Cell Metabolism
Review

Exercise Metabolism and the Molecular Regulation of Skeletal Muscle Adaptation

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Preservation of aerobic fitness and skeletal muscle strength through exercise training can ameliorate metabolic dysfunction and prevent chronic disease. These benefits are mediated in part by extensive metabolic and molecular remodeling of skeletal muscle by exercise. Aerobic and resistance exercise represent extremes on the exercise continuum and elicit markedly different training responses that are mediated by a complex interplay between a myriad of signaling pathways coupled to downstream regulators of transcription and translation. Here, we review the metabolic responses and molecular mechanisms that underpin the adaptation of skeletal muscle to acute exercise and exercise training.

Introduction

Physical inactivity is a known, but modifiable, risk factor that contributes to lifestyle-related diseases, including many causes of "preventable death" (Booth et al., 2012). Worldwide, approximately one in three adults and four in five adolescents do not achieve the recommended quantity and quality of daily exercise (Hallal et al., 2012). Current public health recommendations recognize regular exercise and physical activity as a cornerstone in the prevention, management, and treatment of numerous chronic conditions, including hypertension, coronary heart disease, obesity, type 2 diabetes mellitus (T2DM), and age-related muscle wasting (sarcopenia) (Haskell et al., 2007; Colberg et al., 2010). This acknowledgment predicates the axiomatic understanding that "exercise is medicine." For instance, short-term exercise training partially reverses the progression of metabolic disease (O'Gorman et al., 2006), whereas lifestyle interventions incorporating increased physical activity remain the primary preventive approach for metabolic disease (Knowler et al., 2002). In fact, regular exercise combined with dietary intervention is more successful than pharmacological intervention in the treatment and prevention of T2DM (Knowler et al., 2002) and sarcopenia (Borst, 2004). While the benefits of and adaptations to regular exercise are long known, molecular biologists have recently uncovered networks of signaling pathways and regulatory molecules that coordinate adaptive responses to exercise. The purpose of this review is to describe the metabolic and molecular responses to a single (acute) bout of exercise and chronic exercise training, while contrasting the adaptive response to aerobic and resistance exercise. Key mechanistic studies that utilize transgenic mice and in vitro models of plasticity are also considered. Due to space limitations, this review focuses primarily on skeletal muscle, given its hierarchical role in locomotion, exercise performance, and metabolic responses, as well as the pivotal function in the regulation of metabolic homeostasis.

The Molecular Basis of Skeletal Muscle Adaptation to Exercise

Repeated, episodic bouts of muscle contraction, associated with frequent exercise training, are potent stimuli for physiological adaptation. Over time, skeletal muscle demonstrates remarkable malleability in functional adaptation and remodeling in response to contractile activity (Flück and Hoppeler, 2003; Coffey and Hawley, 2007). Training-induced adaptations are reflected by changes in contractile protein and function (Adams et al., 1993; Widrick et al., 2002), mitochondrial function (Spina et al., 1996), metabolic regulation (Green et al., 1992), intracellular signaling (Benziane et al., 2008), and transcriptional responses (Pilegaard et al., 2003). The widely accepted molecular mechanisms that govern the adaptation to exercise training involve a gradual alteration in protein content and enzyme activities. These progressive changes reflect activation and/or repression of specific signaling pathways that regulate transcription and translation, and exercise-responsive gene expression (Figure 1). Transient postexercise changes in gene transcription include immediate early genes, myogenic regulators, genes of carbohydrate (CHO) metabolism, lipid mobilization, transport and oxidation, mitochondrial metabolism and oxidative phosphorylation, and transcriptional regulators of gene expression and mitochondrial biogenesis (Pilegaard et al., 2003; Mahoney et al., 2005; Coffey et al., 2006a; Louis et al., 2007). On a regulatory level, a single bout of exercise alters the DNA binding activity of a variety of transcription factors, including MEF2 (Yu et al., 2001), HDACs (McGee et al., 2009), and NRFs (Baar et al., 2002; Wright et al., 2007). Protein stability and subcellular localization of transcriptional factor complexes within the nucleus and mitochondrion are

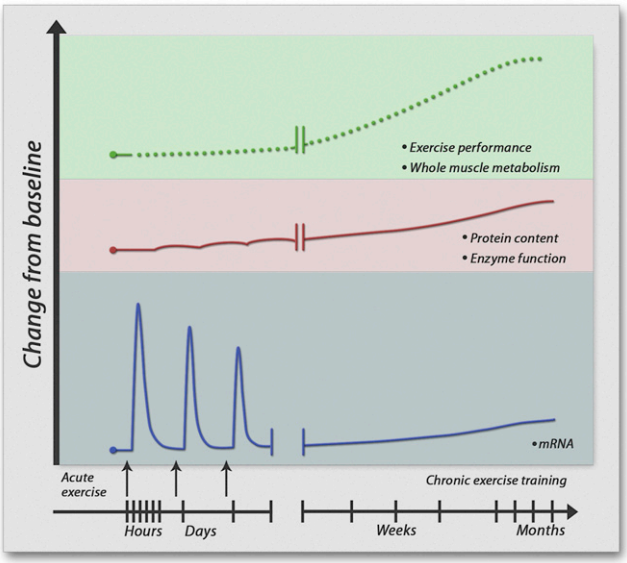

Figure 1. The Molecular Basis of Adaptation to Exercise

Schematic representation of changes in mRNA expression (bottom panel) and protein content (middle panel) over time as a consequence of acute exercise and chronic (repetitive) exercise training. Although each individual bout of exercise is necessary as a stimulus for adaptation, it alone is insufficient to alter the muscle phenotype—training-induced phenotypic adaptation is the consequence of repetition of the stimulus of individual exercise bouts. In order for a gene upregulated by exercise and training, an individual exercise bout elicits a rapid, but transient, increase in relative mRNA expression of a given gene during recovery. Alterations in mRNA expression several-fold from basal levels are typically greatest at 3–12 hr after cessation of exercise and generally return to basal levels within 24 hr. The temporal pattern is specific to a given gene and the exercise challenge. Translational processing and an elevated rate of postexercise protein synthesis result in a modest, same-directional change in protein content. Superimposition of repeated exercise bouts results in the gradual accumulation of protein in response to repeated, pulsed increases in relative mRNA expression. Thus, long-term adaptation to training is due to the cumulative effects of each acute exercise bout leading to a new functional threshold. Training-induced changes in protein content or enzyme function alter metabolic responses to exercise at the level of substrate metabolism, resulting in improved exercise performance (upper panel). As protein half-lives are usually much longer than those of mRNA, changes in protein content are more readily observed than changes in transcript expression in response to training as opposed to acute exercise.

also affected (McGee and Hargreaves, 2004; Little et al., 2011; Safdar et al., 2011b). Moreover, we have recently shown that transient DNA hypomethylation of gene-specific promoter regions precedes increases in mRNA expression in response to acute exercise (Barrès et al., 2012). In turn, these pulses of elevated mRNA during recovery from acute exercise facilitate the synthesis of respective proteins, and provoke gradual structural remodeling and long-term functional adjustments (Perry et al., 2010). In general, these adaptations are intrinsic to the working skeletal muscle, and collectively contribute toward maximizing substrate delivery, mitochondrial respiratory capacity, and contractile function during exercise. The net effect is to promote optimal performance during a future exercise challenge, resulting in a robust defense of homeostasis in the face of metabolic perturbation, and consequently, enhanced resistance to fatigue (Holloszy and Coyle, 1984; Booth and Thomason, 1991).

Skeletal Muscle Biology and Metabolism

Skeletal muscle comprises ~40% of total body mass in mammals and accounts for ~30% of the resting metabolic rate in adult humans (Zurlo et al., 1990). Skeletal muscle has a critical role in glycemic control and metabolic homeostasis and is the predominant (~80%) site of glucose disposal under insulin-stimulated conditions (DeFronzo et al., 1981). Additionally, skeletal muscle is the largest glycogen storage organ, with/having ~4-fold the capacity of the liver. Remarkably, a single bout of acute exercise improves whole-body insulin sensitivity for up to 48 hr after exercise cessation (Mikines et al., 1988; Koopman et al., 2005). Furthermore, exercise increases skeletal muscle glucose uptake through an insulin-independent pathway (Lee et al., 1995), indicating that muscle contraction directly impacts glucose homeostasis.

Mammalian skeletal muscles are comprised of several fiber types, of which the major classifications and biochemical properties have been reviewed in greater detail elsewhere (Schiaffino and Reggiani, 2011). Skeletal muscle fibers are defined as slow- or fast-twitch based on the contractile property of "time-to-peak tension" or "twitch" characteristics (Table 1). This classification coincides with histochemical staining for myofibrillar (myosin) ATPase as type I (slow-twitch) and type II (fast-twitch, highest ATPase activity). A subclassification of type IIa and type IIx exists in humans, while type IIb is primarily found in rodents. Type I muscle fibers are classically red in appearance, type IIx and IIb fibers are white in appearance, and type IIa fibers have an intermediate color. This difference in color reflects the abundance of the oxygen transport protein myoglobin, which is closely related to mitochondrial density and the relative contribution of oxidative metabolism in the respective fiber types (each highest in type I fibers). Immunohistochemical staining and electrophoretic protein separation can independently determine myosin heavy chain (MHC) isoform protein expression, another key criterion of fiber type classification. Each isoform displays distinct contractile properties that parallel ATPase activity and twitch characteristics. Uniform fibers containing MHC1, 2A, and 2X exist, while hybrid fibers containing 1-2A and 2A-2X isoforms have also been reported. Muscle fiber type is genetically determined during development, but the adaptive "transformation" of muscle fibers from one type to another is still hotly debated (Booth et al., 2010). Given an appropriate training stimulus, the plasticity of muscle permits changes in metabolic potential and morphology irrespective of whether a transformation of muscle fiber type measured by change in MHC expression is observed (Phillips et al., 1996; Leblanc et al., 2004).

One striking physiological characteristic of skeletal muscle is a capacity to rapidly modulate rate of energy production, blood flow, and substrate utilization in response to locomotion. Locomotion is powered by actin-myosin crossbridge cycling according to the sliding filament theory of skeletal muscle contraction (Podolsky and Schoenberg, 1983). Hydrolysis of adenosine triphosphate (ATP) by myosin ATPase provides the immediate energy source for crossbridge cycling but is also consumed to a large extent by dynamics of sodium-potassium and calcium exchange necessary for contraction. Skeletal muscle is the principal contributor to exercise-induced changes in metabolism. Maximal exercise can induce a 20-fold increase

Table 1. Contractile, Metabolic, and Morphological Characteristics of Human Skeletal Muscle Fiber Types

		Type II	
	Type I	Type IIa	Type IIx
General Properties			
Alternative nomenclature	SO, ST	FOG, FTa	FG, FTb
Myosin heavy-chain isoform	MHC1	MHC2A	MHC2X
Contractile and metabolic characteristics	Slow twitch, high oxidative, fatigue resistant	Fast twitch, oxidative-glycolytic, fatigue resistant	Fast twitch, glycolytic, fast fatigable
Force production (power output)	Weak	Intermediate	Strong
Endurance capacity	High	Intermediate	Low
Appearance/myoglobin content	Red/high	Red/intermediate	White/low
Time to peak tension [a]	80	30	
Ca^{2+} actomyosin ATPase activity [b]	0.16	0.48	
Mg2+ actomyosin ATPase activity [c]	0.30	0.84	
Recruitment threshold	All intensities	>40%VO_{2max}	>75%VO_{2max}
Morphological Properties			
Capillary density (capillaries per fiber)	4.2	4.0	3.2
Mitochondrial density	High	Intermediate	Low
Fiber size (cross-sectional area) [d]	5310	6110	5600
Percent distribution in whole muscle	54.0 ± 12.2 (50–55)	32.3 ± 9.1 (30–35)	13.0 ± 7.6 (10–20)
Myonuclear domain size	Small	Intermediate	Large
Glycolytic and Oxidative Enzyme Activities[e]			
Creatine kinase	13.1	16.6	
Phosphofructokinase	7.5	13.7	17.5
Glycogen phosphorylase	2.8	5.8	8.8
Lactate dehydrogenase	94	179	211
Citrate synthase	10.8	8.6	6.5
Succinate dehydrogenase	7.1	4.8	2.5
3-hydroxyl-CoA dehydrogenase	14.8	11.6	7.1
Metabolic and Substrate Properties			
Oxidative potential	High	Intermediate-high	Low
Glycolytic potential	Low	Intermediate-high	High
[Phosphocreatine] [f]	12.6	14.5	14.8
[Glycogen] [f]	77.8	83.1	89.2
[IMTG] [f]	7.1	4.2	
Exercise-type dominance	Prolonged low intensity	Moderate duration, high intensity	Short duration, maximal effort

Adapted from Saltin and Gollnick (1983). Relationship between skeletal muscle fiber type and the indicated properties. Data are from m. vastus lateralis from untrained men.
[a] msec.
[b] mmol min^{-1} mg $myosin^{-1}$.
[c] mmol min^{-1} g $protein^{-1}$.
[d] μm^2.
[e] mmol kg^{-1} min^{-1} except creatine kinase in mmol min^{-1} g^{-1}.
[f] mmol kg^{-1} wet weight.

in whole-body metabolic rate over resting values, whereas the ATP turnover rate within the working skeletal muscle can be more than 100-fold greater than at rest (Gaitanos et al., 1993). Although resting intramuscular stores of ATP are small (due to the four negative charges and hydrophilic nature of free ATP), activation of metabolic pathways that drive ATP generation maintains intracellular levels (Figure 2). Skeletal muscle is richly endowed with mitochondria and heavily reliant on oxidative phosphorylation for energy production. During strenuous exercise, dramatic (>30-fold) increases in intramuscular oxygen consumption and local blood flow occur (Andersen and Saltin, 1985; Gibala et al., 1998). Estimated TCA cycle flux increases by ~70- to 100-fold under the same conditions (Gibala et al., 1998). Thus, skeletal muscle is the primary site for CHO and lipid metabolism for energy production. Importantly, the biochemical consequences of contractile bioenergetics can regulate molecular processes governing skeletal muscle adaptation.

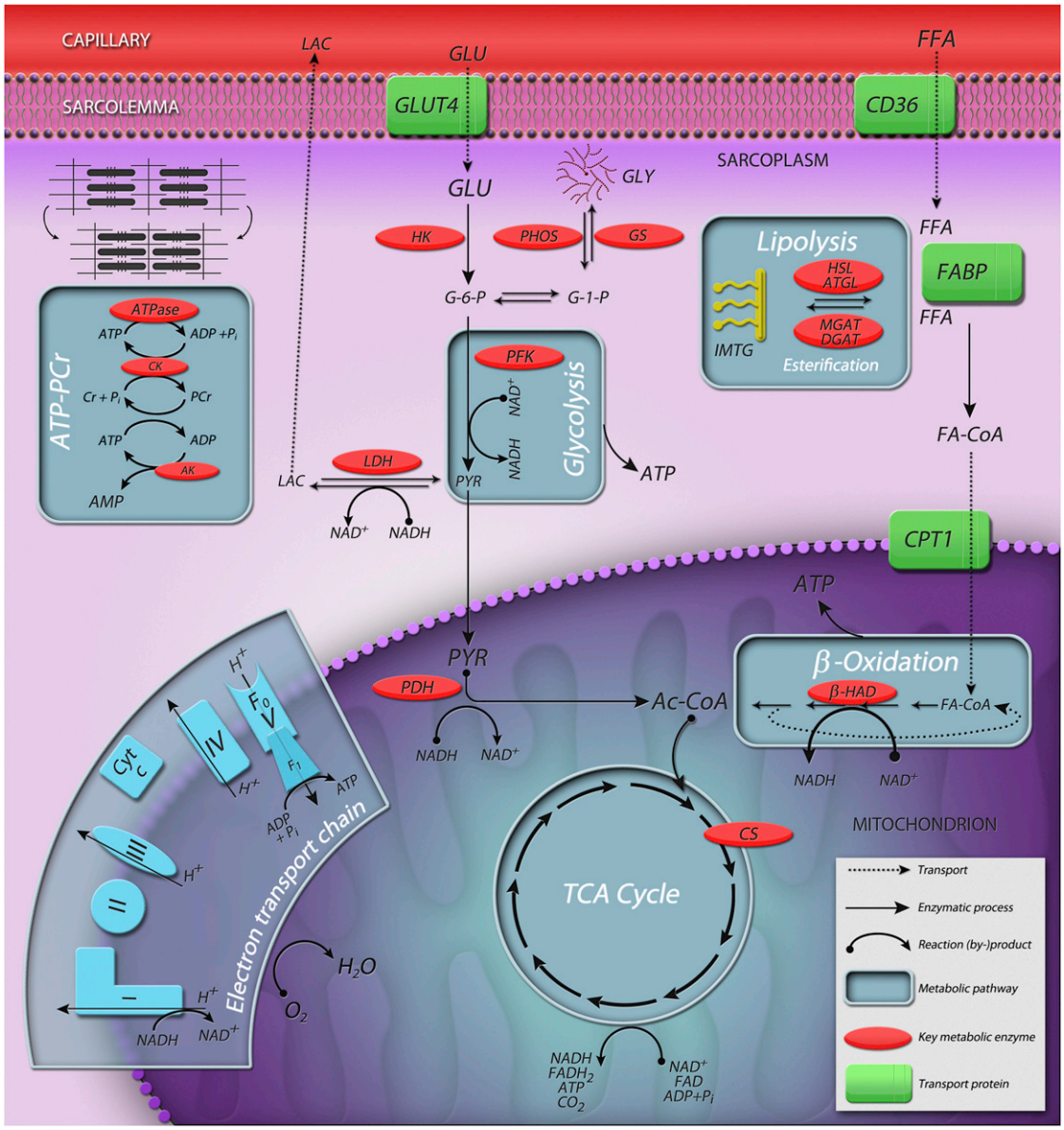

Figure 2. Energy Provision in Skeletal Muscle during Exercise

ATP hydrolysis, catalyzed by myosin ATPase, powers skeletal muscle contraction. Metabolic pathways of ATP generation in skeletal muscle include (1) the ATP-phosphagen system wherein the degradation of PCr by creatine kinase (CK) produces free Cr and P_i, which is transferred to ADP to re-form ATP; the adenylate kinase (AK) (myokinase) reaction catalyzes the formation of ATP and AMP from two ADP molecules; (2) anaerobic glycolysis, where glucose-6-phosphate derived from muscle glycogen (GLY) (catalyzed by glycogen phosphorylase, PHOS) or circulating blood glucose (GLU) (catalyzed by hexokinase, HK), is catabolized to pyruvate (PYR), which is reduced to lactate (LAC) by lactate dehydrogenase (LDH), and produces ATP by substrate level phosphorylation; (3) processes of carbohydrate (glycolysis) and lipid (β-oxidation) metabolism producing acetyl-CoA (Ac-CoA), which enters the tricarboxylic acid (TCA) cycle in the mitochondria, coupled to oxidative phosphorylation in the electron transport chain (ETC). The two main metabolic pathways, i.e., glycolysis and oxidative phosphorylation, are linked by the enzyme complex pyruvate dehydrogenase (PDH). GLUT4 facilitates glucose uptake to the sarcoplasm, which may undergo glycolysis or during rest/inactivity, be stored as glycogen via glycogen synthase (GS). Fatty acyl translocase (FAT/CD36) facilitates long-chain fatty acid transport at the sarcolemma, and, in concert with fatty acid binding protein ($FABP_{pm}$) and carnitine palmitoyltransferase 1 (CPT1), across the mitochondrial membrane. FFAs entering the cell may be oxidized via β-oxidation or be diverted for storage as IMTG via esterification by monoacylglycerol acyltransferase (MGAT) and diacylglycerol acyltransferase (DGAT). Liberation of FFAs from IMTG stores via lipolysis in skeletal muscle during exercise occurs via the activities of HSL and ATGL. All pathways of ATP generation are active during exercise, but the relative contribution of each is determined by the intensity and duration of contraction, as a function of the relative power (rate of ATP production) and capacity (potential amount of ATP produced). CS, citrate synthase; Cyt c, cytochrome c; PFK, phosphofructokinase.

Modalities of Exercise

Exercise is represented by a potential disruption to homeostasis by muscle activity that is either exclusively or in combination concentric, isometric, or eccentric. The use of the term "exercise" in scientific research often encompasses several modifiable variables. These include the modality (e.g., aerobic versus resistance) and the frequency, intensity, and duration of exercise sessions—each of which are mitigating factors

Table 2. Adaptations and Health Benefits of Aerobic Compared to Resistance Exercise

	Aerobic (Endurance)	Resistance (Strength)
Skeletal Muscle Morphology and Exercise Performance		
Muscle hypertrophy	↔	↑ ↑ ↑
Muscle strength and power	↔ ↓	↑ ↑ ↑
Muscle fiber size	↔ ↑	↑ ↑ ↑
Neural adaptations	↔ ↑	↑ ↑ ↑
Anaerobic capacity	↑	↑ ↑
Myofibrillar protein synthesis	↔ ↑	↑ ↑ ↑
Mitochondrial protein synthesis	↑ ↑	↔ ↑
Lactate tolerance	↑ ↑	↔ ↑
Capillarisation	↑ ↑	↔
Mitochondrial density and oxidative function	↑ ↑ ↑	↔ ↑
Endurance capacity	↑ ↑ ↑	↔ ↑
Whole-Body and Metabolic Health		
Bone mineral density	↑ ↑	↑ ↑
Body composition		
Percent body fat	↓ ↓	↓
Lean body mass	↔	↑ ↑
Glucose metabolism		
Resting insulin levels	↓	↓
Insulin response to glucose challenge	↓ ↓	↓ ↓
Insulin sensitivity	↑ ↑	↑ ↑
Inflammatory markers	↓ ↓	↓
Resting heart rate	↓ ↓	↔
Stroke volume, resting and maximal	↑ ↑	↔
Blood pressure at rest		
Systolic	↔ ↓	↔
Diastolic	↔ ↓	↔ ↓
Cardiovascular risk profile	↓ ↓ ↓	↓
Basal metabolic rate	↑	↑ ↑
Flexibility	↑	↑
Posture	↔	↑
Ability in activities of daily living	↔ ↑	↑ ↑

Aerobic exercise training generally encompasses exercise durations of several minutes up to several hours at various exercise intensities, incorporating repetitive, low-resistance exercise such as cycling, running, and swimming. Resistance training generally encompasses short-duration activity at high or maximal exercise intensities, and increases the capacity to perform high-intensity, high-resistance exercise of a single or relatively few repetitions such as Olympic weightlifting, bodybuilding, and throwing events. ↑, values increase; ↓, values decrease; ↔, values remain unchanged; ↑ or ↓, small effect; ↑↑ or ↓↑, medium effect; ↑↑↑ or ↓↓↓, large effect; ↔↑ or ↔↓, no change or slight change.

impacting the metabolic and molecular responses. Aerobic (or endurance-based) and resistance (or strength-based) activities represent two extremes of the exercise continuum (Table 2). Aerobic exercise imposes a high-frequency (repetition), low-power output (load) demand on muscular contraction, whereas resistance exercise imposes a low-frequency, high-resistance demand. Consequently, the metabolic and molecular responses to the different modalities are distinct, and the specificity of a given molecular response is coupled to a functional outcome. This is illustrated by divergent molecular signatures in response to aerobic versus resistance exercise (Coffey et al., 2006a, 2006b), or similar conditions simulated in vitro (Nader and Esser, 2001; Atherton et al., 2005), which is consistent with the divergent physiological and functional adaptations to the respective exercise modalities, e.g., endurance versus hypertrophy phenotype (Booth and Thomason, 1991). Although both aerobic exercise and resistance training can individually promote substantial health benefits (Table 2), divergent effects are observed depending on the parameter of interest. For example, aerobic training more effectively modifies cardiovascular risk factors, whereas resistance training more effectively maintains basal metabolic rate, muscle mass, and physical function in the elderly. However, compared to either modality alone, a combination of aerobic and resistance training is more effective for reducing the insulin resistance and functional limitations in obesity and the metabolic syndrome (Davidson et al., 2009), and improving glycemic control in T2DM (Sigal et al., 2007). The efficacy of combined aerobic and resistance exercise as part of lifestyle intervention is reflected in the recent exercise guidelines (Colberg et al., 2010).

The Metabolic Response to an Acute Bout of Exercise

Substrate Utilization during Exercise

During acute exercise, the contribution of various metabolic pathways to energy provision is determined by the relative intensity and absolute power output of the exercise bout (Figure 3). The absolute power output determines the rate of ATP demand and energy expenditure, whereas the relative exercise intensity influences the relative contributions of CHO and lipid sources, and circulating (extramuscular) and intramuscular fuel stores, to energy provision. The use of indirect calorimetry combined with isotope tracer methodology permitted the assessment of substrate utilization during exercise (Romijn et al., 1993; van Loon et al., 2001). The partitioning of fuel sources utilized from extra- or intramuscular substrates is coordinated quantitatively and temporally to meet the metabolic demands of exercise. At low-to-moderate intensities of exercise, the primary fuel sources supplying skeletal muscle are glucose, derived from hepatic glycogenolysis (or gluconeogenesis) or oral ingestion, and free fatty acids (FFAs) liberated by adipose tissue lipolysis. The contributions of liver and adipose tissue to substrate provision to contracting muscle during exercise are described in detail elsewhere (Kjaer, 2006; Horowitz, 2006) and are largely under the influence of hormonal responses to the onset of exercise (e.g., adrenaline, noradrenalin, glucagon, insulin, cortisol) (Galbo, 1983). With respect to extramuscular fuel sources, as exercise intensity increases, muscle utilization of circulating FFAs declines modestly, whereas utilization of circulating glucose increases progressively up to near-maximal intensities (van Loon et al., 2001). This coincides with increasing absolute rates of CHO oxidation and relative contribution to energy provision (Figure 3A), with a majority of energy at high intensities of exercise being provided by muscle glycogen. When exercise at

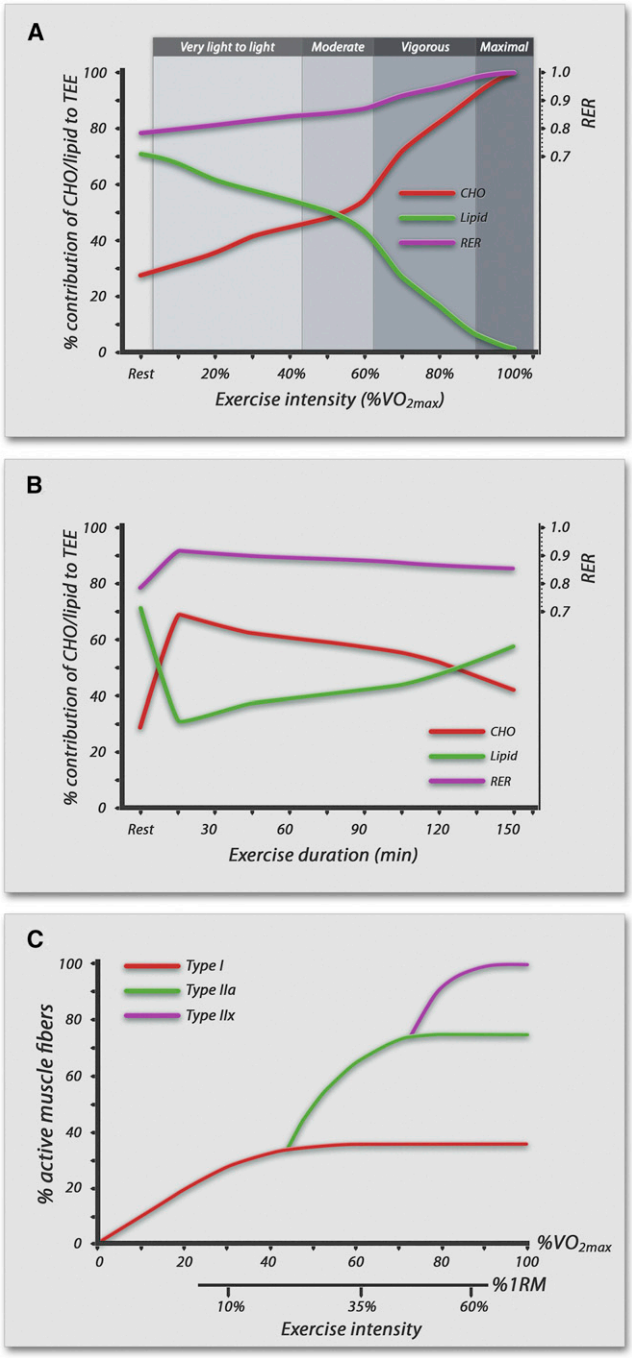

Figure 3. The Effect of Exercise Intensity and Exercise Duration on Substrate Metabolism and Muscle Recruitment during Acute Exercise

The respiratory exchange ratio (RER) is a ratio of CO_2 production (VCO_2) to O_2 consumption (VO_2). A value of 0.707 indicates 100% contribution from lipid sources, whereas a value of 1.0 or greater indicates 100% contribution from CHO sources. (A) and (B) are representative of the metabolic responses to exercise in fasted, physically active humans.

(A) Substrate contribution to exercise of increasing intensity. Up to ~30% VO_{2max}, oxidation of lipid sources (mostly plasma FFAs) accounts for the majority of energy provision. As exercise intensity increases, absolute CHO oxidation rate and relative contribution to energy provision increases. The lipid oxidation rate increases up to ~60%–70% VO_{2max}, after which it declines as intensity increases. In relative terms, the contribution of lipid oxidation to energy provision decreases proportionally with increasing exercise intensity, as reflected by a steady rise in RER.

(B) Substrate contribution to exercise at a fixed intensity (e.g., 65%VO_{2max}) for an extended duration. An initial rise in RER occurs at the onset of exercise, reflecting the increase in relative contribution of CHO to energy provision compared to resting metabolism. Thereafter, a small but steady decline in RER is observed with extended duration of exercise, reflecting the declining relative contribution of CHO to energy provision as a function of the increasing relative contribution of lipid.

(C) Recruitment of muscle fibers is dependent on the intensity and duration of contraction. A hierarchal recruitment pattern of type I to IIa to IIx/b occurs as force output of the muscle increases from low to high. During low-intensity exercise, slow-twitch, type I fibers are recruited, which have a high capacity for fat oxidation and a low capacity for glycogenolysis-glycolysis. An increase in contraction intensity results in a proportional increase in the recruitment of type II muscle fibers, which by their intrinsic characteristics generate more ATP from glycolytic pathways. The metabolic advantage is that these CHO-derived pathways produce ATP at a higher power (mol ATP s^{-1}) and at a lower rate of oxygen consumption (ATP mol O_2^{-1}). Increasing rates of ATP turnover have a feedforward effect on rates of muscle glycogenolysis through a decrease in cellular energy charge.

a fixed intensity is prolonged (>60 min) (Figure 3B), an increasing energy contribution is derived from lipid oxidation. Consequently, the proportion of energy derived from muscle glycogen declines and is replaced by a progressive increase in plasma FFA oxidation (Romijn et al., 1993).

Muscle glycogen is the predominant CHO source during moderate to intense exercise, and the rate of degradation (glycogenolysis) is proportional to the relative exercise intensity. Increased glycogenolysis during exercise occurs via activation of glycogen phosphorylase, which reflects alterations in [calcium]$_i$, [inorganic phosphate (P_i)], cAMP-dependent β-adrenergic stimulation, and allosteric modulation by AMP and IMP (Hargreaves, 2006). Higher rates of glycogenolysis occur when initial muscle glycogen concentrations are high, but as exercise proceeds, degradation rates parallel declining glycogen levels and associated glycogen phosphorylase activity. Conversely, intramuscular triglycerides (IMTGs) constitute only a fraction (~1%–2%) of whole-body lipid stores but are the subject of intense research in exercise metabolism and metabolic disease (Kiens, 2006). IMTGs are an important fuel source during prolonged (>90 min), moderate intensity exercise and provide ~25% of total energy, but tend to contribute less at either higher or lower intensities of exercise (Romijn et al., 1993; van Loon et al., 2001). Following exercise, IMTG stores are reduced by ~60%, predominantly in type I muscle fibers (van Loon et al., 2003; Stellingwerff et al., 2007). IMTG breakdown occurs primarily via hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) (Watt and Spriet, 2010), although the regulation of exercise-mediated lipase activity is incompletely described. As with aerobic exercise, both muscle glycogen and IMTG contribute to energy provision during resistance exercise (Koopman et al., 2006). However, questions remain regarding regulatory control of CHO and lipid utilization during exercise. In summary, skeletal muscle substrate utilization during exercise is influenced by (1) intrinsic exercise-related factors including intensity, duration, and mode of exercise; (2) metabolic factors including muscle recruitment patterns, enzymatic capacities, rates of substrate delivery, energy charge status, and activity of substrate cycles; and (3) external factors including environmental conditions, nutritional status, age, and

body composition (reviewed in Brooks, 1998; Spriet and Watt, 2003).

Free amino acid flux during exercise reflects dynamic activity in de novo synthesis, transamination, deamination, oxidation, and irreversible catabolism of specific amino acids. Several amino acids (alanine, aspartate, glutamate, glutamine, and the branched-chain amino acids [BCAAs] valine, leucine, and isoleucine) contribute to energy production in skeletal muscle (Gibala, 2006), whereas other amino acids contribute to gluconeogenesis during prolonged exercise (Ahlborg et al., 1974). Calculations of substrate utilization during exercise generally assume that the contribution of protein is constant, or alternatively use a nonprotein respiratory exchange ratio (RER). Protein-based energy provision during moderate intensity exercise is estimated at 5%–15%, while energy-compromised states, such as glycogen depletion, demand higher contributions (Wagenmakers et al., 1991; Horton et al., 1998). This energy is obtained from intramuscular protein degradation and oxidation of BCAAs by the branched-chain α-keto acid dehydrogenase complex (Wagenmakers et al., 1991).

Substrate Metabolism during the Postexercise Recovery Period

After the cessation of exercise, the metabolic rate declines but remains slightly elevated (<10%) for up to 24 hr. The extent of this "excess postexercise oxygen consumption" (EPOC) is proportional to the metabolic stress and determined by the intensity, duration, and type of exercise bout (Børsheim and Bahr, 2003). This recovery period is characterized by two major phases: (1) recovery of myocellular homeostasis in the immediate hours after exercise, and (2) cellular contributions to adaptation to exercise. Moreover, the global restitution of homeostasis includes the replenishment of oxygen stores, resynthesis of ATP and phosphocreatine (PCr), lactate oxidation and removal, restoration of fluid balance and fuel stores, and inflammatory and anti-inflammatory responses (Børsheim and Bahr, 2003). In contrast to the reliance on CHO metabolism during exercise, an increase in lipid oxidation and "sparing" of CHO sources for energy provision occurs during the recovery period (Kiens and Richter, 1998). This shift accommodates the high metabolic priority for muscle glycogen resynthesis, whereas the oxidation of lipid from both IMTG and circulating FFA sources is elevated to meet fuel requirements. The prolonged elevation in lipid oxidation in the postexercise period represents a key event in exercise-mediated effects on whole-body lipid metabolism. Lipid oxidation rates can reach 25% of that reported during exercise, and contribute greater than 60% of oxidative metabolism during recovery (Horton et al., 1998). Several other biosynthetic processes contribute to homeostatic recovery at a local level, including elevated rates of mitochondrial and myofibrillar protein synthesis (Wilkinson et al., 2008), lipid reesterification of previously liberated FFAs (Wolfe et al., 1990), and IMTG and glycogen resynthesis (Kiens and Richter, 1998; Schenk and Horowitz, 2007). These largely anabolic events are dichotomous to the catabolic nature of acute exercise.

In contrast to the rapid glycogen depletion during heavy or prolonged exercise, the replenishment of muscle glycogen to pre-exercise levels requires 24–48 hr. This timeline is readily altered by dietary manipulation. High CHO intake often produces a "supercompensation" effect such that glycogen repletion markedly exceeds pre-exercise concentrations. Replenishment of muscle glycogen stores is primarily dependent on (1) the availability of substrates, both glucose and nonglucose sources including lactate and alanine, and (2) noninsulin- and insulin-dependent enzymatic activity of glycogen synthase (Jentjens and Jeukendrup, 2003). Similarly, IMTG replenishment via skeletal muscle lipogenesis is influenced by both nutrient status and activation of triglyceride synthesis via mGPAT, DGAT, and SCD1 (Schenk and Horowitz, 2007). Lipid intermediaries such as diacylglycerol (DAG) and ceramides are reduced in skeletal muscle after exercise, suggesting their incorporation into IMTG during recovery (Schenk and Horowitz, 2007).

Contraction-Induced Signal Transduction Pathways in Skeletal Muscle

Contraction-induced changes in mechanical strain, ATP turnover, calcium flux, redox balance, reactive oxygen species (ROS) production, and intracellular oxygen pressure have all been implicated in the activation of signal transduction cascades regulating skeletal muscle plasticity (Figure 4). In turn, various cellular sensors transduce these homeostatic perturbations to couple contraction and transcriptional processes. The nature of the exercise challenge determines the acute metabolic and molecular responses, which are latterly contiguous with long-term physiological adaptation of exercise training. This provides a framework, known as excitation-transcription coupling, for the continuity and integration between signaling events regulated by cellular bioenergetics and the expression of genes that dictate skeletal muscle phenotype.

Local Tissue Oxygenation and Hypoxia-Inducible Factors

Oxygen sensing is long established in the regulation of adaptive processes in cells. The major signal transduction pathway sensitive to the intracellular partial pressure of oxygen (P_iO_2) is regulated through hypoxia-inducible factor (HIF), a heterodimeric transcription factor composed of two subunits, HIF-1α and HIF-1β. Under normoxic conditions, hydroxylation of HIF-1α occurs by prolyl hydroxylase (PHD) enzymes which act as sensors of cellular oxygen tension. This triggers the binding of the E3 ubiquitin ligase von Hippel Lindau tumor-suppressor protein (pVHL) to HIF-1α and targets it for proteasomal degradation (Maxwell et al., 1999). During hypoxia or conditions of reduced P_iO_2, the hydroxylase activity of PHD enzymes is inhibited, allowing stabilization of HIF-1α, which translocates to the nucleus to form an active complex with HIF-1β. Activation of HIF-1 induces transcription of target genes involved in erythropoiesis, angiogenesis, glycolysis, and energy metabolism (Taylor, 2008) in a manner analogous to exercise (Mahoney et al., 2005; Schmutz et al., 2006). HIF-dependent transcriptional regulation augments survival during low O_2 tension either by increasing O_2 delivery and extraction or by enhancing the ability to obtain ATP from O_2-independent pathways. HIF-1 activates transcription by binding to hypoxia response elements within target genes and recruiting transacting coactivators such as p300 and CBP (CREB-binding protein) (Jiang et al., 1996).

Although the P_iO_2 in resting skeletal muscle is ~1/5th of the oxygen pressure of inhaled air, acute exercise reduces P_iO_2 in contracting muscle to ~1/40th of that of inhaled air (Richardson et al., 1995). Unsurprisingly, HIF-1α protein abundance is

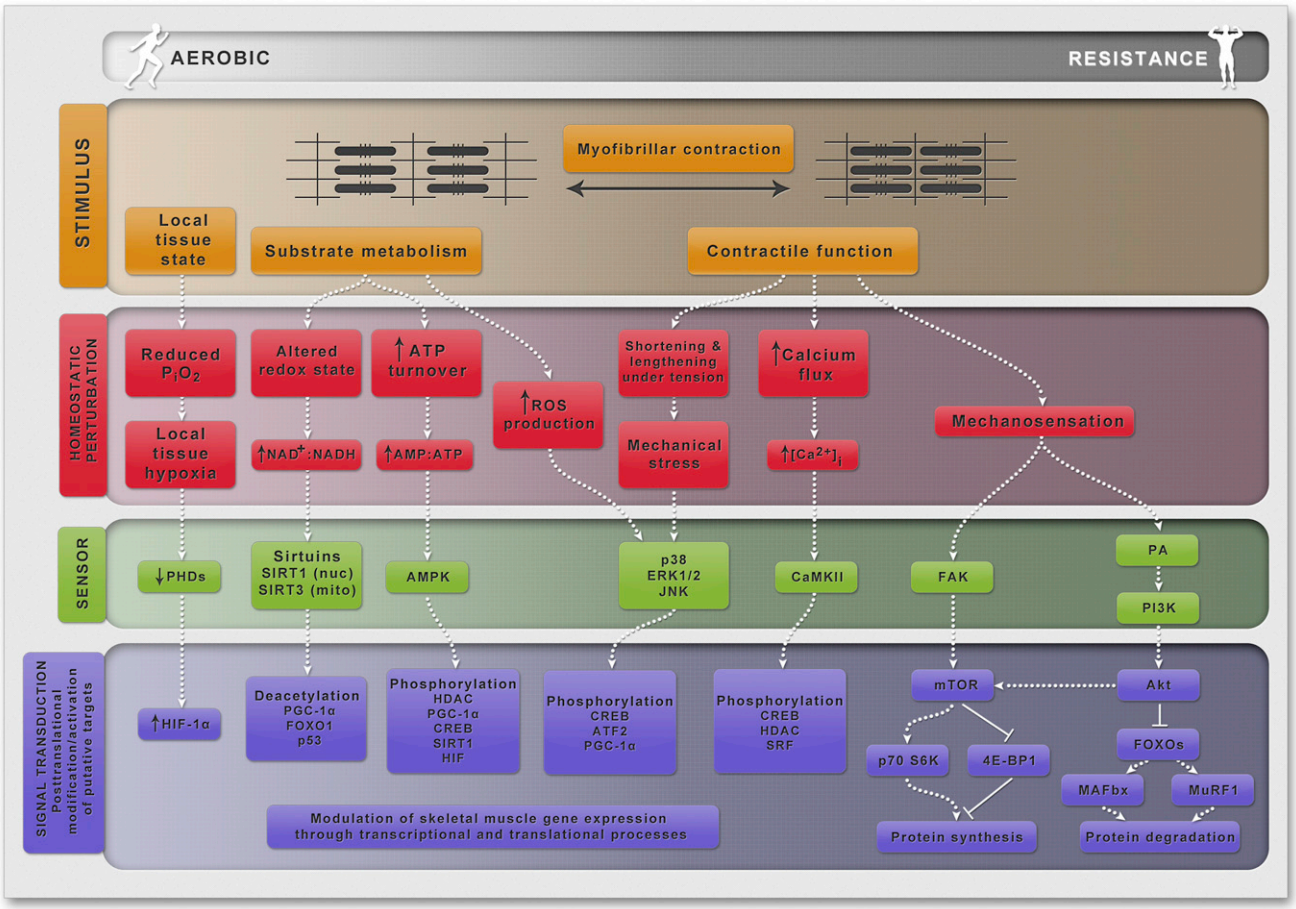

Figure 4. Schematic of Excitation-Transcription Coupling in Skeletal Muscle

The onset of myofibrillar activity via shortening (concentric) and lengthening (eccentric) contractions during exercise results in a milieu of biochemical and biophysical stimuli localized within the contracting muscle. These perturbations in skeletal muscle homeostasis lead the activation of networks of signaling molecules including protein kinases, phosphatases, and deacetylases, which are integrated into physiological processes by downstream targets, including transcription factors and transcriptional coregulators. These events occur in a temporal manner, such that kinase activation and pretranscriptional regulation occur rapidly during exercise and recovery, whereas transcript alterations are subsequently observed. The relative activation, contribution, and magnitude of the described pathways and downstream targets are dependent on the intensity, duration, and mode of the exercise stimulus, and on imposed environmental variables. Here, linear pathways are depicted, but in fact, these pathways demonstrate some degree of dependence, crosstalk, interference, and redundancy in their regulation, making the exact contribution of each signaling pathway to measured changes in gene expression difficult to isolate. A multiple signal transduction-to-transcription-coupled control system with inherent redundancy allows for fine-tuning of the adaptive responses to exercise training.

increased during acute exercise, accumulates in the nucleus, and shows enhanced DNA binding, coincident with a decrease in pVHL expression (Ameln et al., 2005). HIF-related processes are relevant to exercise-induced skeletal muscle metabolism and adaptation (Mason et al., 2004; Formenti et al., 2010) and likely regulate the beneficial effects of simulated altitude training practiced by athletes (Vogt et al., 2001).

Cellular Energy Status, ATP Turnover, and AMP-Activated Protein Kinase Signaling

AMP-activated protein kinase (AMPK) is a serine/threonine kinase that modulates cellular metabolism acutely through phosphorylation of metabolic enzymes (Carling and Hardie, 1989) and, over time, via transcriptional regulation (Bergeron et al., 2001; Jäger et al., 2007). AMPK activation is regulated allosterically by a cellular energy deficit, which is reflected by increases in the AMP/ATP and Cr/PCr ratios (Kahn et al., 2005). In addition to intense exercise (Green et al., 1992; Howlett et al., 1998), cellular stresses that deplete ATP (such as metabolic poisons) or increase the cellular AMP/ATP ratio (such as glucose deprivation or oxidative stress) also activate AMPK (Kahn et al., 2005). Given the rate of ATP turnover during muscle contraction, AMPK acts as a signal transducer for metabolic adaptations by responding to an altered cellular energy status. Acute exercise increases AMPK phosphorylation and enzymatic activity in an intensity-dependent manner (Wojtaszewski et al., 2000; Egan et al., 2010), reflecting intensity-dependent effects of exercise on ATP turnover and adenine nucleotide concentrations (Howlett et al., 1998).

Overall, AMPK activation acts to conserve ATP by inhibiting biosynthetic pathways and anabolic pathways, while simultaneously stimulating catabolic pathways to restore cellular energy stores (Kahn et al., 2005). In skeletal muscle, acute AMPK activation suppresses glycogen synthesis (Carling and Hardie, 1989) and protein synthesis (Bolster et al., 2002), but promotes

glucose transport (Merrill et al., 1997) and lipid metabolism (Winder and Hardie, 1996). Chronic AMPK activation alters metabolic gene expression and induces mitochondrial biogenesis (Bergeron et al., 2001), partly via AMPK-induced modulation of the DNA binding activity of transcription factors including NRF-1, MEF2, and HDACs (Bergeron et al., 2001; McGee et al., 2008).

Calcium Flux and Calcium/Calmodulin-Dependent Protein Kinase Signaling

Calcium is essential for facilitating the crossbridge interaction between myosin and actin during myofibrillar contraction. During contraction, calcium oscillations, whose amplitude and duration are a function of the level of force output by the muscle, are translated into discrete signals that modulate the kinase activity of calmodulin-dependent protein kinases (CaMKs), a class of multifunctional serine/threonine protein kinases implicated in muscle plasticity (Chin, 2010). CaMKII is the dominant isoform in human skeletal muscle (Rose et al., 2006). Exercise increases CaMKII phosphorylation in an intensity-dependent manner (Rose et al., 2006; Egan et al., 2010), possibly due to additional muscle fiber recruitment (Sale, 1987) or to higher calcium concentrations expected at greater force outputs (Howlett et al., 1998). Intensity-dependent CaMKII activation may function as a stimulation-frequency decoder (Chin, 2010). Thus, calcium signaling is sensitive to different types of contraction (i.e., aerobic versus resistance) and could, based on the relative amplitude and frequency of calcium transients depending on the contractile stimulus, thereby result in dramatically different signal transduction patterns (Dolmetsch et al., 1997).

CaMKs and calcium signaling influence glucose transport (Wright et al., 2004), lipid uptake and oxidation (Raney and Turcotte, 2008), and skeletal muscle plasticity (Wu et al., 2002). Transcription factors, such as CREB, MEF2, and HDACs, are CaMK targets implicated in the regulation of skeletal muscle gene expression. For instance, the activation of CaMKII leads to phosphorylation and nuclear exclusion of HDAC4, which relieves repression of MEF2 (Liu et al., 2005). This model couples contraction-induced calcium signaling to an increased rate of transcription of MEF2 target genes such as PGC-1α and GLUT4 (Chin, 2010).

Mechanical Stress and Mitogen-Activated Protein Kinase Signaling

Growth factors, cytokines, and cellular stress impact the activity of the mitogen-activated protein kinase (MAPK) family. Presumably because of the wide variety of biochemical and biophysical processes activated by muscle contraction, acute exercise activates three main MAPK subfamilies in human skeletal muscle: (1) the extracellular-regulated kinase (ERK1/2), (2) c-*jun* N-terminal kinase (JNK), and (3) p38 MAPK. The level of p38 MAPK activation is dependent on exercise status (Yu et al., 2003; Coffey et al., 2006b), while the predominance of eccentric or concentric contractions can influence other MAPK activation patterns (Wretman et al., 2001). MAPKs regulate transcriptional events by phosphorylation of diverse substrates localized in the cytoplasm or nucleus, including transcription factors and coactivators, and thereby regulate a variety of physiological processes such as differentiation, hypertrophy, inflammation, and gene expression (Long et al., 2004). For example, during contraction, p38 MAPK can stimulate upstream transcription factors of the PGC-1α gene, such as ATF2 and MEF2 (Table 3) (Akimoto et al., 2005), which coincides with an increase in PGC-1α expression (Akimoto et al., 2005; Wright et al., 2007; Egan et al., 2010). Constitutive activation of p38 MAPK increases markers of mitochondrial adaptation in skeletal muscle (Akimoto et al., 2005), whereas deletion of the p38γ isoform, but not p38α or p38β, prevents training-induced increases in mitochondrial biogenesis and angiogenesis (Pogozelski et al., 2009).

During contraction, skeletal muscle is a potent site of ROS production via generation of superoxides by electron transport chain complexes I and III, and the activity of NADPH oxidase and xanthine oxidase. ROS activate MAPK signaling and the transcription factor nuclear factor-κB, thereby linking signal transduction to transcriptional processes (Powers et al., 2010). Acute exercise activates JNK signaling in a ROS-dependent manner, as evidenced by attenuated JNK signaling during exercise with infusion of the antioxidant *N*-acetylcysteine (Petersen et al., 2012). Moreover, contraction-induced increases in interleukin-6 (IL-6) secretion, a exercise-associated cytokine with potent multiorgan metabolic effects (Pedersen and Febbraio, 2012), is JNK dependent (Whitham et al., 2012), which attests to the likely importance of JNK signaling in mediating metabolic adaptation to exercise.

Redox Balance, NAD^+:NADH, and Sirtuins

NAD^+ is an electron carrier that plays a critical role in fuel metabolism. NAD^+ couples ATP synthesis with the electron transport chain, through its reduction during glycolysis and reoxidation by lactate generation in the cytosol or mitochondrial shuttle activity, as well as reduction reactions of the TCA cycle. Of interest, the regulation of the sirtuin (SIRT) family of protein deacetylases is NAD^+ dependent (Schwer and Verdin, 2008). The deacetylase activity of SIRT1 (cytoplasmic, nuclear) and SIRT3 (mitochondrial) is sensitive to elevations in [NAD^+] and NAD^+/NADH ratio. The subsequent deacetylation of lysine residues on transcriptional regulators (Nemoto et al., 2005) and mitochondrial enzymes (Hirschey et al., 2010) allows the coupling of alterations in the cellular redox state to the adaptive changes in gene expression and cellular metabolism (Lagouge et al., 2006; Cantó et al., 2009). Enhanced SIRT activity is associated with favorable adaptations in skeletal muscle metabolism, including enhanced mitochondrial function, exercise performance, and protection against obesogenic feeding (Lagouge et al., 2006; Gerhart-Hines et al., 2007).

Dynamic fluctuations in the NAD^+/NADH ratio occur in response to stimuli such as acute exercise and fasting (Sahlin et al., 1987; Cantó et al., 2009). With increasing exercise intensity, the cytosolic NAD^+/NADH ratio declines as the lactate/pyruvate ratio increases (Sahlin et al., 1987; Green et al., 1992). In rodents, elevations in SIRT1 activity peak around 3 hr into recovery (Cantó et al., 2009), which coincides with a dramatic elevation in the NAD^+/NADH ratio, predominantly due to an increase in [NAD^+]. The aforementioned glucose sparing during postexercise recovery coincides with an increase in β-oxidation and reoxidation of NADH to NAD^+. SIRT activation is therefore in contrast to phosphorylation of various protein kinases that tend to be elevated immediately after exercise, and return rapidly to basal values. Conversely, short-term interval training increases SIRT1 expression in skeletal muscle (Little et al., 2010), while higher SIRT3 protein is reported in

Table 3. Evidence Base for Regulatory Roles of Signaling Molecules and Transcriptional Regulators in Skeletal Muscle Metabolic and Mitochondrial Adaptation to Exercise

Gene or Family	Function and Evidence for Regulation of Skeletal Muscle Phenotype[a]	Effect of Acute Exercise and/or Exercise Training on Regulation and Expression in Skeletal Muscle[b]
ATF2	● Activated at p-Thr$^{69/71}$ by p38 MAPK and interacts with CREs present in metabolic and mitochondrial genes	● AEX: ↑ p-ATF2 in humans and rodents (intensity dependent)
	● DN ATF2: ablates contraction-induced increase in PGC-1α gene transcription	
	● p38 MAPK effects on gene expression via p.a. or by c.a. of MKK3/6 are ATF2 dependent	
AMPK	● Chronic AMPK activation by AICAR or β-GPA feeding: ↑ metabolic gene expression and mtBIOG	● AEX: ↑ p-AMPK in humans and rodents (intensity dependent)
	● Effects abolished in AMPK α_2 KO or KD mice	● ↑ α_2 AMPK activity in most AEX models
	● c.a. AMPK (AMPKγ_1^{R70Q} and AMPKγ_3^{R225Q}): ↑ glycogen storage, mitochondrial gene expression, and EXC	● ↑ α_1 AMPK activity during high-intensity/sprint AEX
	● Similar phenotype in HSMCs with human mutation *PRKAG3*^{R225W}	● ↑ p-AMPK during AEX is blunted after EXT
	● LKB1 KO and AMPK α_2 KO: ↓ basal levels of mitochondrial genes	● AMPK α_2 and γ_3 KO: AEX-induced changes in gene expression attenuated, but adaptive response to EXT is similar to WT
CaMKs	● c.a. CaMKIV: ↑ mtBIOG, FAO/ETC gene expression, and fatigue resistance during contraction	● AEX: ↑ p-CaMKII in humans and rodents (intensity dependent)
	● CaMKII inhibition: attenuates gene expression induced by contraction or [Ca^{2+}]-releasing agents	● EXT: ↑ CaMKII expression and enzymatic activity, but ↑ p-CaMKII during AEX is similar
CREB	● Activated by p-Ser^{133} by PKA, CaMKs, and AMPK and regulates gene expression through CRE interaction	● AEX: biphasic response, ↓ p-CREB on exercise cessation, ↑ p-CREB during recovery (intensity dependent)
	● Critical to PKA-dependent regulation of myogenesis	
	● DN CREB: dystrophic phenotype, ↓ MEF2 activity	
ERRs	● ERRα KO: ↓ FAO gene expression; ablates ANG in response to 14 day VWR	● AEX: ↑ ERRα mRNA during recovery
	● ERRγ OE: more oxidative fibers, ↑ mitochondrial enzyme activity, ANG, and EXC	● EXT: ↑ ERRα protein
	● ERRγ$^{+/-}$: ↓ mitochondrial function, FAO gene expression, and EXC	● Data for ERRγ have not been reported
FOXOs	● FOXO1 KO: ↑ MyoD and percentage type II fibers, ↓ EXC	● AEX: ↑ FOXO1 and FOXO3 mRNA during recovery
	● FOXO1 OE: causes fiber atrophy, marked ↓ in muscle mass and locomotor activity	● Resistance EXT: ↑ p-FOXO3 and ↓ FOXO1 protein
	● c.a. FOXO3 drives atrophy through upregulation of the ubiquitin ligases atrogin-1/MAFbx and MuRF1	
HATs and HDACs	● Combinatorial KO of HDAC isoforms (4, 5, 9): ↑ percentage type I fibers and oxidative gene expression	● AEX: ↑ p-HDAC (class IIa) in humans (intensity dependent)
	● c.a. HDAC5: ablates increase in percentage type I and IIa fibers in response to 4 weeks VWR	● ↓ repressive activity of HDAC4 and 5 by p-induced nuclear exclusion
	● HDAC inhibition: variety of effects on myogenesis and mtBIOG	● Coincides with ↓ HDAC-association with MEF2, ↑ MEF2-PGC-1α association, and ↑ GLUT4
HIFs	● HIF-1α mKO: ↓ glycolytic flux, but ↑ oxidative enzyme activity, ANG, and EXC	● AEX: ↑ total and nuclear stabilization of HIF-1α, ↓ Pvhl, and ↑ HIF-1α DNA binding activity
	● HIF-1α OE: ↑ percentage type IIa fibers and fiber CSA and ↓ oxidative enzyme activity	● AEX: ↑ HIF-1α and HIF-2α mRNA during recovery
	● HIF-2α mKO: ↑ percentage type IIb fibers;↓ percentage type I fibers, ANG, and antioxidant gene expression	● EXT: ↓ HIF-1α and HIF-2α mRNA at rest
	● In CP patients (HIF degradation impaired): ↑ mRNA levels of PDK4, PFK, and PK; marked PCr depletion and acidosis during exercise and ↓ maximal exercise capacity	● HIF-1α mKO: adaptive response to EXT is similar to WT

(*Continued on next page*)

Table 3. *Continued*

Gene or Family	Function and Evidence for Regulation of Skeletal Muscle Phenotype[a]	Effect of Acute Exercise and/or Exercise Training on Regulation and Expression in Skeletal Muscle[b]
MEF2	● MEF2 mKO: ↓ oxidative enzyme activity and percentage type I fibers	● AEX: ↑ MEF2 nuclear abundance and DNA binding activity
	● c.a. MEF2: ↑ percentage type I fibers, markers of oxidative metabolism including myoglobin and PGC-1α and doubles EXC	● AEX: ↑ nuclear association of MEF2 with PGC-1α and p-p38 MAPK
NRFs	● NRF-1 mOE: ↑ GLUT4 and oxidative gene expression, but muscle respiratory capacity is unchanged	● AEX: ↑ NRF-1 and NRF-2 mRNA during recovery in rodents, but results are equivocal in humans
	● DN NRF-2: ↓ COX expression	● AEX: ↑ DNA binding activities of NRF-1 and NRF-2 (to cyt c and COXIV promoters, respectively)
	● NRF-2 shRNA: ↓ expression of all ten nucleus-encoded COX subunits	
p38 MAPK	● c.a. MKK3/6 upstream of p38 MAPK ↑ PGC-1α transcription; effect ablated by DN p38 MAPK or p38 inhibition	● AEX: ↑ p-p38 MAPK in response to cycle and running
	● c.a. MKK6: ↑ PGC-1α and COXIV in type II fibers	● Level of activation is dependent on training status
	● p38γ, but not p38α or p38β, mKO: attenuates ANG and ↑ mitochondrial gene expression after 4 weeks VWR	● EXT: ↑ p-p38 MAPK during unaccustomed exercise, i.e., aerobic-trained perform resistance, or resistance-trained perform aerobic
	● Alterations in fiber characteristics after 4 weeks VWR similar in all mKOs	
PPARs	● PPARδ agonists (4 week): ↑ FAO gene expression and oxidative profile of type II fibers	● AEX: ↑ PPARδ mRNA during recovery
	● PPARδ agonist combined with 4 weeks EXT: greater ↑ in oxidative gene expression and EXC compared to EXT alone	● EXT: ↑ PPARδ mRNA after 16 weeks of low-intensity EXT
	● c.a. PPARδ: ↑ percentage type I fibers, oxidative gene expression, mtBIOG, and EXC	
	● PPARδ mOE mice: ↑ state 3 respiration and performance during sprint-type exercise	
PGC Family	● PGC-1α OE in muscle cells: ↑ mtDNA copy number, mtBIOG, and respiratory capacity	● AEX: ↑ in PGC-1α mRNA during recovery (intensity dependent)
	● PGC-1β and PRC OE: similar effects; also important for antioxidant and anti-inflammatory processes, respectively	● AEX: stabilizes PGC-1α protein, ↑ PGC-1α activity (de-Ac), and subcellular localization to the nucleus and mitochondrion
	● PGC-1α mOE: ↑ mtBIOG, respiratory capacity, and antioxidant defense in type II fibers and ↑ EXC	● EXT: ↑ PGC-1α protein in health and disease
	● PGC-1α mKO: fibers with ↑ glycolytic phenotype, ↓ mitochondrial respiration, EXC and recovery from AEX	● PGC-1α mKO: adaptive response to EXT is similar to WT in most parameters except ANG, which is ablated
	● PGC-1α/β dKO: similar derangements, but in the absence of changes in fiber type proportions	
RIP140	● Transcriptional corepressor acting as scaffold protein recruiting chromatin-remodeling enzymes	● AEX: ↑ RIP140 mRNA during recovery
	● RIP140 KO: ↑ mitochondrial oxidative capacity, gene expression, and percentage type IIa/x fibers at expense of type IIb	● EXT: RIP140 protein or mRNA unchanged
	● RIP140 OE: ↓ SDH activity and myoglobin in type II fibers	● RIP140 OE: adaptive response to 6 weeks VWR is similar to WT
SIRTs	● SIRT1 activation with resveratrol: ↑ oxidative gene expression and capacity, mtBIOG, and EXC	● AEX: ↑ SIRT1 mRNA, protein, and enzymatic activity
	● SIRT1 mKO and SIRT3 mKO: no obvious muscle phenotype	● EXT: ↑ SIRT1 mRNA, protein, and enzymatic activity
	● SIRT1 mKO: PGC-1α de-Ac after AEX is similar to WT	● EXT: ↑ SIRT3 mRNA and protein
	● SIRT3 KO: ↓ mitochondrial capacity and ↑ oxidative stress	● SIRT1 mKO: adaptive response to 3 weeks VWR is similar to WT

(*Continued on next page*)

Table 3. *Continued*

Gene or Family	Function and Evidence for Regulation of Skeletal Muscle Phenotype[a]	Effect of Acute Exercise and/or Exercise Training on Regulation and Expression in Skeletal Muscle[b]
Tfam	● Tfam mKO: ↑ mitochondrial myopathy and ragged-red fibers	● AEX: ↑ Tfam mRNA during recovery
	● Compensatory ↑ in mitochondrial mass maintain normal rates of ATP generation	● AEX: ↑ mitochondrial PGC-1α-Tfam bound to mtDNA D loop
	● Rates of fatigue development similar to WT, but ↓ force-generating capacity	● EXT: ↑ Tfam mRNA and protein

Models included in the table are based on demonstration of phenotype related to skeletal muscle fiber characteristics, or the molecular response to exercise and/or training, when compared to noninduced or wild-type (WT) counterparts. ↑, increases; ↓, decreases; $^{+/-}$, heterozygous; Ac-, acetylation; AEX, acute exercise; ANG, angiogenesis; c.a., constitutive activation; CaM, calmodulin; CP, Chuvash polycythemia; DN, dominant-negative; ETC, electron transport chain; EXC, endurance exercise capacity; EXT, exercise training; FAO, fatty acid oxidation; HSMCs, human skeletal muscle cells; KD, kinase-dead; KO, knockout; OE, overexpression; MKK, MAPK kinase; mKO, skeletal muscle-specific KO; mOE, skeletal muscle-specific OE; p-, phosphorylation; VWR, voluntary wheel running.

[a]Evidence refers to transgenic mouse models in vivo, and/or in vitro manipulation in muscle cells, unless otherwise stated. In vivo and in vitro models of hypertrophic regulation are described elsewhere (Schiaffino and Reggiani, 2011).

[b]Aerobic exercise unless otherwise stated.

trained individuals versus sedentary counterparts (Lanza et al., 2008). Interestingly, a reduction in SIRT3 expression has been implicated in the development of skeletal muscle insulin resistance (Jing et al., 2011). This raises the possibility that exercise-induced increases in SIRT3 and associated effects on mitochondrial function may partially explain the therapeutic effects of exercise. Whether changes in SIRTs and NAD^+ metabolism are causative factors or occur in parallel with remodeling of skeletal muscle by exercise training remains to be clarified.

High-Force Stimuli and Mechanosensory Signal Transduction

All forms of muscular contraction result in the application of tension (force) through an active muscle. However, the adaptive muscle growth (hypertrophy) consequent to high mechanical loads present during resistance exercise is largely determined by the activation of skeletal muscle protein synthesis (MPS) consequent to the activation of mTOR, ribosomal protein S6K ($p70^{S6K}$), and downstream targets (Bodine et al., 2001). $p70^{S6K}$ is a key regulator of MPS through canonical pathways of protein translation and ribosome biogenesis involving eukaryotic translation initiation factor 4E (eIF4E) binding protein (4E-BP1) and elongation factor 2 (eEF2). Phosphorylation of 4E-BP1 by mTOR suppresses binding and inhibition of eIF4E by 4E-BP1. This derepression allows eIF4E to directly bind the 5′ end of mRNA to ultimately form an active eIF4F complex, a rate-limiting step in translation initiation. Phosphorylation of S6K leads to the phosphorylation of the 40S ribosomal protein S6 (rpS6) and eIF4B. Collectively these events lead to the formation of the translation initiation complex and activate protein synthesis for cellular hypertrophy (Sandri, 2008).

Mechanosensory regulation of MPS is determined by high-force contractions during resistance-type exercise (Philp et al., 2011). Such contractions transiently disrupt the sarcolemma (the lipid bilayer that surrounds a muscle cell), which increases the concentration of membrane phospholipid phosphatidic acid (PA) through activation of phospholipase D (PLD). PA activates mTOR through interaction with its FRB domain (Fang et al., 2001), resulting in the activation of mTOR and MPS (O'Neil et al., 2009). Conversely, a contraction-induced increase in PA and mTOR activation is attenuated in the presence of PLD inhibition (Hornberger et al., 2006; O'Neil et al., 2009). Mechanosensory regulation of MPS also involves focal adhesion kinase (FAK) proteins, a class of transmembrane receptors that act as protein tyrosine kinases. FAK proteins are key elements for the transmission of contractile force through the skeletal muscle architecture and a central component of integrin signaling. The expression and activity of FAK in skeletal muscle are related to the relative loading (Klossner et al., 2009; Durieux et al., 2009), and contraction results in conformational changes and activation of FAK phosphotransferase activity (Wilkinson et al., 2008; Klossner et al., 2009), which can activate MPS through mTOR-dependent and -independent mechanisms (Philp et al., 2011).

Molecular Regulation of the Endurance Phenotype

Aerobic Exercise—Metabolic and Mitochondrial Adaptations

Mitochondrial biogenesis is a well-established response to aerobic exercise training (Howald et al., 1985) and is defined by an increase in muscle mitochondrial number and volume, as well as concomitant changes in organelle composition. In response to increased contractile activity, half-lives of approximately 1 week are observed for mitochondrial proteins (Booth, 1977; Henriksson and Reitman, 1977). After 6 weeks of exercise training, muscle mitochondrial density increases ~50%–100% (Hood, 2001). Changes occur in all three fiber types, with the difference being somewhat greater in type IIa than in type I and type IIx fibers (Howald et al., 1985). Improvements in exercise performance during the same time frame outpace the relatively small (typically 5%–20%) increases in whole-body aerobic fitness measured by maximal oxygen uptake (VO_{2max}), and reflect enhancements in the intrinsic oxidative capacity of muscle, and the delivery and utilization of substrates in working muscle during subsequent exercise bouts (Phillips et al., 1996; Vollaard et al., 2009). Specifically, these metabolic adaptations reflect increased abundance of proteins involved in mitochondrial ATP production (Holloszy, 1967), the TCA cycle (Egan et al., 2011), mobilization, transport and oxidation of fatty acids (Talanian

et al., 2010), glycolytic metabolism (Tremblay et al., 1994), antioxidant capacity (Powers et al., 1994), glucose transport and glycogen synthesis (Perseghin et al., 1996), and oxygen delivery to and extraction from skeletal muscle (Gavin et al., 2007).

Training-induced increases in metabolic enzyme activities and mitochondrial density result in enhanced respiratory control sensitivity such that a lower [ADP] is required to achieve the same level of oxygen consumption per gram of muscle. Thus, the same cellular rate of oxidative metabolism is attained with less perturbation of adenine nucleotides and a lower rate of oxidative phosphorylation per mitochondrion (Holloszy and Coyle, 1984; Dudley et al., 1987). After training, smaller declines in [ATP] and [PCr], and smaller increases in free [ADP], are observed at the same absolute power output in muscle with increased mitochondrial density (Dudley et al., 1987; Phillips et al., 1996). This reduces the formation of AMP, IMP, P_i, and ammonia and thereby attenuates the allosteric regulation of the rates of glycogenolysis and glycolysis (and lactate production) after training, concomitant with an increase in the fraction of ATP provision from oxidative metabolism. Enhanced respiratory control sensitivity coupled to decreased flux through glycogen phosphorylase and attenuated exercise-induced activation of PDH (Leblanc et al., 2004) results in a reduction of CHO utilization after training, whereas the overall capacity for lipid oxidation is markedly increased (Talanian et al., 2010). Consequently, decreased CHO utilization during exercise in the trained state is compensated for by a proportional increase in lipid oxidation rates at the same absolute and relative intensity (Holloszy and Coyle, 1984). Thus, increased endurance performance observed after training is attributed to enhanced fatigue resistance by virtue of reduced muscle glycogen depletion, tighter coupling of ATP supply and demand, and, thereby, smaller disturbances to homeostasis combined with a consequent reduction in metabolic byproducts.

Regulation of Skeletal Muscle Gene Expression and Adaptation

An increasingly well-defined network of transcription factors and coregulator proteins has emerged that regulates the skeletal muscle phenotype by integrating signals from physiological stimuli and coordinating metabolic adaptation (Figure 5). This network exerts molecular control over contractile, metabolic, and mitochondrial adaptation, illustrated by an ability to alter the expression of key enzymes in CHO and lipid metabolism, and the coordination of myogenesis and mitochondrial biogenesis in response to exercise (Hood, 2001; Flück and Hoppeler, 2003; Coffey and Hawley, 2007). The process of mitochondrial biogenesis is complex and highly regulated, requiring the coordination and coexpression of both the nuclear and the mitochondrial genomes for the assembly and expansion of the reticulum, and the generation of a dynamic mitochondrial network. Appropriate synchronization includes the transcription of nuclear genes, translation of newly formed mRNAs and import of proteins into mitochondria, replication of mitochondrial DNA (mtDNA), transcription and translation of mitochondrial genes, biosynthesis of mitochondrial membrane phospholipids, and assembly of the enzyme complexes (Essig, 1996; Hood, 2001). For instance, nuclear-encoded mitochondrial proteins are chaperoned to the mitochondrion, imported into the different organelle compartments, and assembled with mtDNA-encoded proteins to form multisubunit enzyme complexes required for oxygen consumption and ATP synthesis.

Mechanistic studies using transgenic animals and pharmacological manipulation have explored the roles of key regulators of skeletal muscle phenotype (Table 3). Many regulators are sufficient to stimulate mitochondrial biogenesis, fiber-type transformation, and reprogramming of skeletal muscle metabolism, but many are not necessary for exercise-induced skeletal muscle adaptation. For example, PGC-1α acts as a transcriptional coactivator through recruitment and coregulation of multiple transcription factors that regulate skeletal muscle gene expression, including NRF-1, NRF-2, ERRα, and Tfam (Lin et al., 2005). PGC-1α activity is highly regulated by numerous posttranslational modifications including phosphorylation and deacetylation (Puigserver et al., 2001; Jäger et al., 2007; Cantó et al., 2009). Key upstream kinases and deacetylases regulating these modifications are activated by acute exercise (Wright et al., 2007; Cantó et al., 2009; Egan et al., 2010), coincident with alterations in protein stability, functional activity, and subcellular localization (Little et al., 2011; Safdar et al., 2011b). Ectopic expression of PGC-1α in muscle cells increases mtDNA expression and mitochondrial biogenesis (Wu et al., 1999), whereas altering the activity of PGC-1α induces molecular adaptations that equip the cell to meet the energy demands of a changing environment, including augmentation of cellular respiration rates and substrate utilization (Wu et al., 1999; Wende et al., 2007). Overexpression of PGC-1α in rodent skeletal muscle produces a phenotype remarkably similar to aerobically trained muscle, illustrated by increased mitochondrial density, respiratory capacity, ATP synthesis, antioxidant defense in type II muscle fibers, and improved exercise performance (Wende et al., 2007; Calvo et al., 2008). In muscle-specific PGC-1α KO mice, many of these adaptations are reversed, e.g., muscle fibers exhibit a more glycolytic phenotype, impaired mitochondrial respiratory function, reduced exercise capacity, and impaired recovery from exercise (Handschin et al., 2007; Wende et al., 2007). However, after exercise training, the adaptive increases in myoglobin, metabolic gene expression, and mitochondrial biogenesis are similar to those of wild-type animals (Leick et al., 2008; Geng et al., 2010), whereas training-induced changes in mitochondrial enzyme expression are only modestly reduced (Geng et al., 2010). Notably, exercise-induced angiogenesis is blunted in PGC-1α KO mice (Chinsomboon et al., 2009; Geng et al., 2010). Therefore, despite robust effects on skeletal muscle phenotype, PGC-1α is not *necessary* for the majority of adaptive responses to exercise training.

Several proteins have established roles in the regulation of mitochondrial biogenesis and metabolic gene expression in skeletal muscle (Table 3), but a paucity of information exists regarding the causal involvement of these molecules in exercising human skeletal muscle beyond transient, but robust, changes in expression after a single bout of exercise (Pilegaard et al., 2003; Cartoni et al., 2005) or exercise training (Perry et al., 2010). However, exercise-induced modulation of these pathways is still proposed to be critical to skeletal muscle adaptation and modulation of the mitochondrial phenotype (Hood, 2001; Flück and Hoppeler, 2003; Coffey and Hawley, 2007). Dysfunctional mitochondria have been implicated in sarcopenia (Bua et al., 2002) and insulin resistance (Lowell and Shulman, 2005),

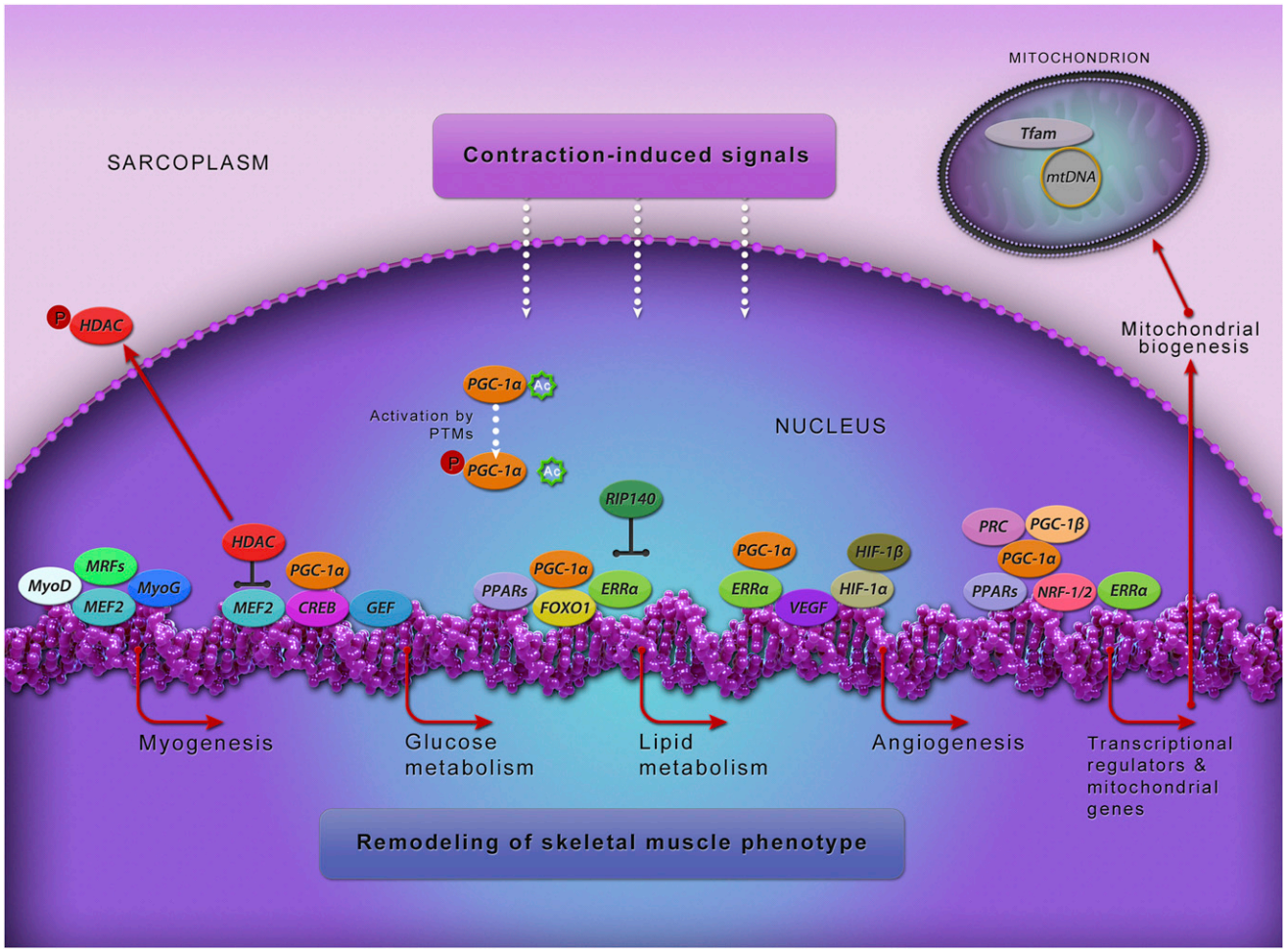

Figure 5. Transcriptional Regulators of Metabolism and Adaptation in Skeletal Muscle

Transcription factors and coregulator proteins can be activated or induced in response to specific cellular signals, cocomplex with a variety of other factors, and/or demonstrate selective activation of specific gene promoters containing binding sites for the given transcription factor. Apart from being crucial to the regulation of gene expression in response to cellular signals, coregulator proteins can be primary targets for contraction-induced signal transduction pathways (Figure 4). Regulation of this transcriptional activity occurs via change in the protein content, subcellular localization, or activity (e.g., posttranslational modifications) of transcriptional regulators. Transcription factors, nuclear receptors, and their transcriptional coregulators integrate contractile stimuli into molecular reprogramming. The interactions of transcriptional coregulators with their cognate transcription factor targets are shown linked to specific adaptive outcomes. These target interactions are not exclusive, and other factors are likely to contribute to a given adaptive program. CREB, cyclic AMP response element binding protein; ERR, estrogen-related receptor; FOXO1, forkhead transcription factor, O box subfamily; GEF, GLUT4 enhancer factor; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; MEF2, myocyte enhancer factor 2; MRFs, myogenic regulatory factors; mtDNA, mitochondrial DNA; MyoG, myogenin; NRF, nuclear respiratory factor; PGC-1, PPARγ coactivator 1; PPAR, peroxisome proliferator-activated receptor; PRC, PGC-1-related coactivator; RIP140, nuclear receptor interacting protein 1; Tfam, mitochondrial transcription factor A; VEGF, vascular endothelial growth factor. p, phosphorylation; Ac, acetylation.

but long-term aerobic exercise training may reverse the age-related declines in health that occur as a function of mtDNA mutations, as recently demonstrated in mtDNA mutator mice (Safdar et al., 2011a). Thus, mitochondrial biogenesis and adaptation with regular exercise are now recognized to have implications for a broader range of health issues, rather than only the enhancement of exercise performance.

Molecular Regulation of the Hypertrophy Phenotype

Resistance Exercise—Myofibrillar Adaptation and Adaptive Hypertrophy

Resistance exercise training elicits a range of morphological and neurological adaptations that contribute to changes in muscle function with respect to size, strength, and power (Booth and Thomason, 1991; Folland and Williams, 2007). Muscle hypertrophy refers to an increase in muscle size, whereas strength refers to the capacity to move an external load but is related to muscle size. These adaptations can support improvements in athletic performance but also improve health-related musculoskeletal function and offset loss of muscle and strength in pathological states (Macaluso and De Vito, 2004). The major morphological adaptations include (1) an increase in muscle crosssectional area (CSA), often preferentially occurring in type IIa fibers (Adams et al., 1993), (2) a change in the angle of pennation of individual muscle fibers, and (3) increases in the proportion of noncontractile tissue such as collagen (Folland

and Williams, 2007). Neurological adaptations favor increased muscle strength via improvements in motor unit activation, firing frequency, and synchrony of high-threshold motor units (Sale, 1988). Neural adaptations occur rapidly and tend to precede hypertrophic adaptations (Moritani and deVries, 1979), which occur at a slower rate since the rate of muscle protein synthesis must exceed degradation for an extended period of time before accretion of contractile protein occurs (Wong and Booth, 1990). An acute bout of resistance exercise results in an increased rate of mixed, mitochondrial, and myofibrillar protein synthesis during recovery (Biolo et al., 1995; Phillips et al., 1997; Wilkinson et al., 2008) and a proportionately smaller increase in the protein degradation rate (Biolo et al., 1995). The net protein synthetic response is critical to exercise-induced skeletal muscle adaptation and is the mechanistic basis for adaptive hypertrophy (Rennie et al., 2004).

Regulation of Skeletal Muscle Protein Synthesis by Contraction

During the exercise-induced adaptive hypertrophy response, the control of protein translation and synthesis drives protein accretion, while the activation and incorporation of satellite cells facilitate the addition of newly formed myofibrils to the contractile machinery. Due to the importance of protein synthesis exceeding breakdown over an extended period of time, the degree of muscle hypertrophy induced by resistance exercise is strongly associated with the degree of $p70^{S6K}$ phosphorylation (Baar and Esser, 1999; Terzis et al., 2008). Contraction-induced $p70^{S6K}$ activation is dependent on mTOR, which integrates nutrient and metabolic stimuli to regulate cell growth and proliferation. Activation of this pathway by contraction through the aforementioned mechanosensory pathway drives translational processes, increases the rate of MPS, and mediates muscle hypertrophy through protein accretion (Rennie et al., 2004). mTOR activation is critical to load-induced muscle growth, as demonstrated by the attenuation of hypertrophic responses and protein synthesis by the mTOR inhibitor, rapamycin (Bodine et al., 2001). The mTOR pathway controls mechanisms of protein synthesis at several levels (e.g., translation capacity, translation efficiency) through increases of translation of specific mRNAs, which culminate in skeletal muscle fiber enlargement. mTOR exists as part of two multiprotein complexes: mTORC1, which contains raptor and confers rapamycin sensitivity, is required for signaling to $p70^{S6K}$ and 4E-BP1, whereas mTORC2, which contains rictor and is rapamycin insensitive, is required for signaling to Akt-FOXO (Sandri, 2008). The effect of mTOR activity on downstream regulators of protein synthesis is principally achieved through contraction-induced regulation of mTORC1 (Philp et al., 2011). Early work on adaptive hypertrophy focused on the (transient) postexercise rise in blood-borne anabolic hormones such as growth hormone and insulin-like growth factor (IGF)-I, and consequent activation of a signaling cascade through phosphatidylinositol 3-kinases (PI3K)-Akt-mTOR by IGF-I interaction with insulin and IGF receptors (Adams and McCue, 1998). Recently, the muscle growth paradigm has shifted focus to IGF-I-independent mechanisms of mTOR activation and adaptive hypertrophy through mechanosensory regulation (Philp et al., 2011). Nutrient-dependent regulation of muscle growth is achieved through insulin- and Akt-dependent activation of the mTOR pathway. These pathways exhibit synergy to promote muscle growth in athletes and disease states and can be augmented by appropriate nutritional intake such as postexercise CHO and amino acid ingestion or increased dietary protein (Rennie et al., 2004).

Regulation of Skeletal Muscle Protein Degradation

The regulation of skeletal muscle protein degradation is primarily dependent on the activity of the ubiquitin-proteasome pathway. This occurs via two muscle-specific E3 ubiquitin ligases, muscle atrophy F box (atrogin-1/MAFbx) and muscle RING finger 1 (MuRF1), which are key regulators of skeletal muscle proteolysis under catabolic conditions (Sandri, 2008). For instance, MHC degradation is regulated by MuRF1-dependent ubiquitination (Clarke et al., 2007). In this model, activation (dephosphorylation) of FOXO transcription factors leads to the transcriptional upregulation of MAFbx/atrogin-1 and MuRF1 (Sandri et al., 2004). The translocation and activation of FOXO members are necessary for the upregulation of atrogin-1/MAFbx and MuRF1, whereas FOXO3 is sufficient to promote atrogin-1/MAFbx expression and muscle atrophy in vivo (Sandri et al., 2004). FOXO activity is primarily regulated by posttranslational modifications that determine its subcellular localization, i.e., phosphorylation by Akt promotes nuclear export of FOXOs to the cytoplasm. Therefore, Akt acts as a critical node at the balance of muscle protein synthesis and degradation. The role of this pathway is firmly established in muscle atrophy but less well established with respect to protein breakdown during adaptive hypertrophy, or to transient changes in protein turnover during and after a single bout of exercise. Acute exercise studies that examine proteolytic gene expression in response to either aerobic or resistance exercise show MuRF1 mRNA expression to be elevated 2–4 hr into recovery, whereas atrogin-1/MAFbx mRNA tends to be elevated early in recovery and decreased later (>12 hr) into recovery (Coffey et al., 2006a; Louis et al., 2007). The induction pattern of these proteolytic genes corroborates well with the biphasic response of muscle protein degradation following resistance exercise (Phillips et al., 1997), although the direct link between these phenomena has not been established in vivo.

Role of Skeletal Muscle Satellite Cells in Adaptive Hypertrophy

While the role of satellite cells in muscle regeneration is well established, the role of satellite cells in hypertrophy of adult skeletal muscle is debated (O'Connor et al., 2007). Skeletal muscle satellite cells are quiescent cells located adjacent to muscle fibers and beneath the fiber basal lamina, which can be induced to divide during conditions of muscle damage or increased activation. Subsequent fusion with an existing myofiber results in the addition of a myonucleus to the fiber syncytium. The proposed role of the satellite cells in muscle hypertrophy revolves around the concept of a myonuclear domain—a theoretical volume of cytoplasm associated with a single myonucleus—and each myofiber being composed of many myonuclear domains (Allen et al., 1999). Satellite cells provide a source for new myonuclei at a rate sufficient to maintain a constant myonuclear domain size during normal skeletal muscle growth, thereby increasing the total number of myonuclei, and thus the total amount of genetic machinery available for protein production with little alteration in the kinetics of

protein synthesis for each nucleus. Nevertheless, in various experimental models including satellite cell depletion (McCarthy et al., 2011) and myostatin inhibition (Wang and McPherron, 2012), skeletal muscle fiber hypertrophy is observed without obligatory satellite cell incorporation. For instance, in skeletal muscle with 90% of the satellite cell population depleted, overload-induced muscle hypertrophy is normal, whereas regeneration from acute muscle injury is impaired, suggesting that the role of satellite cells is markedly different between the two muscle growth paradigms (McCarthy et al., 2011). However, rodent models of adaptive hypertrophy produce supraphysiological gains in muscle size in a short time frame, e.g., functional overload induced by synergist ablation, and may not adequately represent human adaptation (Booth and Thomason, 1991). In human skeletal muscle, large ranges of interindividual variability in the magnitude of hypertrophic response to resistance exercise training are explained by the relative ability to mobilize satellite cells and add myonuclei to existing muscle fibers (Petrella et al., 2006; Petrella et al., 2008).

New Vistas in Molecular Exercise Physiology

Skeletal Muscle as a Secretory Organ

Over half a century ago, a humoral factor associated with exercise but whose source was unknown was speculated to act in an endocrine manner to regulate glycemia independent of insulin (Goldstein, 1961). Although it is unlikely that only a single factor regulated this effect, accumulating evidence today suggests that skeletal muscle itself acts as a secretory organ during exercise, such that cytokines and other metabolically active peptides are produced and released into circulation (collectively known as "myokines"). In turn, these proteins exert wider metabolic effects on organs including fat, liver, gut, and pancreas and act locally on muscle in an autocrine/paracrine manner (Pedersen and Febbraio, 2012). For instance, IL-6 is a cytokine that can regulate glycemia directly by stimulating glucose uptake in skeletal muscle (Glund et al., 2007), and indirectly by acting on L cells in the intestine and α cells in the pancreas to improve β cell function and insulin secretion (Ellingsgaard et al., 2011). Additionally, the exercise-induced effect on postexercise insulin sensitivity is ablated in IL-6-deficient mice (Ellingsgaard et al., 2011). IL-6 is one of many muscle-associated cytokines that elicit a variety of effects potentially involved in exercise adaptation, including hypertrophy and angiogenesis (Pedersen and Febbraio, 2012). However, even at rest, the metabolic status of skeletal muscle impacts whole-body metabolic homeostasis. In vitro studies reveal that glucose-stimulated insulin release from β cells is impaired when exposed to secretions from insulin-resistant muscle cells, but not by secretions from insulin-sensitive cells (Bouzakri et al., 2011). Recently, a novel myokine irisin was discovered to activate the "browning" of white fat, increase energy expenditure, and attenuate diet-induced insulin resistance (Boström et al., 2012). While the initial discovery was in response to supraphysiological PGC-1α expression in skeletal muscle rather than contraction per se, subsequent experiments demonstrated that circulating irisin is modestly elevated in human and rodent training studies, whereas blocking irisin action impairs the adaptive effects of exercise on white adipose tissue remodeling (Boström et al., 2012). Clearly, skeletal muscle as a secretory organ represents a fertile avenue for future research in translational medicine and exploration of interorgan crosstalk in response to exercise, but the extent of this regulation is unknown at present. Using a computational approach to examine all genes expressed in human skeletal muscle, >300 putative secretory proteins have been detected based on the presence of signal peptides for endoplasmic reticulum targeting and transmembrane segments in protein sequences (Bortoluzzi et al., 2006). Almost one-quarter of these proteins remain uncharacterized. Moreover, since transcripts from resting muscle were used to generate these cDNA libraries, other lowly expressed but exercise-responsive transcripts (e.g., IL-6) may have been missed as false negatives. Thus, given the abundance of potential secretory proteins, new targets are likely on the horizon.

Posttranscriptional Regulation of Skeletal Muscle Gene Expression

An emerging paradigm of molecular regulation involves the action of microRNAs (miRNA). This class of short (~18–24 nt), noncoding RNA sequences regulate gene expression posttranscriptionally by inhibiting protein translation or augmenting mRNA degradation through the canonical RNA interference pathway (Ambros, 2004). miRNAs typically bind to complimentary sequences within the 3′UTR of a target gene to initiate this process, but individual miRNAs have multiple gene targets, and each gene target may be regulated by multiple miRNAs, thereby intensifying the complexity of regulation. miRNAs have been implicated in a range of metabolic processes and development. For instance, miR-499, a muscle-enriched miRNA encoded within an intron of the MHC-I gene (*Myh7b*), is part of a miRNA network proposed to regulate muscle fiber type via downregulation of Sox6, Purβ, and Sp3, repressors of MHC-I expression (van Rooij et al., 2009). In mice overexpressing miR-499, a conversion of type II fibers to predominantly type I fibers is observed, which coincides with enhanced oxidative metabolism and improved treadmill running capacity (van Rooij et al., 2009). Furthermore, miRNA expression in skeletal muscle is altered in response to atrophy (McCarthy et al., 2009), overload-induced hypertrophy (McCarthy and Esser, 2007), a single bout of exercise (Nielsen et al., 2010), and exercise training (Davidsen et al., 2011; Keller et al., 2011). The implications for regulation of adaptive changes in skeletal muscle gene expression and function are unclear and require additional mechanistic studies. Large-scale bioinformatics, based on prediction algorithms and reciprocal relationships between miRNAs and their target mRNAs, may prove fruitful for deriving nonobvious hypotheses to investigate the molecular regulation of skeletal muscle adaptation (Davidsen et al., 2011; Keller et al., 2011).

Heterogeneity in the Training Response: Personalized Exercise Medicine

Even when participants engage in carefully controlled exercise training regimens, the nature of the training response is remarkably heterogeneous, allowing the classification of non-, low, and high responders (Bouchard et al., 1999; Hubal et al., 2005), and even adverse responders (Bouchard et al., 2012). This interindividual variability includes a strong genetic component with, for instance, a maximal heritability estimate of ~50% for the response of VO_{2max} when adjusted for age, sex, baseline VO_{2max}, and body composition (Bouchard et al., 1999). Candidate gene studies have demonstrated only modest predictive

value (reviewed in Bouchard, 2012), but recent work using unbiased, combined transcriptomic and genomic approaches to examine the relationship between molecular responses and physiological outcomes in response to exercise training have yielded promising results for both aerobic (Timmons et al., 2010) and resistance (Raue et al., 2012) training interventions. For example, using this approach, a "predictor" gene set of 29 transcripts and 11 single nucleotide polymorphisms (SNPs) explained ~50% of the aforementioned genetic contribution to the gain in VO_{2max} in response to training (Timmons et al., 2010). The key point is that these transcripts were not responsive to training, but rather higher basal expression levels were predictive of greater gains in VO_{2max}. Therefore, an attractive hypothesis is that the exercise response (e.g., aerobic fitness, strength, insulin sensitivity) can be predicted and understood through combined molecular and physiological classifications as a function of the individual and the exercise model (Timmons et al., 2010; Raue et al., 2012). In essence, this would represent the advent of personalized exercise medicine in which the exercise prescription is matched to the individual and the condition or desired outcome, as opposed to the currently broad public health guidelines.

Similarly, a personalized exercise prescription could be used to address factors such as a lack of time and lack of motivation, which are among the most frequently cited barriers to exercise participation (Booth et al., 1997). A lack of time may be addressed by prescribing low-volume, short-duration, high-intensity interval training. Even when total training time and energy expenditure have been reduced by ~80% and ~90%, respectively, improvements of VO_{2max}, muscle oxidative capacity, and insulin sensitivity are comparable to traditional aerobic training (Burgomaster et al., 2008; Babraj et al., 2009). A lack of motivation to exercise represents a more complex phenomenon. Emerging evidence from mice selectively bred for low versus high *voluntary* physical activity shows that peripheral differences in metabolism and physiological function are minimal between groups, and the majority of this biological variation is explained by central factors, most likely at the level of the dopaminergic system (reviewed in Knab and Lightfoot, 2010; Garland et al., 2011). Dissecting the molecular pathways that regulate the motivation and perceived reward from exercise may present a major avenue of future research, which may in turn present new therapeutic targets to enhance exercise participation.

Exercise Mimetics: Fact or Fallacy?

The observation of aerobic training-like phenotypes in transgenic mice (Wang et al., 2004; Calvo et al., 2008; Garcia-Roves et al., 2008), or similar effects produced pharmacologically (Lagouge et al., 2006; Narkar et al., 2008), has ignited interest in developing so-called exercise "mimetics," i.e., pharmacotherapy to replicate the metabolic effects of exercise. The "exercise in a pill" approach has been evaluated in detail elsewhere (Booth and Laye, 2009; Carey and Kingwell, 2009) and highlights that the complexities of the molecular response and systemic multiorgan effects of exercise are beyond the faculty of currently available monotherapeutic approaches. With regard to "mimicking" exercise, a single pill is unlikely to produce the myriad of acute physiological and metabolic responses and consequent benefits. Thus, the term exercise mimetic is a misnomer (Booth and Laye, 2009). Muscle contraction per se, an elevation in energy expenditure, and the turnover of substrates are key features of exercise-mediated effects on metabolic health and the initiation of signal transduction cascades regulating adaptation. A true exercise mimetic would therefore be akin to neuromuscular electrical stimulation, which can bring about adaptive changes through involuntary exercise (Banerjee et al., 2005). Due to the episodic nature of exercise, metabolic homeostasis is maintained through cycling of metabolic proteins in response to this intermittent stimulus. Moreover, transgenic models with supraphysiological expression levels of single proteins, e.g., PGC-1α, may well demonstrate an endurance-like phenotype in skeletal muscle (Calvo et al., 2008) but conversely exhibit insulin resistance and impaired glucose tolerance on a whole-body level (Choi et al., 2008). Nevertheless, the value of pharmacotherapy in exercise-related interventions should not be fully discounted. Pharmacological compounds could serve as adjunct treatment to exercise to potentiate or augment the adaptive response in exercisers. For instance, pharmacotherapy could help overcome adaptive limitations in insulin-resistant individuals with "exercise-resistant" skeletal muscle (De Filippis et al., 2008), or in elderly individuals reported to demonstrate "anabolic resistance" with respect to exercise-induced MPS (Kumar et al., 2009).

Concluding Remarks

The metabolic and therapeutic effects of regular exercise on lifestyle-related chronic disease are long established, but the molecular bases for adaptive changes in skeletal muscle mass and metabolic function remain an area of intense research. The pleiotropic effects of exercise and the complexity of responses at both a metabolic and a molecular level suggest that there is no singular pathway mediating exercise training adaptation. Mechanistic investigations have established many key players in regulation of a healthy skeletal muscle phenotype, but the viablility of these pathways as pharmaceutical entry points remains to be determined. Alternatively, future therapeutic potential may exist in optimizing targeted exercise interventions and training prescription. From a translational perspective, this would mean establishing the molecular signatures of targeted exercise interventions based on factors such as mode, intensity, or duration to optimize aerobic or strength adaptations, despite presence of specific metabolic or muscular dysfunction. In this sense, personalized, targeted exercise interventions may one day complement the existing broad recommendations for exercise in public health policy to address molecular defects present in lifestyle-related chronic disease. This marriage between complementary fields of research represents a new vista in exercise science and illustrates the translational merit in utilizing molecular approaches to explore the mechanistic bases of training adaptation so as to inform exercise prescription.

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