; Zierath 2002). Although not transcription factors themselves, the different MAPK signaling cascades integrate signals from diverse extracellular stimuli, including hormones and growth factors as well as cellular stress, to regulate gene transcription and protein synthesis in various cell culture systems (Pearson et al. 2001). In skeletal muscle, at least three parallel MAPK signaling cascades are

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activated in direct response to exercise. These include ERK1/2 (p42/p44 MAPK), p38 MAPK, and JNK (Long, Widegren, and Zierath 2004; see also figure 8.1).

Exercise results in several adaptations in the muscle cell and leads to the activation of different signaling components, as summarized in figure 8.1. Cellular stress and stretch or injury induce MAPK signaling cascades, leading to the activation of several transcription factors such as nuclear factor of activated T cells (NFAT) and myocyte enhancer factor (MEF). The p38 MAPK also appears to mediate coactivation or alteration of a number of other transcription factors. MAPK activation is thought to control diverse responses ranging from muscle growth to expression of glucose transport to regulation of mitochondrial biogenesis. The neuronal input initiating contraction releases Ca^{++} ions that alter the activity of calcium-sensitive kinases targeting NFAT, MEF2, and NRFs, leading to changes in fiber growth and differentiation and increases in oxidative capacity via mitochondria biogenesis.

The demands of exercise change the energy status of the muscle fiber, leading to the activation of energy-sensing kinases like AMPK. AMPK is thought to mediate signaling that regulates the expression of PGC-1, an important coactivator involved in MEF2, NFAT, ERRα, and PPAR activation. These transcription factors play important roles in regulating mitochondrial density and activ-

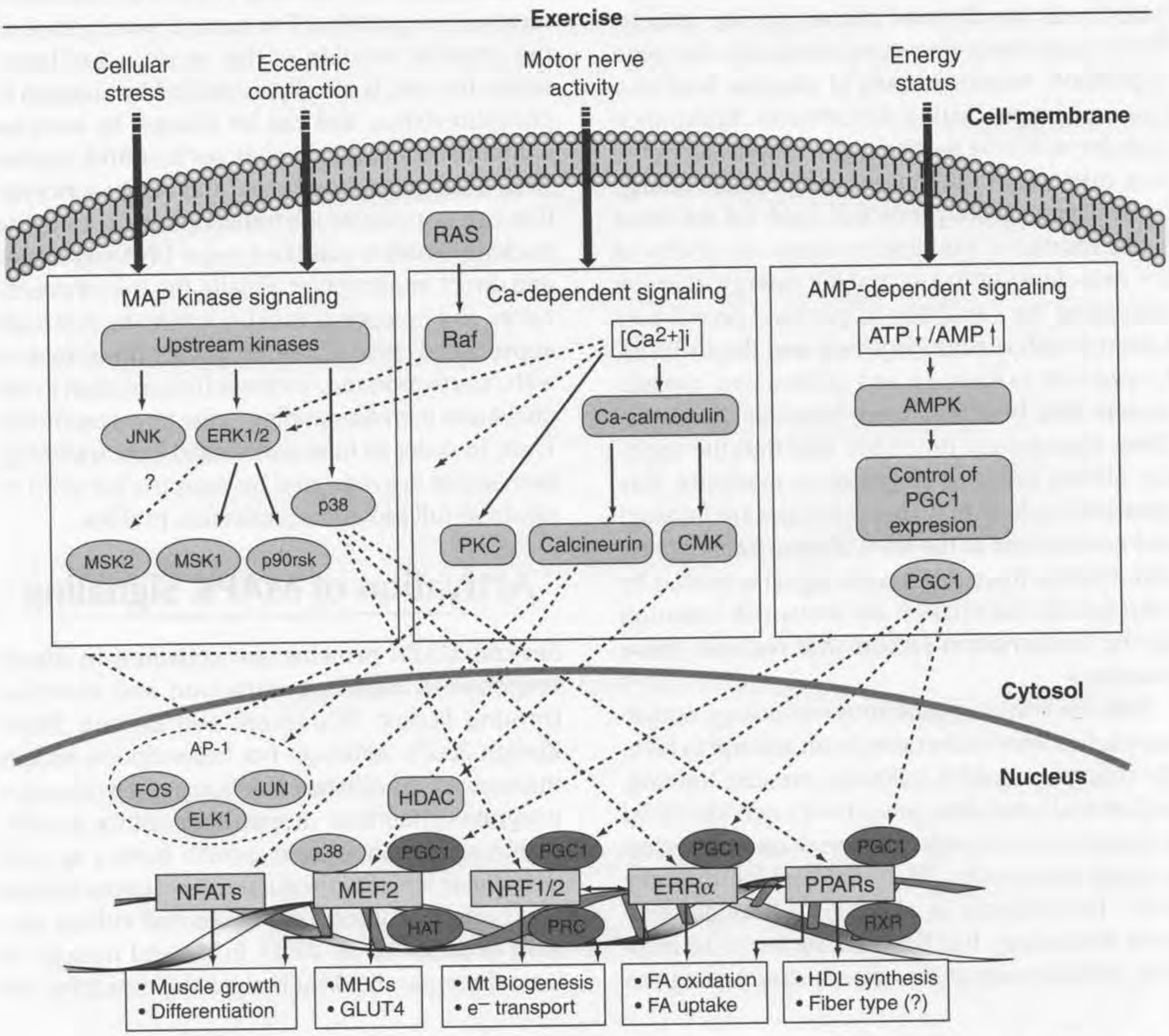

Figure 8.1 Summary of transcription factors regulated by exercise. MHC = myosin heavy chain; FA = fatty acid; HDL = high density lipoprotein; MT = mitochondria.

ity and thus also in regulating various aspects of lipid metabolism.

The ERK1/2 pathway is both rapidly and profoundly activated following acute cycling exercise (Widegren et al. 1998; Yu et al. 2003). By investigating muscle biopsies obtained from subjects performing one-legged cycling (the other leg being kept at rest), we have demonstrated that the activation of ERK1/2 MAPK signaling is specific to the exercising muscle. ERK1/2 is rapidly activated in the exercising muscle, and activity returns to basal levels within minutes of exercise cessation (Krook et al. 2000; Widegren et al. 1998). Furthermore, in vitro contraction of isolated rat skeletal muscle is sufficient to elicit ERK1/2 phosphorylation (Ryder et al. 2000; Wretman et al. 2001). Thus, local contraction-dependent effects rather than systemic exercise effects activate ERK1/2.

In human skeletal muscle, p38 MAPK was activated after acute cycling exercise (Widegren et al. 1998) and following marathon running (Boppart et al. 2000; Yu et al. 2001). In marked contrast to the profound but highly transient ERK1/2 activation, p38 MAPK activation by one-legged cycling is smaller but more persistent. Furthermore, p38 MAPK phosphorylation is increased in the resting leg, indicating the potential influence of a systemic factor (Widegren et al. 1998). It is possible that the mode of exercise influences the activation of different MAPK signaling pathways. In isolated rat skeletal muscle, concentric contractions increase ERK1/2 phosphorylation but do not affect p38 MAPK, whereas eccentric contractions increase phosphorylation along both kinase cascades (Wretman et al. 2001). Training status can also influence the exercise effect on MAPK signaling. Exercise-induced signaling responses for p38 MAPK are more profound in untrained men as compared to highly trained individuals (even at the same relative cycling exercise intensity; Yu et al. 2003). Activation of p38 MAPK may play an important role for the subsequent activation of the MEF2 transcription factor as well as the expression of the coactivator PGC-1α; this effect will be discussed in more detail subsequently.

Activation of the JNK pathway appears to relate somewhat to the degree of injury the muscle sustains with exercise, and JNK is affected more by eccentric as opposed to concentric exercise (Boppart et al. 1999). However, ERK kinase 1, which is an upstream activator of JNK, is activated during one-legged cycle ergometry, an exercise that is not associated with significant muscle injury (Widegren et al. 1998).

Downstream substrates of the various MAPK pathways include p90 ribosomal S6 kinase (p90rsk) and mitogen- and stress-activated kinases (MSK) 1 and 2. Activated p90rsk phosphorylates several transcription factors, including Elk, the cAMP response element-binding protein (CREB), and the AP-1 family (transcription factors consisting of homodimers and heterodimers of c-Jun and c-Fos). Exercise activates some of these downstream targets, including p90rsk and MSK1 and MSK2 (Krook et al. 2000; Yu et al. 2001). Activation of both MSK and p90rsk is rapid and limited to the exercising muscle, an observation suggesting that it occurs primarily via ERK1/2-dependent pathways. Histone H3 is a target of MSK1 (Thomson et al. 1999), and we have shown that exercise increases phosphorylation of histone H3 in human skeletal muscle (Yu et al. 2003). This finding may link contraction-activated signaling to gene expression, since the timing of histone H3 phosphorylation closely corresponds to the transient expression of activated immediate early genes (Thomson et al. 1999). Another target of MSK1 is the transcription factor CREB (Deak et al. 1998). However, CREB phosphorylation has not been reported to increase in skeletal muscle in response to exercise (Widegren et al. 2000). These combined observations underscore the difficulty in translating the results between different cell systems and the importance of studying in vivo responses to exercise in human skeletal muscle.

There is good evidence that exercise induces both MAPK signaling and changes in transcriptional activity, as MAPK has been directly implicated in the phosphorylation of transcription factors (Pearson et al. 2001). The nature of the transcription factors responsive to exercise, however, is not fully understood. Thus, although the transcription factors AP-1 and Elk-1 are targets of MAPK signaling, their role in exercise-mediated gene transcription is not known. Applying mechanical stress directly to skeletal muscle fibers does increase the DNA binding of AP-1 (Kumar et al. 2002). A number of other transcription factors known to be MAPK targets are also good candidates for directing exercise-mediated gene transcription. Some of these, including MEF2, PPAR, NFAT, and PGC-1, will be considered in more detail later in this chapter.

Muscle Hypoxia

Muscle contraction is thought to result in local hypoxia within the working muscle. The exercise effect on insulin sensitivity in muscle can be mimicked by hypoxia (Holloszy 2005). Hypoxia inducible factor 1 (HIF-1) is a transcription factor that acts as a master regulator for the expression of hypoxia inducible genes (Hoppeler et al. 2003). HIF-1 is a heterodimer composed of HIF-1α and HIF-1β, the latter of which is an aryl hydrocarbon receptor nuclear translocator (ARNT). Hypoxia stabilizes the HIF-1α protein, leading to nuclear translocation and activation of gene transcription. Acute exercise in humans enhances downstream HIF-1 function (Ameln et al. 2005). The precise effects of this activation are not fully understood, although it has been suggested to be important for HIF-1 for exercise-induced capillarization (Ameln et al. 2005). The effects of short-term exercise-induced hypoxia in muscle may differ from those of continuous reduced oxygen tension. For example, people who live at higher altitudes have a lower mitochondria density in the skeletal muscle as compared to people living at sea level (Hoppeler et al. 2003).

Calcium-Activated Signaling

Skeletal muscle contraction leads to an increase in intracellular Ca^{++} concentrations. Several signaling pathways are activated as a result of this increase in Ca^{++}, including calcineurin and its downstream targets NFAT, Ca^{++}/calmodulin-dependent protein kinases (CaMK), and Ca^{++}-dependent PKC.

Nuclear Factor of Activated T Cells

Initially the nuclear factor of activated T cells (NFAT) was identified as the transcription factor controlling the induction of the IL-2 gene during T cell activation (Shaw et al. 1988). To date, five NFAT family members have been identified, denominated NFAT1 through NFAT5. A rise in intracellular Ca^{++} activates the phosphatase calcineurin, which dephosphorylates and activates NFAT1 through NFAT4. NFAT5 is regulated by changes in osmotic tension.

In immune cells, NFAT acts in concert with other transcription factors, particularly the AP-1 proteins (Macian, Lopez-Rodriguez, and Rao 2001). In cultured human skeletal muscle cells, NFATc1, NFATc2, and NFATc3 are expressed during distinct stages of differentiation (Abbott et al. 1998). Mice with targeted deletions of NFAT are characterized by skeletal muscle defects; nfatc3–/– animals have reduced muscle mass due to a lower number of both slow and fast myofibers (Kegley et al. 2001), while nfatc2–/– mice exhibit reduced muscle size due to a defect in skeletal muscle growth (Horsley et al. 2001). Hence, NFAT is thought to control skeletal muscle hypertrophy and muscle development and to be crucial in the establishment of fiber types. While NFAT appears to act in concert with other transcription factors such as the MEFs (Schulz and Yutzey 2004), it does not appear to regulate exercise effects on MEF2 in human muscle (McGee and Hargreaves 2004).

Although in principle exercise should augment NFAT activation via Ca^{++} and calcineurin, data on exercise-mediated NFAT activation in skeletal muscle are scarce to date. Moderate acute exercise increases mRNA expression of NFAT1, NFAT2, and NFAT3 in human skeletal muscle in the majority of subjects, and c-Fos mRNA (a component of the AP-1 complex) is significantly induced in skeletal muscle of all subjects (Hitomi et al. 2003). Electrical stimulation of mouse skeletal muscle leads to nuclear translocation of the NFATc1 isoform (Tothova et al. 2006). However, recent evidence suggests that NFAT shuttling into the nucleus is controlled not only by contraction, Ca^{++}, and calcineurin but also by other pathways (Shen et al. 2006). Thus further studies are needed to elucidate NFAT nuclear translocation and activation directly in exercising human skeletal muscle. Furthermore, the effects that appear to be regulated by calcineurin cannot be fully explained by NFAT transcription factors (Parsons et al. 2003), and it is likely that the coordinated regulation of other transcription factors such as MEF2 is necessary (Chin et al. 1998).

Regulation of GLUT4 Expression

Human skeletal muscle expresses the glucose transporters GLUT1 and GLUT4 (Zorzano et al. 1996). The GLUT4 isoform accounts for approximately 90% of the glucose transporter proteins in skeletal muscle; in fact, evidence suggests that GLUT4 may be the only glucose transporter in human skeletal muscle, with GLUT1 being expressed primarily in

endothelial cells from intermuscular capillaries (Ploug et al. 1998). GLUT4 abundance depends on the developmental stage of the skeletal muscle and on the fiber type composition of oxidative versus glycolytic muscle fibers (Kern et al. 1990; Santalucia et al. 1992).

An acute bout of exercise elicits an insulin-independent translocation of GLUT4 to the cell surface and an increase in glucose transport (Douen et al. 1990; Lund et al. 1995) as well as an increase in expression of GLUT4. Expression of GLUT4 was increased approximately twofold 16 h after one prolonged (6 h) swim bout (Ren et al. 1994). GLUT4 expression can be linked directly to muscle innervation and contractile activity, and it can be elevated experimentally by in vivo and in vitro low-frequency stimulation of skeletal muscle contraction in animal models (Etgen et al. 1993; Hofmann and Pette 1994) and by exercise in humans (Dela et al. 1993; Houmard et al. 1991). The increase in GLUT4 is thought to be one of the key factors mediating enhanced insulin sensitivity in exercised skeletal muscle. Transgenic mice that overexpress GLUT4 in adipose and skeletal muscle exhibit improved oral glucose tolerance and insulin-stimulated glucose disposal (Deems et al. 1994; Liu et al. 1993; Ren et al. 1995).

Myocyte Enhancer Factor 2 and GLUT4 Enhancer Factor

Both the myocyte enhancer factor 2 (MEF2) family of transcription factors and the GLUT4 enhancer factor (GEF) have been implicated in the exercise-mediated effects on GLUT4 (McGee et al. 2006). Human skeletal muscle expresses MEF2A, MEF2C, and MEF2D. MEF2A in particular is thought to contribute to the exercise-mediated increase in GLUT4 expression (Mora and Pessin 2000). MyoD and thyroid hormone receptor (TRa1) have promoter binding locations that neighbor the MEF2 site, and, together with MEF and GEF, they appear to be required for full GLUT4 expression (Santalucia et al. 1992). While not fully elucidated, the regulation of MEF2 activity has been shown to be controlled by a variety of factors, including the MEF2 inhibitor class II histone deacetylase (HDAC) coactivators like histone acetyltransferase (HAT; McKinsey, Zhang, and Olson 2001), possibly PGC-1α (McGee et al. 2006), and p38 MAPK (Zhao et al. 1999).

DNA binding by both MEF2 and GEF increases in response to acute exercise (McGee et al. 2006; Yu et al. 2003). How exercise increases the DNA binding is not fully understood, although activation of AMPK is a possible mechanism (Al-Khalili et al. 2004; Holmes et al. 2005). The activity of p38 MAPK is elevated in direct response to exercise, and a docking domain for p38 MAPK has been found on MEF2A (Chang et al. 2002). The exercise-mediated increase in Ca^{++} has also been suggested to be a key signal mediating exercise-induced GLUT4 expression in skeletal muscle via regulation of MEF2, possibly through calcineurin. Expression of activated calcineurin in mouse skeletal muscle results in increased expression of GLUT4 (Ryder et al. 2003). The mechanisms leading to Ca^{++}-mediated activation of MEF2 are under debate; however, phosphorylation of HDAC leads to the dissociation of the MEF2-HDAC complex, allowing for at least a partial transcriptional activity of MEF2 (Lu et al. 2000). Additionally, calcineurin activation of NFAT may recruit coactivators to MEF2 (McKinsey, Zhang, and Olson 2002). However, despite a possible role for calcineurin in both developmental and long-term adjustments in GLUT4 expression following exercise training, a role for calcineurin in the short-term effects on GLUT4 expression has been challenged, and CaMK has been added to the list of possible mediators of the Ca^{++} effect on the MEF2A transcription factor (Garcia-Roves et al. 2005; Ojuka et al. 2002).

Thus there is good evidence that both GEF and MEF2 are important for the expression of GLUT4 in human skeletal muscle following exercise. The MEF2 family of transcription factors is known to be important for the expression of a large number of genes (Black and Olson 1998), and thus it is likely that exercise-mediated activation of MEF2 DNA binding has implications for a number of exercise adaptations and changes in gene expression. However, to date the bulk of our understanding has centered on MEF2 and GLUT4.

Mitochondria Biogenesis and Increased Lipid Oxidation

Endurance exercise has been shown to be of greater benefit than strength exercise in treating type 2 diabetes (Cauza et al. 2005). This finding is thought to reflect the fact that endurance exercise improves oxidative capacity by increasing mitochondrial

density while strength exercise does not appear to have this effect (Davies, Packer, and Brooks 1981; Holloszy and Booth 1976). Furthermore, it has been proposed that a reduced oxidative capacity for fatty acids, possibly due to a decrease in mitochondrial density or function, contributes to the onset of type 2 diabetes in elderly individuals (Petersen and Shulman 2006). Similarly (but less frequently), hereditary mutations that impair mitochondria function may contribute to the onset of type 2 diabetes (Barazzoni 2004). The immediate targets of endurance exercise thought to signal to transcription factors leading to mitochondria biogenesis are Ca^{++} (Freyssenet, Di Carlo, and Hood 1999; Ojuka et al. 2002), AMPK (Atherton et al. 2005; Bergeron et al. 2001), and CaMK (Wu et al. 2002). Important end points of this signaling cascade are nuclear respiratory factor (NRF)-1 (Bergeron et al. 2001); NRF2 (Baar 2004); PGC-1 (Atherton et al. 2005); PPARα, PPARβ/δ; PRC; and TFAM (mTFA).

Nuclear Respiratory Factors 1 and 2

Mitochondria encode and express 13 subunits of the respiratory complexes but need some 100 proteins to function. Consequently these proteins have to be expressed in the nucleus and imported into the mitochondria. Although NRF1 regulates genes that are unrelated to mitochondrial function, it is also considered a key regulator of mitochondrial proliferation and differentiation (Xia et al. 1997). NRF1 is activated in response to an acute bout of exercise in rat skeletal muscle, suggesting that repeated bouts of exercise induce mitochondrial adaptation (Murakami et al. 1998). Similarly, NRF2 acts on a number of mitochondrial respiratory promoters and regulates the expression of several respiratory genes (Virbasius, Virbasius, and Scarpulla 1993). In humans, NRF2 mRNA has been shown to be upregulated 48 h after exercise (Cartoni et al. 2005). NRF2 is also involved in regulating TFAM (also known as *mTFA)*, which is necessary for mitochondrial maintenance and biogenesis (Larsson et al. 1998).

Estrogen-Related Receptor α

Another exercise-responsive transcription factor involved in mitochondrial biogenesis and function is the estrogen-related receptor (ERR)-α. ERRs consist of three isoforms (alpha, beta, and gamma) and are orphan receptors with close homology to estrogen receptors (Giguere et al. 1988). ERRα mRNA is upregulated following exercise (Cartoni et al. 2005) and interacts with PGC-1 coactivators controlling mitochondrial replication and expression of electron transport protein complexes (Ichida, Nemoto, and Finkel 2002). ERRα directly regulates mitochondrial beta-oxidation by interacting with PGC-1α (Sladek, Bader, and Giguere 1997; Vega and Kelly 1997). In skeletal muscle, genes important for fatty acid uptake and utilization have been shown to be regulated via the direct interaction of ERRα with PPARα (Huss et al. 2004) and NRFs (Finck and Kelly 2006). The importance of ERRα in regulating skeletal muscle oxidative phosphorylation was demonstrated using synthetic inhibitors (Mootha et al. 2004). Rather surprisingly, mice with a complete deletion of the ERRα gene exhibit a lean phenotype that resists the development of obesity, seemingly by a disruption of adipocyte development, indicating tissue specificity in the role of ERRα (Luo et al. 2003).

Peroxisome Proliferator-Activated Receptors

PPARs are nuclear receptors and transcription factors that play central roles in substrate utilization and have received attention as pharmacological targets for treating metabolic disease (Berger, Akiyama, and Meinke 2005; Smith and Muscat 2005). PPARs form heterodimers with RXRs. In the absence of an agonist, these heterodimers may recruit corepressors and silence transcription by active repression (Jepsen and Rosenfeld 2002). The PPARs are activated by dietary lipids and are therefore considered to be nutritional lipid sensors and to control lipid homeostasis (Smith and Muscat 2005). PPARs have also been implicated in mechanisms that release anti-inflammatory factors or repress the inflammatory response (Lee et al. 2003; Pascual et al. 2005). All three described PPAR isoforms are expressed in skeletal muscle; PPARδ and PPARα are the most abundant, while PPARγ appears to play a secondary role.

Exercise-Mediated Regulation of PPARs

Although some studies have reported elevated PPARγ mRNA in vastus lateralis muscle from healthy young men 3 h following cycling exercise

(Mahoney et al. 2005) and in rodents after 16 wk of treadmill exercise training (Kawamura et al. 2004), other studies have failed to show exercise effects on PPARγ mRNA levels in either rodents or humans (Gorla-Bajszczak et al. 2000; Russell et al. 2003; Tunstall et al. 2002). Despite this, the PPARγ2 Pro12Ala variant in humans has been associated with an improved exercise response. Carriers of PPARγ2 Pro12Ala demonstrated significantly better exercise-mediated improvement in fasting glucose than a control group demonstrated (Adamo et al. 2005). This finding suggests that the role of PPARγ in response to exercise requires further evaluation, and future studies may need to determine the actual transcriptional activation of PPARγ in addition to changes in mRNA expression.

Both PPARα and PPARδ mRNA are increased following an acute 3 h exercise bout (Watt et al. 2004). Endurance training has also been reported to elevate PPARα mRNA (Horowitz et al. 2000; Russell et al. 2003). Interestingly, nutritional status may influence the exercise effect on PPAR isoforms (Watt et al. 2004), as fasting dramatically increases PPARδ expression in mice (Luquet et al. 2003). Given the additional complexity of hormonal and nutrient regulation of these targets, dissecting exercise from nutritional effects on PPAR expression may be a challenge.

Recently we reported that protein expression of PPARδ in skeletal muscle increased significantly after physical exercise in patients with type 2 diabetes following a 4 mo, low-intensity exercise program (Fritz et al. 2006). Interestingly, the increase in PPARδ expression was associated with improvements in several clinical parameters, and PPARδ expression did not change in subjects who did not improve their clinical profile following exercise. Thus PPARα and δ may be key factors coordinating exercise-mediated changes in metabolism.

Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1

A key feature of most of the transcription factors involved in mitochondrial biogenesis is their binding to the nuclear coactivator peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) or PGC-1-related coactivator (PRC). These coactivators do not bind DNA themselves but interact with DNA-bound transcription factors to regulate gene expression (Finck and Kelly 2006). PGC-1α was the first of three PGC-1 homologues to be described. PGC-1α and PGC-1β share high sequence homology, whereas PRC is more distantly related.

An acute bout of exercise markedly increases PGC-1α mRNA immediately following the activity. PGC-1α then returns to pre-exercise levels within 24 h (Pilegaard, Saltin, and Neufer 2003). Several bouts of exercise training lead to a sustained increase in PGC-1α (Kuhl et al. 2006; Russell et al. 2003; Short et al. 2003). Furthermore, DNA polymorphisms in PGC-1α have been linked to reduced cardiovascular fitness (Ling et al. 2004) and to greater odds of developing type 2 diabetes (Barroso et al. 2006). Whether these polymorphisms are related to how PGC-1α responds to exercise has not yet been investigated.

Interestingly, overexpression of PGC-1α in cultured myoblasts is sufficient to increase mitochondria biogenesis (Wu et al. 1999). Overexpression of PGC-1β is also associated with an enhanced number of mitochondria (Lin et al. 2003; Meirhaeghe et al. 2003). PGC-1β transgenic mice have increased energy expenditure and are protected from obesity by increasing fat oxidation (Kamei et al. 2003).

Myogenic Development and Adaptation

Skeletal muscle utilizes both lipid and glucose as energy sources but prefers one or the other depending on a number of different factors. To a certain extent, substrate preference is programmed during skeletal muscle development. The transcription factors MyoD and MEF2 are part of a large number of proteins that regulate muscle development. These proteins are collectively denominated *myogenic regulatory factors* (MRFs; Blais et al. 2005). A comprehensive review of all MRFs, their interactions, and their targets is beyond the scope of this chapter; however, some of these targets have recently received attention due to their apparent importance in metabolic disease and type 2 diabetes. Among these are the PPARs, whose expression can be regulated by MyoD (Blais et al. 2005), and PGC-1α, whose expression is partly controlled by MEF2 (Czubryt et al. 2003).

Transcription Factors in the Regulation of Skeletal Muscle Fiber Types

Historically, muscle was classified by its appearance (as red or white) in recognition of the fact that its appearance correlates with its contractile properties (slow or fast, respectively; Spangenburg and Booth 2003). These functional properties of the skeletal muscle are closely coupled to metabolic profile: Oxidative, slow-twitch fibers (Type I fibers) carry larger amounts of mitochondria than fast-twitch, glycolytic fibers (Type II fibers) carry (Schiaffino and Serrano 2002; Spangenburg and Booth 2003). The regulation of fiber types is complex and will not be discussed in detail here. Some of this complexity derives from the difficulty in defining a fiber type. With this caveat it is still safe to argue that muscle fiber type composition directly influences exercise performance, and some evidence suggests that exercise training in turn influences fiber type. Furthermore, insulin-stimulated glucose transport is greater in slow-twitch, mitochondria-rich skeletal muscle fibers than it is in fast-twitch, glycolytic fibers (Daugaard et al. 2000; Henriksen et al. 1990; Song et al. 1999). In humans, insulin sensitivity correlates positively with the proportion of slow-twitch fibers (Lillioja et al. 1987). Patients displaying type 2 diabetes and insulin resistance, subjects exhibiting morbid obesity and insulin resistance, and first-degree relatives of patients with type 2 diabetes have a lower percentage of Type I fibers and a higher percentage of Type II fibers, particularly Type IIb fibers, when compared to insulin-sensitive subjects (Marin et al. 1994; Nyholm et al. 1997).

Transgenic animals have been instrumental in highlighting important regulators of muscle fiber type. However, the regulation of fiber type in transgenic animals is a result of altered mRNA expression during muscle development and may not necessarily reflect the regulation of these processes in mature muscle. Also, homogeneity, regulation, and degree of fiber type transformation differ substantially between rodent and human skeletal muscle (Delp and Duan 1996; Holloszy and Coyle 1984), and thus care must be taken when translating results from transgenic animals to humans.

However, some of the key factors implicated in the regulation of muscle fiber type are also known to be regulated by exercise training in mature muscle. These factors include PPARδ and PGC-1α. PGC-1α has been implicated as a master regulator of the slow-twitch, oxidative Type I muscle phenotype in rodents (Lin et al. 2002). Transgenic expression of activated PPARδ increases the proportion of Type I fibers in mice, thereby transforming the skeletal muscle to a slow-twitch, oxidative phenotype (Luquet et al. 2003; Wang et al. 2004).

Do Genetic Variations in Transcription Factor Genes Control Exercise Response?

In this chapter we have discussed how exercise and muscle contraction affect the expression or activity of different transcription factors that subsequently regulate muscle remodeling and metabolism (summarized in figure 8.1). The challenge is to understand the balance and interplay among these different transcription factors as well as the relative importance of the signaling pathways that lead to their activation. Genetic variations in several key genes are also likely to influence the muscle response to exercise, as was exemplified in the previous section for the PPARγ gene (Adamo et al. 2005). Differences in mRNA profiles in skeletal muscle have been mapped between groups of subjects who show a marked difference in the improvement of glucose tolerance following the same 20 wk of exercise training, demonstrating the existence of exercise resistance (Teran-Garcia et al. 2005). We have noted that when subjects with type 2 diabetes exercised for 4 mo, only subjects who had an increase in skeletal muscle PPARδ expression responded to exercise by improving their clinical status (Fritz et al. 2006). Whether the response to exercise is linked to variations within the PPARδ gene or to variations in other genes is currently not known.

Concluding Remarks

Skeletal muscle responds to both use and disuse by changing its gene expression. As we improve our understanding of how skeletal muscle metabolism is regulated, we will begin to unravel how adaptations to exercise and exercise training are regulated at the transcriptional level. Greater understanding of these events has implications not only for improving sports performance but also for identifying molecular targets in the treatment of metabolic disorders such as type 2 diabetes.

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