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MINI-REVIEW

Regulatory networks coordinating mitochondrial quality control in skeletal muscle

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Abstract

The adaptive plasticity of mitochondria within a skeletal muscle is regulated by signals converging on a myriad of regulatory networks that operate during conditions of increased (i.e., exercise) and decreased (inactivity, disuse) energy requirements. Notably, some of the initial signals that induce adaptive responses are common to both conditions, differing in their magnitude and temporal pattern, to produce vastly opposing mitochondrial phenotypes. In response to exercise, signaling to peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) and other regulators ultimately produces an abundance of high-quality mitochondria, leading to reduced mitophagy and a higher mitochondrial content. This is accompanied by the presence of an enhanced protein quality control system that consists of the protein import machinery as well chaperones and proteases termed the mitochondrial unfolded protein response (UPR^{mt}). The UPR^{mt} monitors intraorganelle proteostasis, and strives to maintain a mito-nuclear balance between nuclear- and mtDNA-derived gene products via retrograde signaling from the organelle to the nucleus. In addition, antioxidant capacity is improved, affording greater protection against oxidative stress. In contrast, chronic disuse conditions produce similar signaling but result in decrements in mitochondrial quality and content. Thus, the interactive cross talk of the regulatory networks that control organelle turnover during wide variations in muscle use and disuse remain incompletely understood, despite our improving knowledge of the traditional regulators of organelle content and function. This brief review acknowledges existing regulatory networks and summarizes recent discoveries of novel biological pathways involved in determining organelle biogenesis, dynamics, mitophagy, protein quality control, and antioxidant capacity, identifying ample protein targets for therapeutic intervention that determine muscle and mitochondrial health.

exercise; mitochondrial biogenesis; mitochondrial unfolded protein response; mitophagy; muscle disuse

INTRODUCTION

The adaptive plasticity of skeletal muscle mitochondria in response to alterations in energy demand is firmly established. Mitochondrial content increases in response to exercise and diminishes following periods of disuse. These dramatic changes have an impact on the efficiency of metabolism, substrate utilization, fatigue processes, as well as muscle phenotype and performance. However, the regulatory processes that control mitochondria in muscle are incompletely understood. Novel pathways continue to be discovered that add additional layers of complexity to already redundant systems that are in place to mediate changes in mitochondrial synthesis (i.e., biogenesis) and degradation (i.e., mitophagy). Regulation of these two arms of the organelle "turnover" pathway must be finely tuned to refresh and maintain a high-quality organelle pool over time. In addition, knowledge of these pathways continues to be important for the identification of molecular targets that, if amplified, can have therapeutic benefits for muscle health.

REMODELING OF THE MITOCHONDRIAL RETICULUM

Characteristics of the Mitochondrial Network

Skeletal muscle mitochondria exist in a dynamic network, or reticulum, that is extensively distributed throughout the cell (1), in a cell type and metabolic state-dependent manner. For example, in contrast to muscle, such as in the liver and kidney, mitochondria can resemble the classic, textbook depictions as singular, oval-shaped structures (2). This difference between cell types may be a result of the unique topology of energy utilization within elongated muscle cells, with a dispersion of ATPases within myofibrils that span the entire length of the cell. The energy requirements of muscle contraction require a unique mitochondrial phenotype that facilitates the rapid, large-scale diffusion of adenosine triphosphate (ATP), along with the propagation of the membrane potential, which serves as the driving force for ATP synthesis (3).

The mitochondrial reticulum in muscle is capable of expansion or fragmentation. This morphological plasticity

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is made possible by changes in the balance of organelle fission and fusion processes, resulting in the remodeling of the organellar network in response to altered physiological demands. Localized mitochondrial dysfunction stimulates fission, whereby a portion of the defective organelle is retracted from the network and ultimately degraded within the lysosome via mitophagy. Fission is regulated by the cytosolic GTPase dynamin-related protein 1 (Drp1), mitochondrial-localized fission 1 protein (Fis1), and anchored receptors mitochondrial fission factor (MFF), MiD49 and MiD51. Fis1 performs outer mitochondrial membrane (OMM) fission and recruits Drp1 where it can bind to Fis1 and the other receptors. Drp1 subsequently oligomerizes and arranges in a ring-like structure to break off mitochondrial fragments in a GTP-dependent manner. The deletion of Drp1 causes an accumulation of dysfunctional organelles with impaired respiration, likely a result of impaired mitophagy, and yields a severe myopathic phenotype characterized by muscle weakness and atrophy (4, 121). The overexpression of Drp1 also leads to these detrimental muscular outcomes, possibly due to the altered localization of mitochondria (5, 6).

Conversely, mitochondrial membrane fusion occurs through extension of the preexisting network. Fusion of the OMM is orchestrated by mitofusins, mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2), whereas optic atrophy 1 (OPA1) permits the fusion of the inner mitochondrial membrane I (IMM), having a significant impact on cristae organization. Mfn2 ablation in skeletal muscle generates reductions in mitochondrial respiration, observed concomitantly with increases in reactive oxygen species (ROS) emission and muscle atrophy (7), whereas the deletion of OPA1 is embryonic lethal. Interestingly, balancing fission and fusion through the knockdown of Drp1 in OPA1 knockout (KO) animals improves oxidative stress and the muscle phenotype (8), indicating that a balance between fission and fusion regulatory proteins is critical for the maintenance of the organelle network.

Mitochondrial Dynamics in Exercise and Disuse

Regularly performed exercise alters the balance of regulatory protein expression in muscle, favoring fusion and organelle network formation, evident in both animals and humans (9, 10). There are physiological advantages to this network configuration, with improved mitochondrial respiration, shorter diffusion distances for substrates and O_2, a better platform for lipid diffusion and subsequent oxidation, with the potential of reducing lipotoxicity and insulin resistance (11, 12). Indeed, exercise can also serve to correct the deficits in mitochondrial dynamics and morphology evident in cancer cachexia (13) and during chronic muscle disuse (14). Mfn-1 and -2 appear to be critical for this adaptation, since the absence of these isoforms in combination results in impaired oxidative phosphorylation, poor endurance performance, and cannot be rescued by a period of exercise training (15). Taken together, these data indicate that physiologically meaningful improvements in mitochondrial morphology occur following chronic contractile activity and a period of exercise training, yielding a more reticular morphology and enhanced organelle quality.

Conversely, more fragmented and "simple" muscle mitochondria are observed in conditions of disuse-induced atrophy, aging, metabolic diseases, and mitochondrial myopathies, and contribute to decrements in organelle quality and function (17, 18). Denervation and hindlimb unloading, two models of muscle disuse, produce a cellular environment that favors mitochondrial fission. Reductions in the protein expression of fusion machinery are observed, concomitant with the activating phosphorylation of Drp1 in the early stages of unloading (10, 14, 19). A prolonged period of disuse achieved with 7 days of denervation yields in a reduced fusion:fission regulatory protein balance (10; Table 1). The effects of muscle disuse might be preventable via muscle preconditioning by performing an exercise training protocol before unloading. This could attenuate the detrimental alterations in mitochondrial dynamics and rescue reductions in mitochondrial content and respiration brought on by disuse (14). Collectively, these findings illustrate the importance of consistent network remodeling and the optimal regulation of mitochondrial distribution as a necessary facet of mitochondrial quality control in skeletal muscle.

MITOCHONDRIAL BIOGENESIS

Regulation of Mitochondrial Biogenesis

Changes in mitochondrial volume in muscle are mediated by transcriptional regulators that induce a host of nuclear- and mitochondrially encoded genes. The synthesis of mitochondria requires ~1,200 protein gene products, with the vast majority originating from the nucleus, and an additional 13 protein gene products transcribed from mtDNA (52). Thus, changes in functional mitochondrial content necessitate the coordinated expression of both nuclear- and mitochondrially derived genes. Here, we briefly highlight the important roles of traditional and newly uncovered regulators of mitochondrial biogenesis under conditions of exercise and disuse.

PGC-1α.

The transcriptional coactivator peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) has long been heralded as the master regulator of mitochondrial biogenesis (53). PGC-1α drives the expression of genes transcribing respiratory complex subunits, protein import machinery (PIM), and antioxidants via its interaction with various transcription factors, such as PPARα/δ, transcription factor (TF)β1, estrogen-related receptors (ERRs) and perhaps most notably, nuclear respiratory factors-1 and -2 (NRF-1 and -2), which regulate the expression of the transcriptional regulator mitochondrial transcription factor A (TFAM; 120, 122). Overexpression of PGC-1α augments mitochondrial content and the proportion of type I fibers, culminating in enhanced endurance capacity and fatigue resistance (54). Conversely, studies using PGC-1α KO animals, or using in vitro PGC-1α silencing, reveal reductions in mitochondrial content and quality (55), and a muscle-specific shift in fiber type composition toward a more glycolytic phenotype (56). An isoform of PGC-1, PGC-1β, is also capable of regulating the expression of nuclear-encoded mitochondrial genes, although PGC-1β KO studies indicate that PGC-1α may be the predominant regulator of mitochondrial biogenesis (57). In addition, PGC-1α splice variants also add complexity to the molecular adaptations of muscle to exercise. Transcription of the alternative promoter of PGC-1α and subsequent splicing yields PGC-1α4, responsible for inducing IGF-1 expression, in contrast to the classic oxidative phosphorylation (OXPHOS)

Table 1. *Summary of signaling and changes in mRNA and protein expression leading to mitochondrial adaptations in response to short-term and long-term exercise training or disuse in skeletal muscle*

	Exercise Training			Disuse		
	Early	Late	References	Early	Late	References
Signaling						
Cytosolic Ca^{2+}	↑	↔	(20)	↑	↑	(21)
ROS emission	↑	↓	(22, 23, 24)	↑	↑↑	(25, 26, 27)
AMPK activation	↑↑	↑	(22, 28, 29)	↑	↑	(14, 30, 31)
mRNA						
PGC-1α	↑	↔	(24, 28)	↓	↓	(14, 30)
p53	↓	↓	(24, 32)	↑	↑	(30)
TFAM	↑	↔	(24, 32)	↓	↑	(30, 33)
Nrf2	↑	↑	(34, 35)	↑	↑	(26, 30, 36)
UPR^{mt}	↑	↑	(37, 38)	?	↓	(39)
Proteins						
PGC-1α	↑	↑↑	(24, 40)	↓	↓↓	(14, 26, 27)
p53	↑	↓	(24, 41)	↑	↑	(30)
TFAM	↑	↔	(24, 28)	↓	↓↓	(27)
Nrf2	↑	?	(42, 43, 44)	↑	↓	(45, 46)
UPR^{mt}	?	↑	(37, 38)	↓	↑	(39, 47)
Processes						
Fusion:fission ratio	↑	↑	(9, 10)	↓	↓	(10, 14, 48)
Mitophagy	↑	↓	(22, 23, 49)	↑	↓	(25)
Cellular outcomes						
Mitochondrial content	↑	↑↑	(23, 37, 40)	↓	↓↓	(33, 47)
Mitochondrial respiration	↑	↑↑	(23, 50)	↓	↓↓	(25)
Mitochondrial network expansion	↑	↑↑	(1, 51)	↓	↓	(10, 48)
Mitochondrial network fragmentation	?	↓	(1, 51)	↑	↑	(10, 48)

AMPK, AMP-activated protein kinase; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor gamma co-activator-1 alpha; ROS, reactive oxygen species; TFAM, mitochondrial transcription factor A; UPR^{mt}, mitochondrial unfolded protein response. ↑, increase; ↑↑, further increase; ↓, decrease; ↓↓, further decrease; ↔, no change; ?, still in question.

targets of PGC-1α, thereby promoting hypertrophy in response to resistance exercise (58). In addition, endurance exercise stimulates the transcription of the PGC-1α-b and PGC-1α-c variants originating from the alternative promoter, which may account for the majority of the total increase of PGC-1α mRNA with acute exercise (59). However, although PGC-1α protein expression is sufficient to drive changes in mitochondrial content and function, its presence is not necessary for mitochondrial biogenesis in muscles subjected to exercise (60).

TFAM.

The regulation of TFAM by PGC-1α provides a mechanism in which mtDNA gene expression can parallel the transcription process occurring at the nucleus. TFAM facilitates the transcription of mitochondrially encoded genes by unwinding the mtDNA promotor region for the binding of transcriptional regulators within the D-loop region (61). In addition, TFAM mediates mtDNA replication and packaging (62), promoting enhanced mtDNA copy number and stability to match the increasing mitochondrial volume during biogenesis. The absence of TFAM results in embryonic lethality in knockout mice (63), and even partial knockdown of TFAM results in decreases in mtDNA copy number and mitochondrial respiration, resulting in negative consequences for muscle force production (63, 64). However, overexpression of TFAM is also deleterious, perhaps as a result of excessive DNA compaction resulting in suppression of DNA transcription. This suggests the importance of maintaining TFAM at optimal levels within the organelle.

p53.

Widely regarded as a potent tumor suppressor protein implicated in a variety of cancers since its discovery 40 yr ago, the functions of p53 as a contributor to mitochondrial turnover are now being appreciated (24, 39). p53 influences the transcription of genes encoded by both the nuclear and mitochondrial genomes, whereas also physically interacting with TFAM in the mitochondrion and modulating mtDNA transcription (32). Coinciding with changes in gene expression, the mitochondrial localization of p53 and binding to TFAM on mtDNA is observed in the recovery period, notably 3 h postexercise (32). The transcription factors PGC-1α, TFAM, NRF-1, the assembly factor SCO2, and mitochondrially derived cytochrome c oxidase subunit II (COX-II) are some of the downstream targets of p53, establishing a role for this protein in the maintenance of mitochondrial content and function basally, and under stress conditions (28, 39). Whole body p53 knockout animals display reduced basal mitochondrial content, diminished COX enzyme assembly, and poor organelle function in muscle (65, 66). However, muscle-specific p53 knockout mice do not harbor the same degree of mitochondrial derangements (24, 67), supporting the existence of pathway redundancies in the basal regulation of mitochondrial biogenesis in muscle. Nevertheless, the importance of p53 in organelle homeostasis in muscle is further underscored when assessing mitochondrial adaptations under stress conditions such as exercise or disuse.

Mitochondrial Biogenesis in Exercise and Disuse

The signaling for mitochondrial biogenesis in skeletal muscle is fine-tuned to the imposed energy demands, which change dramatically during exercise or inactivity. A single exercise bout elicits a myriad of intracellular changes that converge on the upstream activators described earlier. For instance, during exercise, an increase in cytosolic Ca^{2+}, the rapid hydrolysis of ATP into AMP, and transient increases in

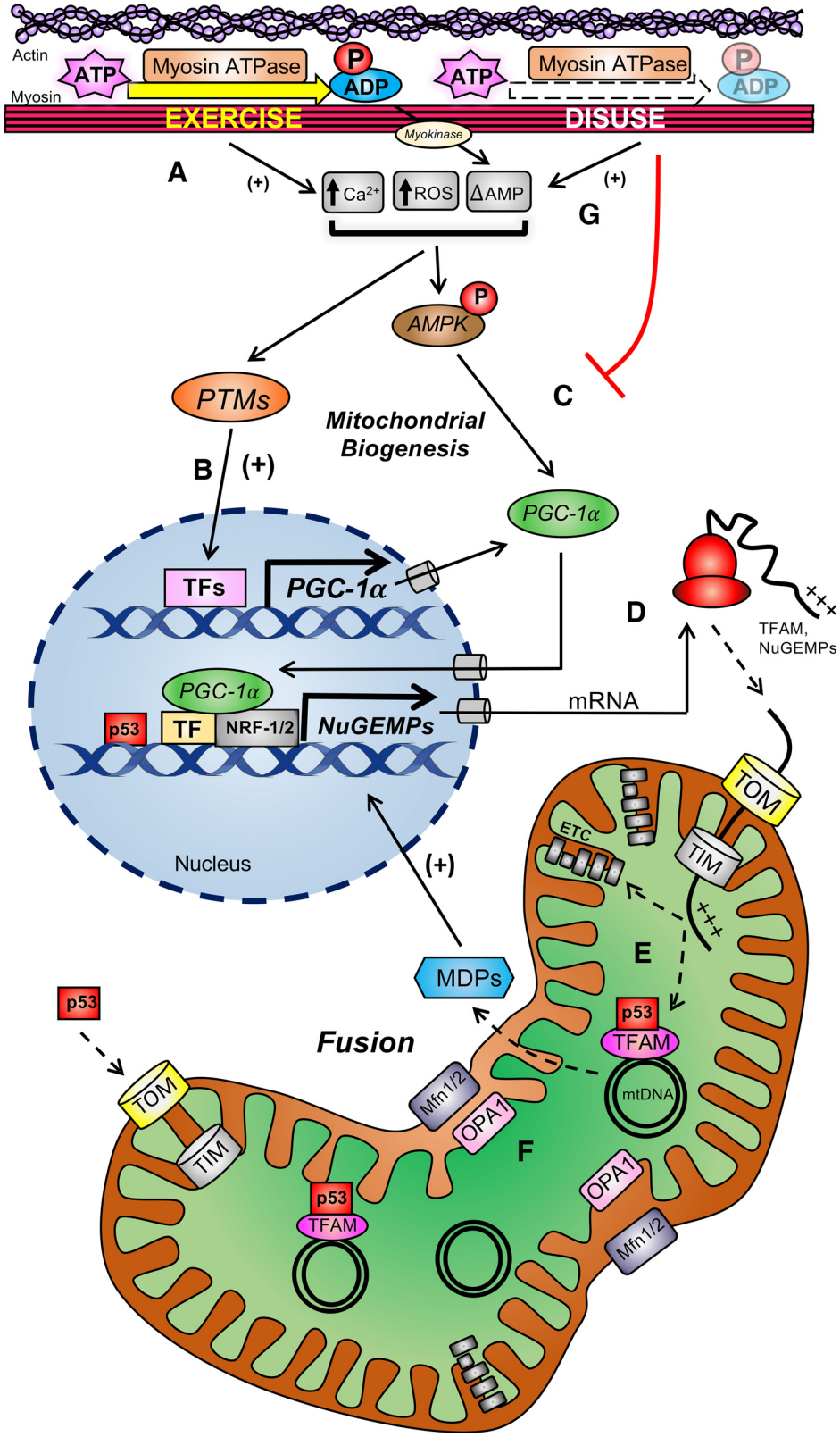

Figure 1. Mitochondrial biogenesis and fusion. *A*: muscle contraction evokes the rise of intracellular signals to promote mitochondrial biogenesis. These include cytosolic Ca^{2+}, ROS, and AMP levels, the latter arising as a product of ATP turnover. *B*: these signals activate kinases including AMPK, as well as phosphatases and other enzymes to promote posttranslational modifications (PTMs) of transcription factors that converge to facilitate the transcription of PGC-1α and other regulators. *C*: the activation of AMPK stimulates the nuclear activity of PGC-1α. PGC-1α enhances the transcriptional function of many nuclear receptors present on the promoters of NuGEMPs. *D*: upon the transcription of NuGEMPs, mRNAs exit the nucleus and are translated into proteins on cytosolic ribosomes. These gene products, including TFAM, are imported through TOM and TIM channels in the OM and IM, respectively. *E*: once imported, these proteins can serve enzymatic functions, or in the case of TFAM, bind to mtDNA and act as a transcription factor for mtDNA-derived electron transport chain complex subunits. The mitochondrial localization of p53 is also induced, forming a complex with TFAM on mtDNA. *F*: in organelle fusion, OPA1 facilitates expansion of the IM, whereas Mfn1 and 2 permit fusion of the OMs of adjacent organelles, resulting in the expansion of the mitochondrial reticulum. MDPs from the mitochondrial genome, such as MOTS-c, activate transcription factors to promote the expression of NuGEMPs. *G*: conversely, a lack of contractile activity during muscle disuse results in similar initial intracellular signals as during exercise, but their patterns and temporal durations differ markedly. Notably, there is an absence of ATP turnover-driven signaling, which removes the drive for mitochondrial biogenesis, leading to reduced mitochondrial content and quality (red line). ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; ETC, electron transport chain; IM, inner membrane; Mfn1/2, mitofusins 1 and 2; MOTS-c, mitochondrial ORF of the 12S rRNA type-c; mtDNA, mitochondrial DNA; NuGEMPs, nuclear genes encoding mitochondrial proteins; OM, outer membrane; OPA1, optic atrophy protein 1; PGC-1α, peroxisome proliferator-activated receptor gamma co-activator-1 alpha; ROS, reactive oxygen species; TFAM, mitochondrial transcription factor A; TIM, translocase of the inner membrane; TOM, translocase of the outer membrane.

ROS associated with contractile activity stimulate a plethora of kinases, (Fig. 1; Table 1), which are each capable of activating PGC-1α (68, 69). Furthermore, PGC-1α, p53, and TFAM are subject to posttranslational modifications, promoting their protein stability, or their nuclear or mitochondrial localization, and enhanced DNA binding to influence transcription. The cumulative effect of many acute exercise signaling events increases the expression and activity of these key biogenesis regulators, leading to the coordinated upregulation of both nuclear and mitochondrially encoded genes (32), culminating in

their enhanced protein expression with multiple exercise bouts in both animals (70, 71) and humans (72; Table 1). As a result, chronic exercise promotes enhanced mitochondrial volume and respiratory chain function, thereby improving muscle metabolic health.

In contrast to the mitochondrial augmentation observed with exercise, chronic muscle disuse results in reduced biogenesis, perhaps in an effort to prevent the maintenance of redundant organelles that may become toxic to the cell if no longer utilized effectively (73). Various models of chronic muscle disuse such as denervation, immobilization, hindlimb suspension, and even ventilator-assisted respiration diminish the contractile stimulus or abolish it entirely (74). Interestingly, elevations in cytoplasmic calcium and ROS are also observed during periods of muscle disuse in rodent models accompanying decrements in mitochondrial respiration (21, 25; Table 1), whereas these changes are not always observed in human subjects (75). It is important to note that the magnitude and temporal nature of these signals differ markedly from the transient changes observed with bouts of contractile activity (Fig. 1; Table 1). These discrepancies in molecular signaling during both physical activity and disuse generate divergent outcomes with regard to changes in mitochondrial content and organelle quality (Fig. 2). Further, there is no increase in contractile activity-induced ATP turnover during disuse, which suggest this as a dominant signal in mediating upward changes in mitochondrial content, as predicted earlier (76, 77). In the absence of contraction-induced signaling, there are reductions in mitochondrial content, a culmination of the reduced protein expression of PGC-1α, TFAM, and other regulators (27; Table 1). Interestingly, p53 expression is elevated during muscle disuse, mitigating a further decline in mitochondrial content, and it is required for mitophagy and organelle turnover to help prevent the accumulation of dysfunctional organelles in the absence of contractile activity (39).

Additional Regulators of Mitochondrial Biogenesis

Although PGC-1α, TFAM, and p53 are established, traditional rheostats of mitochondrial turnover, recent exciting work has revealed the influence of other potential regulators in muscle. For example, chronic exercise has been shown to elevate levels of the cytokine IL-13, which seems to be required for endurance training-induced mitochondrial biogenesis. Although its direct mechanism of regulation is incompletely understood, it is proposed that IL-13 acts via the signal transducer and activator of transcription 3 (STAT3)-ERRα/γ axis to mediate the expression of a wide variety of mitochondrial genes (78, 79). Further, the synthesis and secretion in muscle of brain-derived neurotrophic factor (BDNF) during exercise have important benefits for neural health, whereas also regulating aspects of mitochondrial quality control in muscle (80). In addition, short open reading frames (sORFs) encoded within the mitochondrial genome have been recently shown to produce bioactive mitochondrial-derived peptides (MDPs) with a range of physiological functions (81). Mitochondrial ORF of the 12S rRNA type-c (MOTS-c) is an exercise-inducible, muscle-derived MDP. The activation of MOTS-c appears to be acute in nature during exercise stress. Although increased levels of muscular MOTS-c are evident immediately postexercise, levels of this MDP increase in the blood during the exercise bout (81). MOTS-c regulates nuclear-encoded mitochondrial gene expression, facilitated by its AMP-activated protein kinase (AMPK)-dependent nuclear translocation upon metabolic stress (82), and is thus regarded as a novel "mitokine" that acts as a regulator of adaptation to metabolic stressors (82) and physical capacity (81). Recent studies of vitamin D receptor (VDR) expression have revealed that its decreased expression is associated with muscle atrophy-inducing conditions, in which mitochondrial content and function are also diminished (83). The aging process is associated with elevations in prostaglandin E2 (PGE2)-degrading enzyme (15-PGDH), which acts to reduce the levels of prostaglandin E2 (PGE2) in muscle. Normal levels of PGE2 are required for the incorporation of muscle stem cells into myofibers to promote muscle growth (84). Inhibition of 15-PGDH in aged muscle results in improvements in muscle mass, mitochondrial content and function, possibly via the activation of transcriptional regulators with cAMP response elements in their promotors, such as PGC-1α (84). Finally, the ablation of neuromedin B (NMB), a bombesin-like peptide that binds to the NMB receptor (NBR), improves mitochondrial content and oxygen consumption in the skeletal muscle of female mice (85). These findings are in line with previous data observing that NBR KO mice exhibit partial metabolic resistance to obesity induced by a high-fat diet (86). In summary, the discovery of these novel regulators expands the existing knowledge of the signaling networks coordinating mitochondrial quality in skeletal muscle, and may be exploitable in the future for therapeutic metabolic purposes.

MITOPHAGY

Mitophagy

The maintenance of an optimal mitochondrial pool within muscle requires a mechanism, whereby mitochondria of poor quality (i.e., with reduced respiration, elevated ROS emission, and/or impaired membrane potential) are actively removed from the reticulum through events of organelle fission to yield small fragments for their eventual degradation at the lysosome, a process termed mitophagy. A number of signaling mechanisms coordinate the selection of mitochondria for degradation via mitophagy, and interestingly, these signals also provoke organelle biogenesis (Figs. 1 and 2), illustrating the possibility of coordinated control of organelle turnover.

The most well-described pathway for mitophagy in muscle involves PTEN-induced putative kinase 1 (PINK1) and Parkin, whereby PINK1 accumulates on the OMM upon its attenuated import with the loss of the organelle membrane potential. The autophosphorylation of PINK1 (87) and subsequent phosphorylation of ubiquitin recruit the E3 ligase Parkin, which polyubiquitinates various OM proteins. This serves as a flag to recruit the growing autophagosomal membrane. These ubiquitin chains then tether the dysfunctional cargo to the autophagosome via adaptor proteins, such as p62 and optineurin, which connect ubiquitin to microtubule-associated protein 1A/1B-light chain 3 (LC3)-II present in the autophagosome (88). Ubiquitin-independent signaling methods also exist and rely on the phosphorylation of receptors present on the outer membrane, such as BNIP3, NIX, AMBRA1, and FUNDC1, to directly bind the organelle to LC3-II.

As the terminal site for all autophagy-related processes, the quantity and quality of lysosomes must be considered when

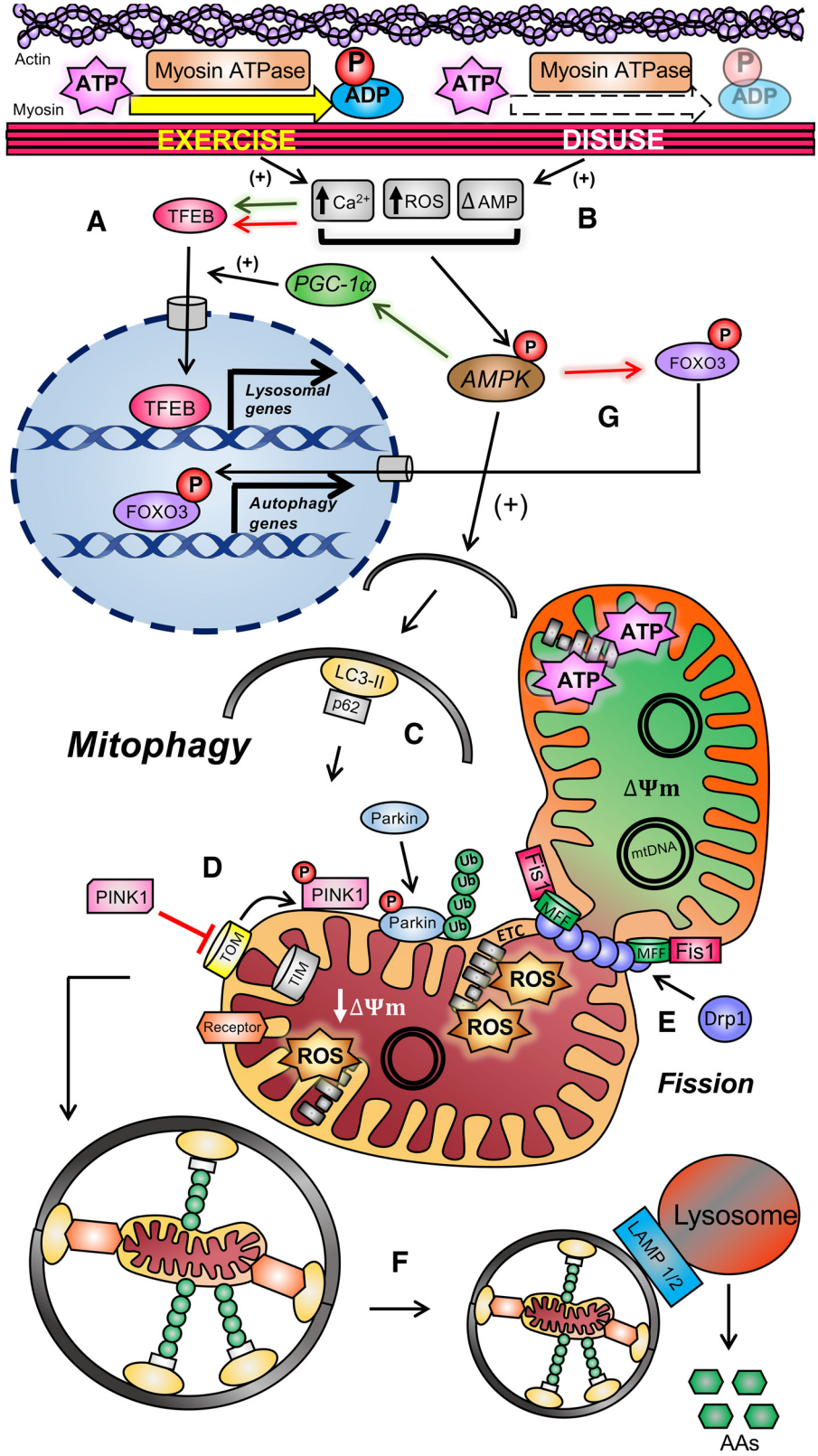

Figure 2. Mitophagy and mitochondrial fission. *A*: increases in cytosolic Ca^{2+} and AMPK activation during exercise promotes the nuclear translocation of TFEB. TFEB binds to the promoter of lysosomal genes to promote lysosomal biogenesis. *B*: AMPK phosphorylation also induces the activation of PGC-1α, which can promote the nuclear translocation of TFEB and aid in the transcription of lysosomal genes. *C*: AMPK promotes the initiation of autophagy, including the activation of LC3-II and nucleation of the phagophore with bound LC3-II and the adaptor protein p62. *D*: mitochondrial dysfunction, including elevated ROS emission and a drop in membrane potential prevents the import of PINK1, which accumulates on the OM to recruit parkin. Parkin ubiquitinates OM proteins that will attach the dysfunctional organelle to the growing phagophore via p62. *E*: the organelle is removed from the network in the fission process by Drp1, Fis1, and MFF. Fis1 is bound to the OM, whereas Drp1 is recruited from the cytosol and binds to MFF. Drp1 oligomerizes around the constriction site to break off a mitochondrial fragment. *F:* subsequently, the mitochondrion is enveloped in the double-membraned autophagosome, which fuses to the lysosome via LAMP1 and 2 for degradation. *G*: mitophagy is also induced during muscle disuse, in part as a result of increased ROS-induced AMPK activation. These signals promote FOXO3 nuclear translocation, which induces the transcription of autophagy genes, contributing toward the mitophagic degradation of mitochondria during disuse. It is important to note that both the pattern and duration of intracellular signals during exercise and disuse ultimately influence downstream signaling, generating differences in the cellular outcomes in each condition. Green arrows represent signaling during exercise, whereas the red arrows indicate that during disuse. AAs, amino acids; AMPK, AMP-activated protein kinase; ΔΨm, mitochondrial membrane potential; Drp1, dynamin-related protein 1; ETC, electron transport chain; Fis1, mitochondrial fission 1 protein; FOXO3, forkhead box protein O3; LAMP1/2, lysosomal-associated membrane protein 1 and 2; LC3, microtubule-associated protein 1A/1B-light chain 3; MFF, mitochondrial fission factor; OMM, outer mitochondrial membrane; PGC-1α, peroxisome proliferator-activated receptor gamma co-activator-1 alpha; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; TFEB, transcription factor EB.

discussing the regulation of mitophagy. These organelles are replete with enzymes responsible for recycling the autophagosomal cargo into its constituents. Lysosomes are primarily regulated by the microphthalmia family of transcription factors, of which TFEB and TFE3 appear to be the most important. Upon activation, TFEB and TFE3 translocate into the nucleus to regulate the transcription of autophagy-related and lysosomal genes (89). Impairments in lysosomal function

can result in declines in autophagy and the accumulation of indigestible material known as lipofuscin, common in aging and prolonged muscle disuse (90, 91).

Mitophagy in Exercise and Disuse

Concomitant with the transient increases in the expression of genes regulating mitochondrial dynamics and biogenesis, a single bout of exercise is capable of initiating mitophagy signaling in both human (92) and animal models (22, 93; Table 1). The classic exercise-induced intracellular signals (Figs. 1 and 2) also serve to stimulate mitochondrial degradation during contractile activity. The energetic imbalance brought on by ATP hydrolysis and the formation of AMP stimulates AMPK, a kinase that seems to be required for exercise-induced mitophagy (22; Table 1). AMPK coordinates *1*) the formation of the autophagosome (22), *2*) the nuclear localization of TFEB and TFE3, and *3*) it appears to also localize to mitochondria to stimulate exercise-induced mitophagy (94). ROS have been shown to aid in the intralysosomal breakdown of organelles via sensitization of MCOLN1, the lysosomal calcium channel, although the increase in cytoplasmic Ca^{2+}, either via the lysosome or the sarcoplasmic reticulum, activates calcineurin, serving to dephosphorylate TFEB and TFE3 and allowing their nuclear translocation (95). As discussed earlier, these signals also converge to activate PGC-1α, which may help to coordinate the induction of mitophagy following exercise (93), as it is known to impact TFEB transcription and cellular localization (96).

Although multiple mitophagy pathways are stimulated with acute exercise, Parkin seems to be required for initiating mitophagy flux in muscle, suggesting that it acts as the predominant pathway in this tissue (97, 98). The overexpression of Parkin is also protective against the metabolic decrements and muscle atrophy observed in aging muscle, likely by enhancing mitochondrial clearance (99). When exercise is repeated in the form of endurance training, phenotype changes not only include an increase in mitochondria but are also accompanied by augmentations in lysosomal content, increasing the capacity for cellular recycling (23). Despite this, exercise-induced mitophagy flux is unchanged or even reduced following training in comparison with untrained muscle (23, 49). The reason for this appears to be attenuated cellular signaling in muscle with a high mitochondrial content and quality (29), resulting in a lower stimulus for mitophagy (and biogenesis) pathway activation. Nonetheless, with training, muscle cells have adapted to the appropriate machinery and are primed for mitochondrial clearance, improving the capacity of the cell to maintain optimal organelle quality in response to a future stressor.

In contrast, conditions of muscle disuse result in mitochondrial dysfunction and concomitant atrophy. Mitochondrial content diminishes within the first week, accompanied by early increases in mitophagy flux, in concert with the expression of numerous lysosomal proteins (39, 100). Subsequently, a decline in mitophagy markers has been observed, indicating possible impairments in the autophagy machinery during more prolonged disuse (25, 101; Table 1). However, it should be noted that some groups have reported increased mitophagy with disuse, for example during 14 days of hindlimb unloading, likely stemming from divergent approaches used to measure mitophagy flux (102). Since mitochondrial dysfunction is universally apparent with disuse, it seems that the need for clearance does not match the capacity for degradation. The appearance of undigested lipofuscin and autophagosomes accumulated in muscle supports this concept (91), indicating that the terminal stages of autophagy, including autolysosomal fusion and degradation, may be impaired. Whether the enhanced expression of lysosomal proteins, or enhanced lysosomal activity, could also prove to be therapeutic in muscle wasting associated with disuse and aging remains to be established and is an exciting direction for future work.

MITOCHONDRIAL PROTEIN QUALITY CONTROL

Mechanisms of Protein Quality Control

Mitochondria are equipped with internal protein machinery that trigger adaptive responses during stress to sustain organelle protein homeostasis. In this respect, the regulation of protein quality control (PQC) is of great interest, since the accumulation of toxic protein aggregates is associated with many disease states, particularly noteworthy in neurodegeneration. PQC involves the correct import, targeting, folding, and turnover of proteins, in appropriate stoichiometry, to maintain optimal respiratory chain function. To facilitate this, a specialized protein import machinery (PIM) is localized in the outer and inner membranes as the translocase of the outer membrane (TOM) and translocase of the inner membrane (TIM) complexes, respectively, for the selective import of proteins toward specific mitochondrial sub-compartments (103). Within the organelle, chaperones such as 60 kDa heat shock protein (HSP60), HSP10, and mtHSP70 act to mobilize and refold proteins, whereas proteases in the matrix such as lon protease 1 (LONP1), caseinolytic mitochondrial matrix peptidase proteolytic subunit (ClpP), and membrane-bound m-ATPase associated with diverse cellular activities (m-AAA) protease serve to degrade unwanted and misfolded proteins. An additional family of proteases exists in the intermembrane space (IMS) to also serve this function, including presenilins-associated rhomboid-like protein (PARL), YME1 like 1 ATPase (YME1L1), high-temperature requirement factor A2 (Htra2/OMI), and OMA1. These proteases monitor protein quality, and they are also involved in determining cell fate. For example, IMS proteases cleave OPA1 to influence mitochondrial morphology (4), PARL modulates mitophagy by degrading PINK1 (104), and LONP1 is responsible for the degradation of TFAM to maintain optimal levels of this transcription factor, thereby modulating mtDNA transcription (105).

The Mitochondrial Unfolded Protein Response (UPR^{mt})

The mitochondrial unfolded protein response (UPR^{mt}) is a PQC mechanism, involving the increased expression of proteostatic enzymes in response to various forms of mitochondrial dysfunction. It also invokes retrograde signaling to the nucleus to trigger an adaptive transcriptional program with the aim of improving protein folding capacity and mitochondrial function (106). The upregulation of the UPR^{mt} -regulating activating transcription factors ATF4, ATF5, and CHOP, as well as expression of UPR^{mt} machinery in muscle, is observed in mitochondrial myopathy (107) and during high-fat feeding (108), two conditions characterized by decrements in respiration and increases in ROS emission. Investigations of the UPR^{mt}

and implications for the regulation of mitochondrial function have thus far been largely carried out in cardiac muscle. Activation of the UPR^{mt} mediates mitochondrial recovery during cardiac ischemia-reperfusion injury, an outcome that is reliant on the expression of ATF5 (109), which localizes to the nucleus to aid in the transcription of UPR^{mt} genes during mitochondrial stress (106). This novel protective role of ATF5 may be reliant on PGC-1α, creating a link between the regulation of protein homeostasis and organelle biogenesis (110).

Adequate function of both the protein import system and resident mitochondrial PQC enzymes is imperative for the maintenance of organelle quality in muscle. For example, ablation of the proteases LONP1 or ClpP, or of chaperone HSP60, elicits the development of severe clinical mitochondrial cytopathies, triggered by respiratory chain defects, ROS production, and a loss of mtDNA, manifesting in myopathy and cardiomyopathy (111, 112). In particular, the muscle-specific loss of LONP1 generates a detrimental phenotype characterized by atrophy, weakness, reduced oxidative capacity, function, and excessive mitophagy (113). Alternatively, the attenuation of protein import by knocking down a component of the TIM complex, Tim23, induces the expression of UPR^{mt} targets in muscle and increases ROS emissions, indicative of mitochondrial dysfunction (103). Although research in this area remains in its infancy, these findings demonstrate that the molecular machinery in PQC has a significant role in the maintenance of mitochondrial homeostasis, promoting the health of mammalian striated muscle.

Mitochondrial Protein Quality Control in Exercise and Disuse

Recent work using chronic contractile activity in rodents has shown that UPR^{mt} activation and expression of mitochondrial chaperones precedes organelle biogenesis signaling (37). Treadmill training also improves the expression of UPR^{mt} markers in aged rodents, coinciding with improvements in mitochondrial content (38; Table 1). Chronic exercise also blunts the increases in UPR^{mt} gene expression in response to an acute bout of exercise. This is indicative of attenuated proteotoxic stress during contractile activity due to a larger abundance of protective PQC machinery, as an adaptation to transient spikes in UPR^{mt} signaling, affording long-term protection against stress (114). The "mito-nuclear balance," referring to the stoichiometric proportions of proteins encoded by the nuclear and mitochondrial genomes, may also be used as an assessment of mitochondrial PQC. It appears that endurance-trained individuals retain a smaller mito-nuclear protein ratio in comparison with untrained subjects, suggesting that improved PQC with chronic exercise may contribute to improved mitochondrial content and aerobic capacity (17).

In contrast to the response evident with exercise, the phenotype brought about by chronic muscle disuse is one of the poor quality organelles, despite the enhancement of mitophagic processes. Using denervation as a model of disuse, recent findings indicate that the muscle-specific ablation of LONP expression, a downstream UPR^{mt} target of ATF5, exacerbates denervation-induced reductions in muscle size and strength (113). Furthermore, denervation results in the induction of UPR^{mt} protein targets, and in particular, induces the rapid nuclear localization of ATF5 (39; Table 1). These findings occur in conjunction with enhanced autophagy and signaling toward lysosomal biogenesis, intertwining the UPR^{mt} with other established mitochondrial quality control pathways in the molecular response to energetic stress in muscle disuse.

COORDINATION OF MITOCHONDRIAL REDOX MECHANISMS

Antioxidant Machinery

The antioxidant system protects the cellular environment from excessive ROS production, thus preserving the integrity and quality of the mitochondrial reticulum. However, when produced in moderate amounts, ROS act as signaling molecules to regulate antioxidant enzyme expression and mitophagy. Thus, there is a necessity for ROS levels to be tightly controlled in the balancing act of regulating muscle and mitochondrial health.

At the forefront of antioxidant signaling is the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is normally sequestered in the cytoplasm by its negative regulator Keap1, rendering it inactive and prone to degradation by the proteasome. Oxidative stress disrupts Nrf2-Keap1 binding to promote Nrf2 nuclear translocation and the subsequent transcription of antioxidant genes (34). In the nucleus, Nrf2 heterodimerizes with small Maf proteins, which bind to antioxidant response element (ARE) sequences on the promoter region of target genes, including antioxidant enzymes such as NAD(P)H quinone dehydrogenase 1 (NQO1) and heme oxygenase-1 (HO-1; Fig. 3). Surprisingly, the ablation of Nrf2 does not appear to influence basal mitochondrial content and quality in muscle (43). This suggests the existence of pathway redundancies in mitochondrial redox control in muscle. However, the value of the Nrf2-Keap1 system is more evident under conditions in which ROS are modulated across a wider range, such as that which occurs during exercise, disuse, and aging.

Nrf2 and Antioxidants in Mitochondrial Adaptations to Exercise and Disuse

Coinciding with increases in mitochondrial ROS emission, an acute bout of exercise enhances Nrf2-ARE binding (43), and increases Nrf2 and HO-1 mRNA (34, 115; Table 1). However, whether Nrf2 protein is increased with training remains in question (43, 115). In conditions of enhanced physiological demand such as acute and chronic exercise, Nrf2 is required for the upregulation of antioxidant capacity (34), mitochondrial content, bioenergetics (116), as well as improvements in muscle mass and function (117). Recent work has also shown that Nrf2 also mediates fission by regulating the stability of Drp1, contributing to training-induced improvements in mitochondrial morphology. Furthermore, treatment with the Nrf2 activator sulforaphane rescues mitochondrial dysfunction and the sarcopenic phenotype in aged animals, improving exercise capacity and reducing frailty (116).

Chronic disuse, including during spaceflight, denervation, and hindlimb unloading, results in increases in Nrf2 within muscle, most likely serving to counteract increases in ROS emission that occur under these conditions (118, 119). Hindlimb unloading for 3 days upregulates Nrf2, but is reduced by *day 7*, coinciding with the opposite pattern observed in H_2O_2 emission (26; Table 1). In fact, the loss of Nrf2 during disuse

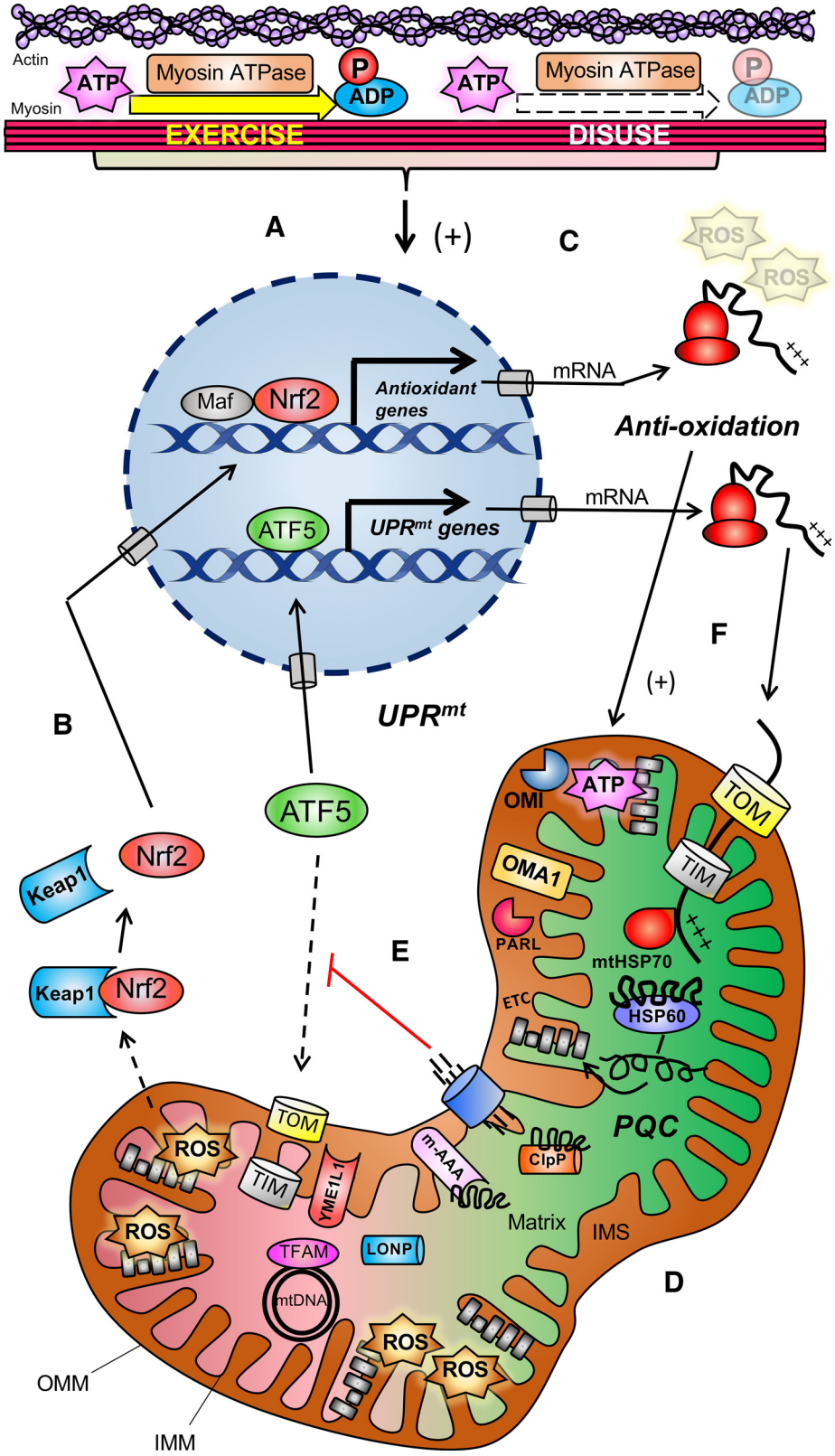

Figure 3. Antioxidant capacity and protein quality control. *A*: contractile activity and muscle disuse both induce signaling toward the expression of antioxidant and mitochondrial protein quality control machinery. *B*: increased ROS production causes the disassociation of the transcription factor Nrf2 from inhibitory KEAP1 to promote its nuclear translocation. Binding to ARE elements on DNA, Nrf2 promotes the transcription of antioxidant genes including NQO1 and HO-1. *C*: these enzymes contribute toward ROS scavenging in the cytosol. *D*: mitochondrial PQC encompasses the import, folding, transport, and degradation of proteins within the organelle. Matrix chaperones include mtHSP70 and HSP60, which assist in the import and folding of proteins. LONP, ClpP, and membrane-bound m-AAA are matrix proteases, whereas those in the IMS include PARL, OMI, OMA1, and membrane-bound YME1L1. *E*: the efflux of peptides into the cytosol derived from ClpP-mediated proteolysis is suggested to inhibit the mitochondrial import of the transcription factor ATF5, subsequently prompting its nuclear localization. There, ATF5 binds to UPR^{mt} elements on DNA and assists in the transcription of UPR^{mt} genes, as a retrograde signal from the mitochondrion. *F*: these UPR^{mt} genes include mtHSP70, HSP60, and LONP, which are then imported to enhance the proteomic folding and handling capacity of the organelle. ARE, antioxidant response element; ATF5, activating transcription factor 5; ClpP, caseinolytic mitochondrial matrix peptidase proteolytic subunit; FOXO3, forkhead box O3; HO-1, heme oxygenase-1; HSP60, 60 kDa heat shock protein; Htra2/OMI, high-temperature requirement factor A2; IMS, intermembrane space; KEAP1, kelch-like ECH-associated protein 1; LONP, lon protease; Maf, muscular aponeurotic fibrosarcoma; mtHSP70, 75 kDa mitochondrial heat shock protein; NQO1, NAD (P)H quinone dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; PARL, presenilins-associated rhomboid-like protein; PQC, protein quality control; UPR^{mt}, unfolded protein response; YME1L1, YME1 like 1 ATPase.

aggravates increases in oxidative stress (36) and shifts metabolism toward glycolysis (118) but does not influence the degree of muscle atrophy (118). Collectively, these findings implicate the Nrf2 regulatory network alongside mitochondrial dynamics, turnover, and PQC in the maintenance of mitochondrial and skeletal muscle health with exercise, and in the ROS-induced myopathic phenotype during inactivity.

CONCLUSION

Coordinated by multiple branches of regulatory signaling, the morphology, quantity and quality of mitochondria are subject to significant regulation basally and during physiological stressors, granting muscle with its infamous malleable nature. Understanding the traditional pathways, and discovering novel biological networks that coordinate mitochondrial fine-tuning in skeletal muscle, including organelle remodeling, biogenesis, mitophagy, PQC, and antioxidant capacity is essential in interpreting the molecular adaptations of muscle to imposed stressors, such as exercise and disuse. This comprehension helps us to conceptualize the chronology and progression of pathway activation during physiological challenges, culminating in energetically proficient organelles that are integral for superior oxidative and metabolic function. The existence of redundant regulatory networks that control mitochondrial function presents opportunities for these pathways to be exploited for therapeutic interventions in the prevention of metabolic diseases, for enhancing muscle performance, and ultimately to improve muscle health and well-being.

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No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.B.S. and D.A.H. conceived and designed research; M.B.S. prepared figures; M.B.S., J.M.M., A.N.O., N.M., and D.A.H. drafted manuscript; M.B.S. and D.A.H. edited and revised manuscript; M.B.S., J.M.M., A.N.O., N.M., and D.A.H. approved final version of manuscript.

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