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REVIEW ARTICLE

Skeletal muscle mitochondrial remodeling in exercise and diseases

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Skeletal muscle fitness and plasticity is an important determinant of human health and disease. Mitochondria are essential for maintaining skeletal muscle energy homeostasis by adaptive re-programming to meet the demands imposed by a myriad of physiologic or pathophysiological stresses. Skeletal muscle mitochondrial dysfunction has been implicated in the pathogenesis of many diseases, including muscular dystrophy, atrophy, type 2 diabetes, and aging-related sarcopenia. Notably, exercise counteracts the effects of many chronic diseases on skeletal muscle mitochondrial function. Recent studies have revealed a finely tuned regulatory network that orchestrates skeletal muscle mitochondrial biogenesis and function in response to exercise and in disease states. In addition, increasing evidence suggests that mitochondria also serve to "communicate" with the nucleus and mediate adaptive genomic re-programming. Here we review the current state of knowledge relevant to the dynamic remodeling of skeletal muscle mitochondria in response to exercise and in disease states.

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THE SPECIALIZED SKELETAL MUSCLE MITOCHONDRIAL SYSTEM

Skeletal muscle structural and functional plasticity is a key feature that allows for adaptation to myriad physiological stimuli. Physiological conditions are often dictated by acute and chronic changes in physical activity and workload of the muscle. As such, muscle responds through changes in contractile machinery, calcium handling, and energy metabolic capacity. In particular, mitochondrial ATP production must match demands imposed by changes in physical activity and exercise. Accordingly, the skeletal muscle mitochondrial system has evolved for this purpose.

Based on subcellular location, skeletal muscle mitochondria can be generally classified into subsarcolemmal (SS) and intermyofibrillar (IMF). SS mitochondria are characterized by a large, lamellar shape located underneath the sarcomere, while the IMF mitochondria are relatively smaller, more compact and located between the contractile filaments. Based on recent three-dimensional electron microscopy findings, skeletal muscle mitochondria can be further classified into paravascular mitochondria (PVM), I-band mitochondria (IBM), fiber parallel mitochondria (FPM), and cross fiber connection mitochondria (CFCM).[1] All four different mitochondrial populations are highly connected with each other to form a complex network that can rapidly distribute energy throughout myofibers.[1]

Skeletal muscle mitochondria are highly dynamic organelles, undergoing remarkable remodeling in response to a variety of physiological and pathophysiological stresses to meet energy and contraction demands of the muscle. Changes in energy demands of the muscle are most often associated with changes in physical activity. For example, increases in mitochondrial content and mass (biogenesis) accompany endurance exercise training (reviewed in ref.[2]). Likewise, decreases in mitochondrial content and oxidative energy metabolism are associated with obesity, diabetes and aging. It should be noted, however, that solely increasing mitochondrial biogenesis is not sufficient to support high oxidative respiration. A highly regulated system exists as a quality control mechanism to replace damaged mitochondria through orchestrated autophagy and mitophagy in muscle. Finally, mitochondrial biogenesis and mitophagy most likely do not exist independently as there is increasing evidence that at least in certain instances, these pathways are coordinately regulated. In this review, we focus on the mitochondrial remodeling that takes place in response to exercise and disease. Skeletal muscle possesses a highly integrated system that senses and coordinates changes in physical activity or extracellular cues with the control of mitochondrial biogenesis. In addition, we discuss quality control of muscle mitochondria through autophagic and mitophagic mechanisms. Finally, we review the relationship between muscle mitochondrial remodeling and disease and aging.

INTEGRATION OF PHYSICAL ACTIVITY WITH MUSCLE MITOCHONDRIAL BIOGENESIS

A nuclear receptor network controls mitochondrial fuel selection and respiratory function in muscle

Nuclear receptors constitute a large family of DNA-binding transcription factors. Several of these factors are critical regulators of muscle fuel metabolism and mitochondrial biogenesis and function. The peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors was originally identified as a regulator

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of peroxisome biogenesis.[3] The prototypical member of this family, PPARα, plays a central role in the regulation of muscle fuel preferences. Specifically, PPARα drives mitochondrial fatty acid oxidation (FAO) enzyme gene expression in skeletal muscle and other oxidative tissues such as heart and liver.[4–7] PPARα expression also parallels the oxidative capacity of specific muscle fibers, exhibiting the highest expression in slow, oxidative type I fibers.[8] PPARα, as well as the other two members of this family PPARβ (also known as PPARδ) and PPARγ, binds to their cognate DNA elements as an obligate heterodimer with the retinoid X receptor (RXR). The PPAR factors also have large hydrophobic ligand binding domains that bind a variety of endogenous fatty acid or fatty acid-derived ligands.[9–11] Although the precise endogenous ligands for PPARα, and the more closely related PPARδ, have remained elusive, long-chain unsaturated fatty acids have been shown to bind and activate these receptors.[12] In this way, PPARα serves as a cellular sensor for increased delivery of fatty acids into muscle and subsequent upregulation of the enzymatic machinery needed for mitochondrial FAO and ATP production. Supporting this notion, overexpression of PPARα in mouse skeletal muscle results in a robust increase of the expression of genes involved in fatty acid import, binding, and oxidation as well as increased FAO rates.[13] Interestingly, this comes at the expense of glucose utilization and is accompanied by a decrease in glycolytic enzyme expression, glucose intolerance and reduced exercise capacity.[13,14] Somewhat surprisingly, FAO rates in skeletal muscle of PPARα knockouts (KO) are lower than wild-type controls in the fasted but not fed state.[15] This most likely reflects compensation by PPARδ in muscle. Although not identical, there is a large degree of overlap in the gene targets of PPARα and PPARδ.[16,17] Remarkably, activation of PPARδ synergizes with exercise to promote endurance capacity.[17] In addition to direct effects on FAO, increases in the exercise capacity by PPARδ may be a result of glucose sparing.[18]

The estrogen-related receptor (ERR) is also a critical regulator of mitochondrial biogenesis in muscle. The ERR family is composed of 3 members (α, β, and γ) and characterized as orphan receptors as no endogenous ligand has been identified.[19] The ERR factors have been shown to activate almost all aspects of mitochondrial energy metabolism including FAO, the TCA cycle, and electron transport chain and oxidative phosphorylation (ETC/OXPHOS) in many cell types.[20] Multiple lines of evidence support a critical role for ERR signaling in maintenance of skeletal muscle energy metabolism and function. ERRα-deficient mice display lower activity and impaired exercise performance concomitant with lower expression of muscle mitochondrial energy metabolic genes.[21] ERRα KO mice also have diminished muscle mass suggesting a possible crosstalk between energy metabolism and the control of muscle growth.[21] ERRα also activates PPARα in skeletal muscle providing a feed forward loop to activate oxidative metabolism.[22] ERRα is also linked to muscle repair and regeneration. ERRα KO mice have impaired regeneration following muscle injury.[23] In addition to ERRα, overexpression of ERRγ in muscle results in marked activation of oxidative metabolic pathways, mitochondrial biogenesis and a corresponding increase in slow type I fibers.[24,25] The switch to type I fibers by ERRγ is mediated by direct activation of the slow myosin heavy chain 7 and 7b (*Myh7*, *Myh7b*) genes and expression of the miR-499/208b pathway that reinforces the slow fiber phenotype.[26,27] ERRγ is also correlated with type I fiber %, ATPmax, and VO_{2max} in human skeletal muscle.[26] As such, this ERR-triggered circuit provides a mechanism to coordinately regulate slow myosin heavy chain expression with high rates of mitochondrial ATP production.

Integration of upstream signaling pathways with mitochondrial biogenesis in muscle

The increased metabolic demands of exercise require a system to match increased energy requirements with enhanced oxidative capacity to generate ATP. A key discovery in this regard was the identification of PPARγ coactivator-1α (PGC-1α) as a cold-inducible transcriptional coactivator in brown adipose tissue.[28] Subsequent studies demonstrated that PGC-1α directly interacts and coactivates multiple nuclear receptors, often in a ligand-dependent manner, to increase oxidative metabolism and mitochondrial biogenesis in multiple cell types.[29–31] A key link between exercise and control of mitochondrial biogenesis came with the discovery that expression of PGC-1α is induced in skeletal muscle following an acute bout of exercise.[32–34] Forced expression of PGC-1α in muscle in transgenic mice results in a robust mitochondrial biogenic response, an increase of type I and oxidative type IIa fibers and improved fatigue resistance.[35] Conversely, loss of PGC-1α and the closely related PGC-1β in muscle leads to markedly reduced mitochondrial respiration, expression of ETC/OXPHOS genes and exercise performance.[36,37] However, loss of PGC-1 does not alter fiber-type composition in muscle.[36,37] Furthermore, loss of PGC-1α does not affect training-induced increases in OXPHOS/ETC gene expression.[38–40] These results suggest that PGC-1 signaling in muscle is required for developmental mitochondrial biogenesis and to respond to acute dynamic physiological stresses but not necessarily chronic metabolic adaptations in response to exercise.

PGC-1α is a highly inducible transcriptional coregulator providing a mechanism to integrate extracellular and intracellular signals with the control of mitochondrial energy metabolism and quality control. Multiple signaling pathways appear to converge on regulation of PGC-1α (Fig. 1). Exercise-induced activation of PGC-1α expression is mediated, at least in part, by β-adrenergic signaling.[41] PGC-1α expression is highly responsive to cAMP and activation of the cAMP response element binding protein (CREB).[42] This almost certainly is a key mechanism downstream of β-adrenergic signaling in muscle. Exercise-induced activation of PGC-1α can be also mediated by the AMP-activated protein kinase (AMPK). AMPK is activated by depletion of ATP levels following exercise in muscle. AMPK was demonstrated to activate PGC-1α either via direct phosphorylation of PGC-1α or by promoting Sirt1-mediated PGC-1α activation.[43,44] In skeletal muscle, AMPK activation is sufficient to drive the PGC-1α regulatory circuit and mitochondrial function.[17] Signaling through the calcium-dependent protein phosphatase, calcineurin, and kinase, calmodulin-dependent kinase, has also been shown to activate PGC-1α following exercise.[45] Induction of PGC-1α expression by calcium is also mediated by the MEF2 transcription factor which is repressed by histone deacetylase (HDAC) and activated by de-repression.[46] The identification of insulin response sequences (IRS) in the promoter of PGC-1α also confirms insulin signaling as a key regulator of PGC-1α expression.[47] Increases in PGC-1α in heart in response to exercise are also dependent on the insulin receptor substrate 1 and 2 (IRS1 and IRS2) molecules that act as key mediators of insulin signaling.[48] Finally, considerable evidence demonstrates that skeletal muscle PGC-1α expression is diminished in diabetics.[49,50] Although a direct causal relationship between diminished PGC-1α signaling and insulin resistance has not been established, a clear correlation between them exists.

Other factors also converge on PGC-1/nuclear receptor signaling providing additional layers of regulation. For instance, the PGC-1 and ERR-induced regulator in muscle 1 (PERM1) is activated in muscle by exercise and required for maximal activity of PGC-1α in muscle.[51] Although its precise function is not clear, ectopic expression of PERM1 in skeletal muscle also increases ERRα and PGC-1α expression, mitochondrial content and respiratory capacity.[51] The Krüppel-like factors (KLF) are zinc finger transcription factors that also regulate skeletal muscle metabolism and mitochondrial function. Early work demonstrated that one KLF, KLF15, positively regulated the insulin-responsive glucose transporter 4 (GLUT4) in muscle.[52] It was subsequently shown that KLF15 is induced in muscle acutely in human exercise and regulates a broad array of lipid and fatty acid metabolic genes in both muscle and heart.[53,54] Further, KLF15 knockout mice have

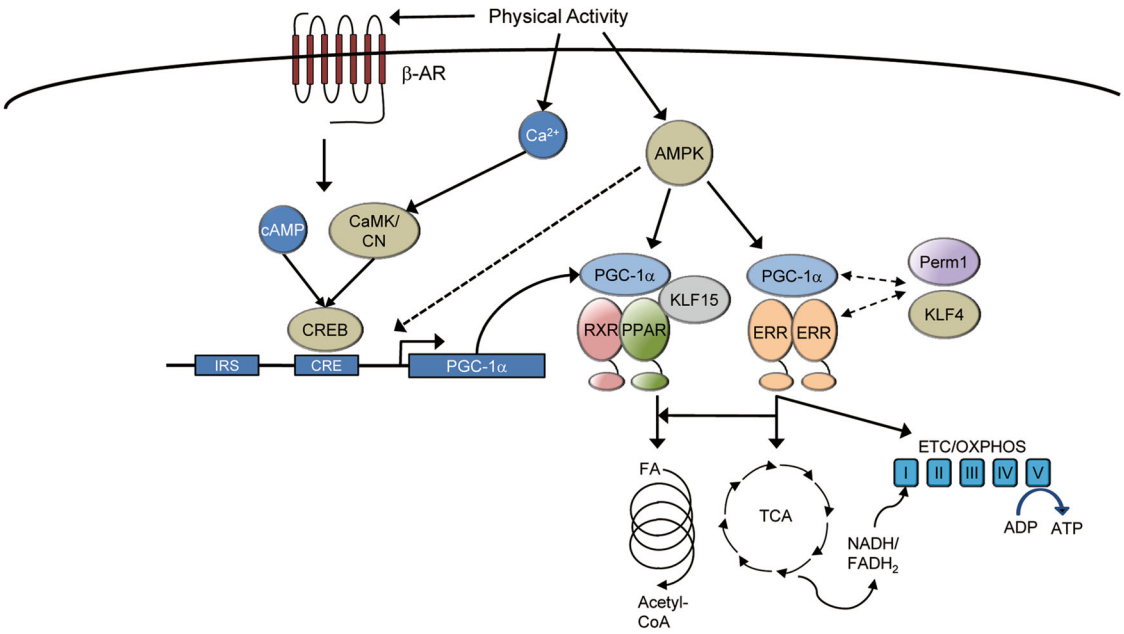

Fig. 1 Integration of upstream signaling pathways with mitochondrial biogenesis in the muscle. Multiple signaling pathways in the skeletal muscle serve to transmit changes in physical activity or other extracellular signals to mitochondrial biogenesis. Many of these pathways directly activate the peroxisome-proliferator activated receptor γ (PPARγ) coactivator-1α (PGC-1α). PGC-1α interacts directly with its effector nuclear receptors such as the estrogen-related receptor (ERR) and the peroxisome-proliferator activated receptor (PPAR) to regulate genes involved in virtually all aspects of mitochondrial energy metabolism. CaMK calmodulin-dependent kinase, CN calcineurin, AMPK AMP-dependent kinase, β-AR beta adrenergic receptor, IRS insulin response sequence, CRE cAMP response element, CREB cAMP response element binding protein, RXR retinoid X receptor, KLF Krüppel-like factor, FA fatty acid, ETC electron transport chain, OXPHOS oxidative phosphorylation

reduced endurance capacity and an increased reliance on carbohydrates during exercise.[53] There is also evidence that actions of KLFs are regulated in coordination with nuclear receptors. For instance, KLF15 directly interacts with PPARα to regulate mitochondrial FAO enzyme gene expression.[55] Likewise, KLF5 may be a direct negative regulator of PPARδ in skeletal muscle and inhibit activation of genes involved in mitochondrial fatty acid oxidation and energy uncoupling.[56] In heart, KLF4 cooperates with ERR and PGC-1α to regulate mitochondrial biogenesis and is necessary for maximal mitochondrial function.[57] A similar role of KLF4 in muscle has not yet been elucidated. Other transcription factors in skeletal muscle also cooperate with PGC-1α. Yin Yang 1 (YY1) was identified through a computational approach to be a common target interacting with both PGC-1α and mTOR, perhaps linking nutrient sensing with mitochondrial biogenesis.[58] Muscle-specific YY1 knockout mice display profound defects in mitochondrial structure and energy production.[59] Additional factors also act as negative regulators of PGC-1 signaling. For instance, loss of the nuclear receptor corepressor RIP140 in muscle results in increased FAO and ETC/OXPHOS gene expression.[60] These effects are meditated through RIP140 action on multiple nuclear receptors including PPAR and ERR.[61] In addition, knockout of the gene encoding folliculin (*Flcn*) or its partner folliculin interacting partner 1 (*Fnip1*), has also been shown to induce the PGC-1α cascade and mitochondrial function in muscle cells.[62–64] The inhibitory effects of the FLCN/FNIP1 complex on PGC-1α signaling may be mediated through suppression of AMPK signaling.[64]

ORCHESTRATION OF MUSCLE MITOCHONDRIAL QUALITY CONTROL AND BIOGENESIS

Mitochondrial dynamics

Mitochondria are highly adaptable organelles that require continuous surveillance to maintain their function integrity. First, mitochondria constantly undergo fission and fusion. Two mitochondria can form a single, tubular like mitochondria by fusing their outer and inner membranes. Conversely, mitochondrial fission fragments the tubular mitochondria network into small organelles. The sophisticated regulation of mitochondrial fission and fusion has been an area of intense interest and research. The membrane bound GTPases mitofusin1 (MFN1) and mitofusin 2 (MFN2) initiate the outer membrane (OM) fusion of two mitochondria, followed by the fusion of the inner membranes (IM) mediated by the optic atrophy protein 1 (OPA1). Loss-of-function studies have demonstrated that MFN1, MFN2 and OPA1 are essential for mitochondrial fusion. Cells lacking both MFN1 and MFN2 are unable to undergo mitochondrial fusion, whereas cells lacking OPA1 do undergo mitochondrial OM fusion, but fail to complete the IM fusion.[65] Mitochondrial morphology can be rapidly affected by mitochondrial fission and fusion, thus, these morphologic changes of mitochondria can reflect the relative rates of fusion and fission. Surprisingly, different muscle fiber types display distinct patterns of mitochondrial dynamics. In fast-twitch muscle fibers, small block-like mitochondria are arranged in rows and columns, while in fibers from slow-twitch muscle, mitochondria are more elongated and interconnected to each other from multiple sarcomeres.[66] Furthermore, switching from glycolytic to oxidative muscle fiber promotes mitochondria elongation in parallel.[66] Given the distinct energy metabolic profiles of slow and fast fiber types, it is tempting to speculate that changes in mitochondrial dynamics adapt to match a change in fuel substrate preference.

Multiple studies support a critical role for mitochondrial fusion in skeletal muscle quality control. Skeletal muscle *Mfn2* KO mice display reduced mitochondrial respiration function, impaired muscle insulin signaling, and features of age-related sarcopenia.[67,68] Although the exact role of Mfn2 in ER-mitochondrial interactions is under debate,[69–73] notably, loss of MFN2 has been shown to activate an ER stress signaling in skeletal

muscle.[67] Remarkably, mice with targeted ablation of both *Mfn1* and *Mfn2* genes show a profound muscle atrophy phenotype.[74] Combined deficiency of *Mfn1* and *Mfn2* in skeletal muscle causes significant mitochondrial dysfunction, compensatory mitochondrial proliferation and mtDNA depletion as well. As expected, the muscle-specific *Mfn1/2* double-KO mice are exercise intolerant and have a higher post-exercise blood lactate level.[74] Transgenic and gene knockout approaches in mice have also been used to define the physiological roles of OPA1 in skeletal muscle. Two independent studies have shown that overexpression of OPA1 can improve muscle mitochondrial respiration function.[75,76] OPA1 transgenic mice are protected against denervation-induced muscle atrophy and the transgene expression rescues muscle loss in a model of myopathy caused by COX15 deletion in muscle.[75,76] In contrast to the gain-of-function models, muscle-specific KO of *Opa1* results in a severe detrimental phenotype including mitochondrial dysfunction, muscle loss and premature death.[77,78] Specifically, muscle-specific *Opa1* deletion in newborns is lethal, while acute tamoxifen-induced deletion of *Opa1* in 5-month-old mice leads to a precocious aging phenotype including metabolic derangement in multiple organs, a systemic inflammatory response and precocious epithelial senescence.[77] Interestingly, mice with a skeletal muscle-specific, tamoxifen-induced *Opa1* deficiency show an improved glucose tolerance and insulin sensitivity at basal level and in response to a HFD challenge despite reduce muscle mass, and the favorable metabolic phenotype is linked to muscle-derived FGF21.[77,78] The importance of mitochondrial fission in skeletal muscle has also been studied. Overexpression of dynamin related protein 1 (Drp1) in skeletal muscle induces muscle mass loss and decreased exercise performance.[79] Interestingly, similar to the *Mfn2* KO mice, manipulation of OPA1 or Drp1 in skeletal muscle also activates mitochondria-stress signals, as discussed below.[77–79] Taken together, these data clearly demonstrate that proper maintenance of mitochondria dynamics, i.e. the balance between fission and fusion, is necessary for optimal muscle mitochondrial function and fitness.

Mitochondrial proteolysis

Mitochondria adopt two main mechanisms for quality control, proteolysis and mitophagy, that respond to damage caused by oxidative stress, misfolded or damaged proteins, or defects in the electron transport chain. Mitochondrial proteases serve as the first line of quality-control mechanism against low degree of mitochondrial stress. Both ATP-dependent and ATP-independent mitochondrial proteases have been identified for selective clearance of the excess non-assembled, misfolded, or damaged proteins within mitochondria. The two ATP-independent proteases are mitochondrial inner membrane metalloprotease Atp23 homolog (ATP23) and serine protease HTRA2. There are four main ATP-dependent proteases comprising the ATPases associated with diverse cellular activities (AAA+) superfamily. The intermembrane AAA (i-AAA) member such as YME1L1, has a protease domain facing the intermembrane space. The membrane-bound AAA (m-AAA) protease faces the mitochondrial matrix and is comprised of homo- or heterohexamers of the *AFG3L2* and *SPG7* gene products. The other AAA+ proteases are the Lon protease homolog (LONP, encoded by the *LONP1* gene), and Clp protease proteolytic subunit (CLPP).[80] Approximately two thirds of the 1200 mitochondrial proteins reside in the matrix, thus the main matrix AAA proteases such as LONP and CLPP, serve as the major protein-folding homeostasis control mechanism in mitochondria.

Mutations in the main mitochondrial matrix proteases LONP and CLPP have been implicated in genetic diseases in human. For example, mutations in the human *LONP1* gene result in CODAS syndrome, a multisystem developmental disorder characterized by cerebral, ocular, dental, auricular, and skeletal anomalies.[81] Mutations in the human *CLPP* gene cause Perrault syndrome, a heterogeneous autosomal recessive disease characterized by sensorineural hearing loss and ovarian failure.[82] Both in vitro and in vivo studies have demonstrated that LONP and CLPP are key regulators of mitochondrial proteostasis.[83,84] Several proteins such as aconitase (ACO), cytochrome c oxidase subunit 4 isoform 1 (Cox4i1), steroidogenic acute regulatory protein (STAR), and transcription factor A (TFAM) have been identified as targets for degradation by LONP under basal or stress conditions.[80] Most interestingly, as discussed below, mitochondrial matrix proteases LONP and CLPP have been implicated in the mitochondrial unfolded protein response (UPRmt) and their expression is induced in response to UPRmt in mammalian cells.[85,86]

LONP is also essential for survival given the embryonic lethality of mouse with deletion of the *Lonp1* gene.[87] However, unlike the extensive studies of mitochondrial dynamics in skeletal muscle, there is no animal model of conditional tissue-specific LONP knockout. Therefore little is known about the contribution of mitochondrial matrix proteases to mitochondrial function and tissue homeostasis in skeletal muscle in vivo. Similarly, the function of CLPP in muscle is also not entirely clear. Homozygous deletion of the gene encoding CLPP in mice causes infertility, hearing loss, and growth retardation,[88] thus limiting the study of the role for CLPP in skeletal muscle. Taken together, although mitochondrial proteolysis has been implicated to be critical for maintenance of mitochondrial function, the causal link between the derangement of muscle mitochondrial proteostasis and physiological outcomes under normal and disease states remains unclear.

Skeletal muscle mitochondrial quality control through mitophagy

Emerging evidence demonstrates that mitophagy serves as a critical quality-control mechanism for selective targeting and removal of damaged or dysfunctional mitochondria.[89–92] Both ubiquitin-dependent and receptor-dependent mitophagy pathways such as those involving PINK1/Parkin, NIX/BNIP3, FUNDC1, BCL2L13, and PBH2 have been identified in mammals.[91–95] Elegant studies in cultured cells have demonstrated that these pathways engage the core autophagy machinery to activate mitochondrial clearance in response to various stress stimuli. Among those mitophagy mediators, the role of PINK1-Parkin signaling has been well studied. PINK1 mainly serves as a sensor for the mitochondrial polarization state. Under normal conditions, PINK1 is transported into the mitochondria for degradation by the serine protease presenilins-associated rhomboid-like protein (PARL). Upon acute mitochondrial stress, mitochondrial depolarization stabilizes PINK1, which phosphorylates MFN2 and subsequently recruits the E3 ubiquitin ligase Parkin onto mitochondria.[96] Parkin acts downstream of PINK1 to trigger selective autophagy of depolarized mitochondria.[91] Recent results demonstrate that Parkin is required for maintenance of baseline mitochondrial function in skeletal muscle and for exercise-induced increases in mitophagy flux.[97] However, in different stress conditions, mitophagy receptors such as NIX/BNIP3, FUNDC1, BCL2L13, and PBH2 have been shown to mediate the degradation of damaged mitochondrial independently of PINK1/Parkin, by interacting directly with LC3. For example, in response to hypoxia, the mitophagy receptor FUNDC1 is dephosphorylated to enhance its interaction with LC3 through a LC3-binding motif, thereby triggering mitophagy.[92,94,98] Loss of FUNDC1 in muscle leads to significantly reduced mitophagy flux, mitochondrial energetics and exercise performance.[99] Interestingly, however, muscle FUNDC1 deficiency alleviates HFD-induced obesity and improves systemic glucose homeostasis.[99] NIX and BNIP3 expression are also induced during hypoxia, likely promoting the clearance of unwanted mitochondria complementary to the FUNDC1 pathway.[90,92]

Although several pieces of evidence have suggested an important role for general autophagy or mitophagy in regulating

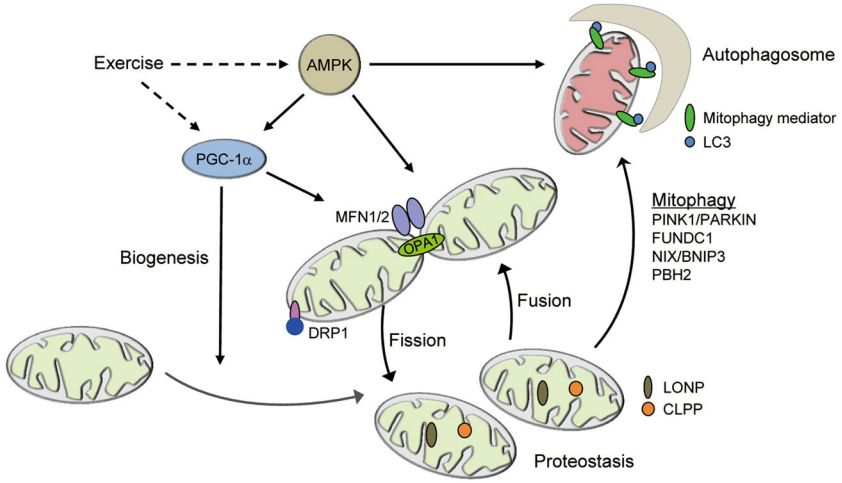

Fig. 2 Integration of mitochondrial quality control and biogenesis. Muscle mitochondria undergo extensive turnover and remodeling in response to a variety of physiological stimuli. PGC-1α activates mitochondrial biogenesis. Mitochondrial fission is mediated by DRP1 and its receptors. Mitochondrial fusion is mediated by MFN1/2 for the fusion of the outer membrane and OPA1 for the inner membranes. The main mitochondria matrix proteases such as LONP and CLPP maintain mitochondrial proteostasis and regulate mitochondrial function. The damaged or dysfunctional mitochondria are cleared via mitophagy. Mitophagy is mediated by mitophagy mediators such as PINK1/PARKIN, FUNDC1, NIX/BNIP3, and PBH2 in mammals. Exercise coordinately regulates mitochondrial biogenesis, mitochondrial dynamics, and mitochondrial quality-control program via AMPK and the PGC-1α. Mfn1/2 mitofusin 1/2, Drp1 dynamin-related protein 1, OPA1 optic atrophy 1, LONP Lon peptidase 1, CLPP caseinolytic mitochondrial matrix peptidase proteolytic subunit, PINK1 PTEN-induced putative kinase 1, FUNDC1 FUN14 domain containing 1, Bnip3 BCL2 interacting protein 3

muscle mass and metabolism, our understanding of the in vivo physiological relevance and mechanisms of mitophagy in skeletal muscle remains largely incomplete. Notably, previous studies suggested that finely tuned regulation of autophagy flux is necessary for maintaining muscle metabolic homeostasis and quality. Genetic manipulations that inhibit muscle autophagy/mitophagy lead to conflicting results when examining HFD-induced glucose intolerance.[99–101] Whether and how the various mitophagy pathways contribute to the impact of autophagy on muscle metabolism is unclear. An important future goal is to establish the metabolic impact of the divergent mitophagy pathways in skeletal muscle under physiological and pathological conditions.

Integration of mitochondrial quality control and biogenesis

Accumulating evidence suggests that there is an integrated signaling mechanism that coordinately regulates mitochondrial biogenesis, mitochondrial dynamics, and mitochondrial quality control (Fig. 2). An interesting interconnection between muscle mitochondrial biogenesis and dynamics was discovered in PGC-1α/β double KO mice. As described above, combined deficiency of PGC-1α/β in skeletal muscle results in a dramatic exercise performance deficit related to a severely impaired mitochondrial function.[37] Mitochondria from PGC-1α/β double KO muscle show significant heterogeneity in size, including many small, fragmented mitochondria juxtaposed to elongated, thin mitochondria, indicative of a defect in mitochondrial dynamics as well as biogenesis.[37] The levels of several proteins critical for mitochondrial fusion and fission were also downregulated in the PGC-1α/β-deficient muscle, including MFN1, MFN2, and Drp1.[37] Mechanistically, PGC-1α regulates MFN1 and MFN2 expression through ERRα.[102,103] These results support a direct link between the transcriptional regulation of mitochondrial biogenesis and mitochondrial dynamics. PGC-1α has also been recently shown to regulate mitophagy in a denervation-induced muscle atrophy model as well as acute exercise.[104,105] Given that nuclear receptor PPARα is found to bind to a broad array of autophagy gene promoters in liver,[106] it is possible that PGC-1α signaling may also regulate expression of autophagy genes in skeletal muscle by co-activating nuclear receptors. Taken together, these results demonstrate a PGC-1α–mediated mechanism for the coordination of mitochondrial biogenesis and quality control in skeletal muscle.

There is also evidence to suggest a close link between mitochondrial dynamics and mitophagy. Fusion between healthy and damaged mitochondria is known to dilute the damaged organelles into the healthy mitochondrial network, thus maintaining overall mitochondrial fitness.[107] In contrast, mitochondrial fragmentation allows the segregation of damaged components from the mitochondrial network, triggering the mitophagy process.[108] Consistently, defective mitochondrial fusion in *Mfn2* KO skeletal muscle cells leads to activation of mitophagy.[68]

Direct links between mitophagy and mitochondrial biogenesis may also exist. Expression of a MFN2 mutant lacking PINK1 phosphorylation sites prevents induction of PGC-1α and mitochondrial biogenesis in the postnatal heart.[109] One potential mechanism linking mitophagy to mitochondrial biogenesis involves the Parkin-interacting substrate (PARIS).[110] PARIS regulates mitochondrial biogenesis by transcriptionally repressing PGC-1α, likely through binding of the IRS within the PGC-1α promoter region. Phosphorylation by PINK1 primes PARIS for ubiquitination by Parkin resulting in the degradation of PARIS and subsequent de-repression and activation of PGC-1α expression (Fig. 3).[111] In skeletal muscle, recent results demonstrate that loss of Parkin results in an increase in nuclear-localized PARIS and a subsequent decrease in PGC-1α following exercise.[112] Although these regulating systems are likely active in skeletal muscle, further investigation is needed to determine the role of these systems in the regulation of mitochondrial quality control and biogenesis.

Extensive studies have supported an important role of AMPK in orchestrating mitochondrial biogenesis, dynamics and mitochondrial quality control. Firstly, as described above, AMPK can activate mitochondrial biogenesis through a PGC-1α dependent mechanism.[43] AMPK activation in skeletal muscle is sufficient to drive fatty acid oxidation and mitochondrial biogenesis. In addition, AMPK

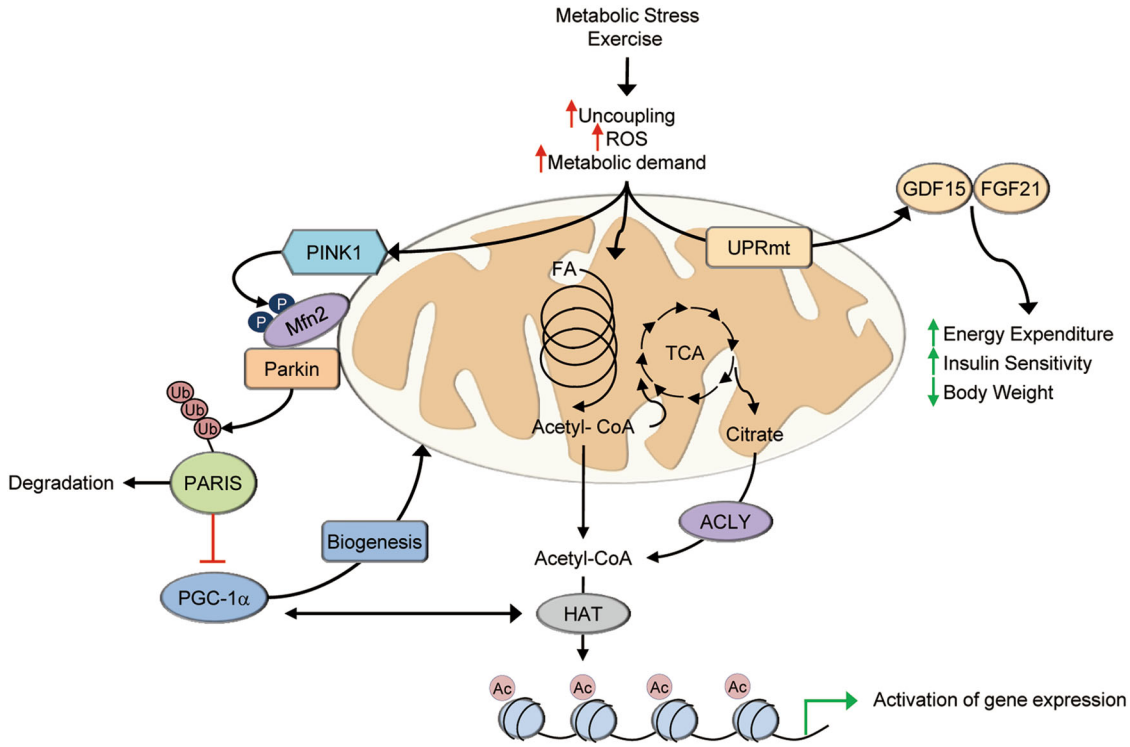

Fig. 3 Skeletal muscle mitochondria serve as cellular sensors of metabolic demand and stress. Various forms of metabolic stress including exercise triggers responses in muscle mitochondria that result in signals to other cellular compartments or tissues. Increased mitophagy is integrated with biogenesis through activation of PGC-1α, either directly or through mechanisms such as PARIS. Activation of gene expression by PGC-1a also occurs in cooperation with histone acetyltransferases (HAT). Acetyl-CoA generated by increased mitochondrial respiration can donate acetyl groups for histone modifications. Paracrine or endocrine signals can also be generated, at least in part, by activation of the mitochondrial unfolded protein response (UPRmt) that leads to increases in GDF15 and FGF21 production and secretion. PARIS Parkin interacting substrate, ACLY ATP citrate lyase, HAT histone acetyltransferase, Ac acetyl, Ub ubiquitin, FA fatty acid, UPRmt mitochondrial unfolded protein response

has been shown to promote mitochondrial fission by direct phosphorylation of mitochondrial fission factor (MFF), a receptor for Drp1.[113] Moreover, AMPK is able to directly phosphorylate and activate the unc-51 like autophagy activating kinase 1 (ULK1),[114] triggering the autophagic cascade and mitophagy. More recently, it has been shown that exercise-induced mitophagy in skeletal muscle depends on AMPK-ULK1 signaling.[115] Together, in this fashion, AMPK serves as a critical regulator of muscle mitochondria function through coordinate regulation of mitochondrial biogenesis and mitophagy. Consistent with the central role of AMPK in maintenance of muscle mitochondrial function, muscle-specific AMPK β1β2 double-KO in mice results in significantly impaired exercise performance related to reduced mitochondrial content and function.[116]

Exercise training is well known to enhance muscle mitochondrial function, leading to improvements in whole-body metabolic homeostasis.[2] Exercise activates signaling networks that coordinately control mitochondrial remodeling, including mitochondrial biogenesis, dynamics, and mitophagy. Given that AMPK and PGC-1α are induced by exercise training, it is tempting to speculate that AMPK/PGC-1α signaling may orchestrate the activity of multiple pathways in response to exercise to control mitochondrial biogenesis, dynamics and quality control in skeletal muscle. The actions of AMPK and PGC-1α on mitochondrial remodeling could lead to a net effect of replacing existing unhealthy mitochondria with new functional mitochondria. This may also be necessary for remodeling of mitochondria to a more oxidative phenotype that is known to occur following exercise. However, future studies are needed to fully understand the coordinate control of mitochondrial biogenesis and quality that define muscle fitness.

MUSCLE MITOCHONDRIA AS A METABOLIC SENSOR HUB IN RESPONSE TO PHYSIOLOGICAL STIMULI

Mitochondria-to-nucleus communication (retrograde response)

Increasing evidence suggests that mitochondria are not only the powerhouse of the cell that generates ATP but also function as a central node for cellular signaling. Evidence is emerging that mitochondria can communicate to the nucleus (retrograde) to alter the transcription of nuclear genes in response to various cellular stresses.[117] Among these mitochondrial retrograde responses, the mitochondrial unfolded protein response (UPRmt) has been the best studied. The UPRmt is provoked when there is an accumulation of unassembled mitochondrial respiratory proteins triggering an unknown mechanism to communicate with the nucleus, leading to the induction of genes involved in maintaining mitochondrial protein-folding homeostasis.[85,118,119] Although originally identified in mammalian cells, UPRmt signaling has been extensively described in *Caenorhabditis elegans*. The transcription factor ATFS-1 is responsible for the UPRmt response in *C. elegans*. Under basal conditions, the ATFS-1 is imported into the mitochondrial matrix for degradation by the Lon protease. Multiple forms of mitochondrial stresses including accumulation of unfolded proteins, OXPHOS defects, accumulation of ROS, or mitochondrial–nuclear protein imbalance can lead to reduced mitochondrial import of ATFS-1. This results in accumulation of ATFS-1 in the cytosol and its translocation to the nucleus with consequent activation of a broad array of stress response genes to maintain mitochondrial function.[120] Activation of the UPRmt response by various forms of mitochondrial stress has also been validated in mammalian cells. Interestingly, the mitochondrial matrix proteases LONP and CLPP have been linked to the mammalian UPRmt and their expression is induced in response

to unfolded protein stress.[85,121] Recent studies conducted in *C. elegans* have also demonstrated that UPRmt can trigger a non-cell-autonomous mitochondrial regulatory pathway that has profound effects on aging and metabolism.[122] In addition to UPRmt, recent studies have also suggested that intermediary metabolites derived from mitochondrial metabolism signal to the nucleus resulting in epigenetic modifications to regulate gene expression (reviewed in ref.[123]). For example, acetyl-CoA can be generated from citrate, a product of the mitochondrial TCA cycle, through the action of ATP-citrate lyase (ACLY), as well as from mitochondrial FAO, providing a source of acetyl groups for histone acetylation (Fig. 3).[124,125] Interestingly, increases in histone acetylation by fatty acids were associated with activation of genes involved in fatty acid utilization suggesting a specificity to this pathway.[125] Similarly, *S*-adenosylmethionine is an essential substrate for histone or DNA methylation.[126]

Muscle mitohormesis

Skeletal muscle comprises ~40% of total body mass and is the largest consumer of glucose and fatty acids, via mitochondrial oxidation. As such, mitochondria function in skeletal muscle is a critical determinant of systemic metabolic homeostasis. Numerous studies in mice, and in humans, have shown a close association between derangements in muscle mitochondrial function and the development of insulin resistance.[127,128] As discussed further below, evidence suggests that mitochondrial dysfunction in skeletal muscle results in a reduction of FAO, leading to the accumulation of various lipid species and derangements in insulin signaling.[128–130] However, other studies have shown that mice with defective mitochondrial function in skeletal muscle are more insulin sensitive and protected against diet-induced obesity. For example, muscle-specific deletion of *Aifm1* (apoptosis inducing factor mitochondria associated 1) results in impaired mitochondrial oxidative activity but protection against HFD-induced obesity and insulin resistance.[131] Likewise, mice with targeted ablation of *Tfam* in skeletal muscle also exhibit enhanced glucose tolerance, despite reduced mitochondrial DNA content and function in skeletal muscle.[132] In addition, defective autophagy in muscle-specific *Atg7* KO mice leads to impaired muscle mitochondrial function but resistance to HFD-induced obesity with improved systemic insulin sensitivity and glucose tolerance.[101] Mice lacking FUNDC1 in muscle show mitophagy defect but are protected against chronic HFD-induced obesity and insulin resistance despite reduced muscle mitochondrial energetics.[99] Acute muscle *Opa1* deficiency in 4-week-old mice also causes mitochondrial defects but protection against HFD-induced obesity and insulin resistance.[78] Therefore, whereas mitochondrial dysfunction may contribute to insulin resistance, it is not a pre-requisite and depending on the defect, may actually lead to insulin sensitivity. Some data suggest that the seemingly contradictory phenotypes may be related to a non-cell-autonomous role of the muscle mitochondrial stress response.[78,99,101]

The observation that perturbations in muscle mitochondrial function and quality control influence systemic metabolism suggests the intriguing possibility that this response may involve extracellular signals. This notion is consistent with the concept of mitohormesis, an adaptive response triggered by mild mitochondrial stress that was originally postulated based on observations in *C. elegans*.[133,134] The concept of "mitokines" (soluble factors that can be released from cells with stressed mitochondria) was put forth to explain systemic metabolic benefits in the context of mitochondrial stress in skeletal muscle (Fig. 3). In mammals, the hormones FGF21 and GDF15, and mitochondria-derived peptides have been described as putative mitokines (Fig. 3).[99,101,135,136] FGF21 has been shown to be a direct ATF4 target downstream of UPRmt,[99,101] while GDF15 secretion is induced in a CHOP-dependent manner during UPRmt.[135] The identification of FGF21 as a mitokine is of interest given its well known favorable effect on systemic metabolic control.[137–139] In multiple mouse models of mitochondrial defects and in human patients, skeletal muscle secretes FGF21 into circulation to exert an endocrine effect.[78,99,101,140,141] GDF15 has also been shown to be induced and released from skeletal muscle upon multiple forms of mitochondrial stress.[121,135] Similar to FGF21, pharmacological administration of recombinant GDF15 leads to many effects including decreased food intake and reduced body weight, improved insulin sensitivity, and increased energy expenditure in obese mice.[135] Other potential mitokines have been identified including a short peptide encoded by the mitochondrial open-reading-frame of the 12S rRNA-c (MOTS-c).[136] MOTS-c also exerts beneficial effects on obesity and insulin resistance.

These data taken together provide significant evidence that muscle mitochondria are not merely the "powerhouse of the cell" but act as cellular sensors of increased energy demand or other cellular stresses and subsequently signal to other cellular compartments such as the nucleus or other organs in the body (Fig. 3). These signals influence gene expression and epigenomic status of the cell in addition to direct effects on the mitochondria, e.g. mitophagy. These responses can also generate a mitohormesis signal that results in beneficial effects for metabolic diseases. It is also tempting to speculate that muscle mitochondria may function as an early checkpoint prior to the propagation of energy metabolic stress. This raises several interesting questions: (1) Are there other mitokines that may mediate muscle mitochondrial communications? (2) Although a few mitokines have been identified, what are the mechanism by which the muscle UPRmt or other pathways trigger the expression of such factors? (3) Will it be possible to exploit such muscle mitochondrial signals as treatment strategies?

MUSCLE MITOCHONDRIAL REMODELING IN DISEASE STATES

Muscular dystrophy

Duchenne muscular dystrophy (DMD), caused by mutations in the X-linked gene dystrophin, is the most common and severe form of muscular dystrophy and remains incurable to date.[142–144] Individuals with DMD display muscle weakness and increased muscle exhaustion. Interestingly, fast glycolytic myofibers are more sensitive to the dystrophic pathology in DMD patients as well as in the preclinical mdx mouse model of DMD.[145] Previous studies have shown mitochondrial dysfunction in DMD muscle,[146,147] contributing to a vicious cycle and further promoting the progression of muscular dystrophy. Conversely, numerous studies have demonstrated that enhancing the muscle mitochondrial functional capacity in the mdx mouse model of DMD may prevent or ameliorate dystrophic pathology. For example, overexpression of PGC-1α specifically in skeletal muscle was shown to improve muscular dystrophy.[148,149] In addition, activation of PGC-1α through upstream signaling pathways such as AMPK or Sirt1 also prevents the hallmarks of muscular dystrophy in mdx mice.[150–152] Recent work has also demonstrated that promoting autophagy may have therapeutic benefits in muscular dystrophy.[153,154] It is certainly possible that muscle function could be enhanced by promoting the clearance of defective mitochondria, contributing to a favorable impact on the muscular dystrophy phenotype. Interestingly, direct manipulation of miR-499 is able to restore the oxidative muscle mitochondrial program and prevent the hallmarks of DMD, including serum CK release and diminished exercise capacity in mdx mice.[64] In addition, *Fnip1* knockout mice on an mdx genetic background have also been shown to be protected against muscular dystrophy.[63] Notably, activation of miR-499 directly inhibits FNIP1, leading to activation of PGC-1α signaling in skeletal muscle.[64] As many of the routes to muscular dystrophy rescue in mdx mice converge on the activation of PGC-1α, this provides intriguing evidence that PGC-1α and mitochondrial energy metabolism are central to the pathogenesis of

muscular dystrophy and suggests a therapeutic approach for DMD.

Dysregulation of mitochondrial energetics during disuse atrophy

Skeletal muscle mass is controlled by a fine balance between protein synthesis and degradation pathways (reviewed in ref.[155]). This balance is sensitive to changes in physical activity levels. For instance, decreased activity as a result of bed rest, chronic illness or even microgravity experienced during space flight results in a loss of muscle mass. Prolonged disuse can produce a loss of approximately 0.5–0.6% of skeletal mass per day.[156] Muscle strength and the intrinsic contractile capacity of the myofiber are also decreased with disuse or immobility.[157,158] Elderly individuals are particularly susceptible to disuse atrophy. Studies have shown that older individuals do not fully recover muscle function following disuse.[159,160] This can lead to a vicious cycle of muscle atrophy followed by incomplete recovery and subsequent debilitating events or illnesses that exacerbate immobility and reduce independence. Recent studies have shown that adverse mitochondrial remodeling occurs in muscle during disuse atrophy. For example, 1 week of strict bed rest in healthy young adults results in diminished OXPHOS protein expression and citrate synthase activity.[161] Multiple preclinical and clinical studies have now demonstrated that a reduction in PGC-1α expression accompanies these changes in mitochondria in various forms of muscle atrophy.[162–165] In addition, a protective role for preserved mitochondrial function during muscle atrophy is supported by numerous preclinical studies. Overexpression of PGC-1α or PGC-1β prevents or reduces muscle atrophy in various experimental conditions such as hindlimb unloading, denervation and heart failure.[165–169] Although the precise mechanism involved in this cross-talk is not fully understood, studies have shown that PGC-1 inhibits FoxO3-mediated induction of the ubiquitin ligases, muscle ring-finger 1 (MuRF1) and atrogin-1, without affecting protein synthesis pathways.[165,168]

A decline in mitochondrial function in aging and sarcopenia

Sarcopenia is defined as the steady decline in muscle mass and function that occurs with aging. Numerous factors contribute to the decline in muscle structure and function including reduced rates of protein synthesis and increased proteolysis, insulin resistance, changes in the neuromuscular junction, etc. A number of studies have shown a decline in oxidative capacity and mitochondrial content in aging muscle.[170–172] Not surprisingly, both PGC-1α mRNA and protein levels are reduced in aged muscles.[172–175] More recently, changes in mitochondrial function are recognized as a contributing factor in muscle performance in sarcopenia. For instance, maximal mitochondrial ATP production (ATPmax), as determined by measurements of phosphocreatine recovery using ^{31}P magnetic resonance spectroscopy (MRS), is negatively correlated with fatigability in a walking test in older adults.[176] ATPmax and mitochondrial respiration rates measured in permeabilized muscle fibers also correlate with walking speed in older adults.[177,178] Walking speed and function is a particularly relevant readout as this is directly related to functional independence in the elderly.

Animal studies have also implicated dysregulation of mitochondrial dynamics in the progression of sarcopenia during aging. During aging, increased reactive oxygen species (ROS) production causes damage to mitochondrial proteins.[179] The expression levels of many autophagy and mitophagy components such as Atg7, p62, beclin1, Bnip3, Parkin, and LAMP2 are known to decline with age.[180–182] Interestingly, muscle-specific *Atg7* knockout mice display many features of aging including muscle loss and weakness suggesting a possible link between impaired autophagy and mitophagy with sarcopenia.[183]

Targeting mitochondria as a therapeutic approach for muscle disease

The abundant data demonstrating deficits in mitochondrial function and content in a number of muscle diseases make therapeutic targeting of these pathways attractive. These discoveries have popularized the somewhat fanciful notion of "exercise in a pill" for muscle and metabolic diseases. Regardless of whether this is actually achievable or not, certain aspects of this concept are attractive as therapeutic strategies and certain molecules have shown promise in preclinical proof-of-concept studies. Several approaches have been shown to increase mitochondrial function and oxidative capacity in muscle. For instance, PPARδ activating ligands were shown to synergize with exercise and improve running endurance.[17] PPARδ ligands are now progressing into the clinic for treating DMD. Recently, there has also been intense interest in activation of the sirtuin pathway as a mechanism for boosting mitochondrial function and oxidative metabolism. The primary means to achieve this has been the use of NAD^+ analogs and precursors such as nicotinamide riboside (NR) to activate sirtuin 1. NR supplementation in mice was recently shown to increase muscle NAD^+ levels and activate expression of mitochondrial energy metabolic genes.[184] Other studies have also shown that NR enhances muscle energetics and function in the mdx model of DMD.[185] An increase in mitochondrial respiration has been demonstrated in permeabilized skeletal muscle fibers from human subjects following 2 weeks of supplementation with acipimox, another NAD^+ precursor.[186] Although a corresponding increase in muscle NAD^+ levels was not reported, this provides further evidence for the promise of targeting this pathway to boost muscle mitochondrial oxidative metabolism. These data warrant further investigation of these agents in conditions of impaired muscle function including DMD or other muscular dystrophies, disuse atrophy, and sarcopenia.

CONCLUSIONS AND PERSPECTIVES

Mitochondria are highly dynamic organelles that require continuous surveillance to maintain their functional integrity. A complex regulatory network is required to orchestrate skeletal muscle mitochondrial biogenesis, respiratory function, and maintenance in response to exercise and in disease states. It is clear that these mitochondrial quality control mechanisms are essential for maintaining skeletal muscle metabolic homeostasis. This is particularly important to maintaining muscle function in response to a myriad of physiological stressors such as changes in physical activity, altered fuel substrate availability, and even aging. Mechanisms have evolved to regulate and coordinate mitochondrial biogenesis, proteolysis, and mitophagy to maintain mitochondrial health and function. Although several pathways of proteolysis and mitophagy have been identified, it will be important to further understand how these quality control pathways contribute to the maintenance of muscle mitochondrial function under physiological and pathological conditions. Importantly, mitochondrial quality control pathways do not exist independently. Mitochondrial biogenesis, dynamics, proteostasis, and mitophagy are highly interconnected and regulated by a tightly linked regulatory network. In this way, the skeletal myocyte coordinates biogenesis of healthy mitochondria with replacement of damaged mitochondria to maintain optimum muscle function.

Mitochondria also communicate with the endoplasmic reticulum, lysosomes, and nucleus to relay information regarding energy metabolic status and stress. These communications may occur in the form of direct contact as in the case of mitophagy or through the generation of certain metabolites that signal to other organelles such as the nucleus to influence gene expression. Finally, mitochondria have developed non-cell-autonomous mechanisms to communicate on an organism-wide basis.

Messengers for this type of communication include secreted myokines or mitokines.

The progress made in understanding the role of mitochondria in skeletal muscle health has created a desire to develop therapeutics directed at mitochondria. Some of these proposed therapies could be touted as "exercise mimetics"; however, one should treat with caution the notion that a single therapeutic is capable of mimicking the multitude of effects produced by exercise. Further, increasing mitochondrial function or energy metabolic capacity through a single focused target or without a corresponding increase in demand may produce untoward and unintended consequences. Nonetheless, despite these caveats, the importance of mitochondrial quality to muscle and cardiovascular/metabolic fitness justifies pursuit of therapies aimed at mitochondria for many skeletal muscle or metabolic diseases.

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ADDITIONAL INFORMATION

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