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The Secret Messages between Mitochondria and Nucleus in Muscle Cell Biology

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Abstract

Over two thousand proteins are found in the mitochondrial compartment but the mitochondrial genome codes for only 13 proteins. The majority of mitochondrial proteins are products of nuclear genes and are synthesized in the cytosol, then translocated into the mitochondria. Most of the subunits of the five respiratory chain complexes in the inner mitochondrial membrane, which generate a proton gradient across the membrane and produce ATP, are encoded by nuclear genes. Therefore, it is quite clear that import of nuclear-encoded proteins into the mitochondria is essential for mitochondrial function. Nuclear to mitochondrial communication is well studied. However, there is another arm to this communication, mitochondria to nucleus retrograde signaling. This plays an important role in the maintenance of cellular homeostasis, and is less well studied. Several transcription factors, including Sp1, SIRT3 and GSP2, are activated by altered mitochondrial function. These activated transcription factors then translocate to the nucleus. Based on the mitochondrially generated molecular signal, nuclear genes are targeted, which alters transcription of nuclear genes that code for mitochondrial proteins. This review article will mainly focus on this interactive and bi-directional communication between mitochondria and nucleus, and how this communication plays a significant role in muscle cell biology.

Introduction

Mitochondria are considered as a center of integration of several key cellular processes, such as cellular growth, cellular development, cell survival and cell death [1–3]. A major function of mitochondria is the production of ATP through oxidative phosphorylation (OXPHOS), but mitochondria also play a critical role in many other metabolic functions, which include fatty acid oxidation, calcium signaling, assembly of iron-sulfur clusters in proteins, heme biosynthesis, and amino acid metabolism [4–6]. As multitasking stress sensors, mitochondria integrate multiple metabolic pathways. Critical metabolic regulators, such as NADH/NAD⁺, ATP/ADP, ATP/AMP, succinate/ α -ketoglutarate, etc. are set by the mitochondria [7].

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Mitochondria are maternally inherited, and derived from a bacterial ancestor, with its own circular DNA (mtDNA) which is about ~16.5 kb long [8]. Although mtDNA encodes 22 tRNAs, 2 rRNAs and 13 subunits of the OXPHOS genes [9], there are more than 2000 proteins expressed in the mitochondria. Most of these proteins are encoded by the nuclear genome and ultimately are imported into the mitochondria [10]. Therefore, mitochondrial function is dependent on nuclear gene transcription. Based on cellular requirements, this anterograde process can decrease or increase mitochondrial activity, and can promote mitochondrial biogenesis. Conversely, mitochondria can also generate retrograde signals to the nucleus to alter nuclear gene expression, which can modify cellular function and reprogram cell metabolism. The integration of these anterograde (from nucleus to mitochondria) and retrograde (from mitochondria to nucleus) signals is also known as mito-nuclear communication [11]. Mito-nuclear communication is bi-directional, integrating both anterograde and retrograde signaling. This mito-nuclear communication plays an indispensable role to maintain cellular homeostasis.

Mitochondrial dysfunction is associated with many diseases and it is estimated that 1 in every 5000 individuals is affected by a mitochondrial disorder [12]. Several pathological conditions, which include MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome), neurodegenerative diseases such as Alzheimer and Parkinson syndromes, muscular disorders, cardiomyopathy, diabetes, and cancer can be caused by mitochondrial dysfunction [13–18]. The important role of mitochondrial dysfunction in various diseases has led to intense research into the role of mito-nuclear signaling to develop potential therapeutic interventions [19–21]. In this review, we will focus on different factors and pathways that can alter the communication between the mitochondria and the nucleus.

Anterograde signals

The aim of nuclear-to-mitochondria anterograde signals is to achieve fine-tuned mitochondrial bioenergetics and functional population of mitochondria. These molecular pathways can modulate mitochondrial activity, copy number, status, and morphology. Thus, anterograde signals can promote four main mitochondrial events, such as biogenesis, mitophagy, fusion/fission and movement. Depending on the cellular requirements, anterograde signals can also promote cellular growth and cell survival [22–25].

Anterograde signals regulate the expression of nuclear gene encoded mitochondrial proteins through some important transcription factors, e.g. Nuclear Respiratory Factor 1 (NRF1) and GA-Binding Protein α (GABP α ; also known as NRF2 α) [26–28]. Other nuclear receptors, such as Peroxisome Proliferator-Activated Receptors (PPARs) and the Estrogen-Related Receptors (ERRs), can also activate the expression of nuclear encoded mitochondrial proteins [29, 30]. For example, PPAR δ , stimulates the expression of enzymes involved in mitochondrial fatty acid oxidation; and ERRs (α , β and γ) regulate the tricarboxylic acid (TCA) cycle, OXPHOS and fatty acid oxidation through alterations in nuclear encoded mitochondrial protein expression [31, 32]. Transcription factors are often coordinately regulated by transcriptional co-activators or co-repressors to precisely control gene expression [33]. To induce mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma coactivator 1-co-activator 1 (PGC-1) α , β and the PGC-related co-activator

(PRC) activate transcription factors such as NRF, ERR and PPAR [34–36]. Alternatively, co-repressors such as nuclear receptor co-repressor 1 (NCoR1), receptor-interacting protein 140, and thyroid hormone receptors (SMRT) can inhibit transcription factor activity by directly binding at the interaction domains [37–39].

Part of the anterograde response serves to maintain mitochondrial bioenergetics by controlling metabolites produced by the mitochondria. Under different physiological conditions, the cell triggers a compensatory anterograde response when indices of energetic balance change, such as ATP/AMP, NAD^+/NADH , and acetyl-CoA [40]. Important metabolic sensors include AMP-activated Protein Kinase (AMPK) and Sirtuin 1 (SIRT1). The AMP/ATP ratio controls the activation of AMPK signaling, and AMPK activation stimulates metabolic pathways that affect the AMP/ATP ratio. SIRT1 on the other hand is regulated by the cellular levels of NAD^+ [41–43]. Furthermore, NAD^+ is a substrate for two other enzymes families, the poly ADP ribose polymerase (PARP) family, and the SIRT family of NAD^+ -dependent deacetylases (SIRT), that play a critical role in the DNA repair response [44–48]. SIRT1, one of the key SIRT proteins, and PGC-1 α have been shown to activate anterograde responses. It has been shown that nuclear stress activates poly (ADP-ribose) polymerase (PARP) 1 and 2, which represses mitochondrial function by depleting cellular NAD^+ levels. This results in the inhibition of SIRT1 activity, which inhibits the PGC-1 α program that induces mitochondrial biogenesis [49].

Changes in inner mitochondrial membrane potential (Ψ_m) and in mitochondrial matrix Ca^{2+} levels ($[\text{Ca}^{2+}]_m$) influence the cytoplasmic NAD^+/NADH ratio. When matrix Ca^{2+} levels rise, production of NADH in the mitochondrial matrix is accelerated, which is ultimately shuttled to the cytoplasm and alters the cytosolic NAD^+/NADH ratio [50–52]. This altered NAD^+/NADH ratio affects the NAD^+ interaction with the SIRT family, which ultimately influences Ca^{2+} influx and can provoke mitochondrial dysfunction [51]. Canto *et al.* [53], has shown that a precursor of NAD^+ can restore NAD^+ levels and activate the anterograde response, involving the SIRT1–PGC-1 α pathway.

The transcription factor MEF2 (Myocyte Enhancing Factor 2) has been described as a regulator of genes, such as glucose transporter 4 (GLUT4) [54], troponin I type 1 (a component of slow muscle fibers) [55] and PGC-1 α [56] in skeletal muscle. However, MEF2 also appears to have mitochondrial functions. MEF2 can regulate the NADH dehydrogenase 6 (ND6) gene as well as activating the gene product ND6, which is crucial for function of complex I of the ETC [57, 58]. MEF2 is a target of mitochondrial apoptotic caspases and blocking MEF2 function in mitochondria decreases complex I activity, increases cellular hydrogen peroxide levels and reduces ATP production [58].

Retrograde signals

To maintain cellular homeostasis, mitochondria constantly send molecular signals to the nucleus (retrograde signaling), reflecting metabolic status and mitochondrial activity. Cellular stress can alter retrograde signals, which leads to cellular adaptation or death. Mitochondria generate a wide range of retrograde signals that alter expression of nuclear genes involved in metabolic reprogramming or stress defense. The retrograde signals can

also be considered as a complementary mechanism to the mitochondrial quality control system [59].

In 1987, Parikh *et al.*, [60] identified in yeast a communication pathway from the mitochondria to the nuclear genome. However, until 1991, the identity of the molecular mechanism that can initiate the retrograde response was unknown. Liao and co-workers [61] were the first to identify CIT2, which mediates the retrograde response. CIT2 is a peroxisomal citrate synthase. Other genes, such as RTG1p, RTG2p and RTG3p, positively regulate retrograde responses [62, 63]. On the other hand, genes like *Lst8p* [64], *Mks1* [65–67], *Bmh1p*, and *Bmh2p* negatively regulate retrograde responses [68]. Both RTG1 and RTG3 genes activate transcription of several transcription factors by directly binding to a specific promoter region (GTCAC) denoted R box. RTG3p partial dephosphorylation and RTG3p-RTG1p complex nuclear translocation can facilitate RTG1p/RTG3p binding to the GTCAC region of the promoter region of transcription factors [69]. A proximal sensor of mitochondrial dysfunction, RTG2p, acts upstream of the Rtg1p/Rtg3p transcriptional complex [69]. The RTG pathway can activate various important genes, which includes the citric acid cycle genes CIT1, ACo1, IDH1, and IDH2. Thus, the RTG pathway can compensate for mitochondrial dysfunction by increasing citric acid cycle activity [70]. Among the proposed the signaling molecules that can regulate the RTG pathway is glutamine [71], glutamate [70], and ammonium [72].

Another identified pathway, which is independent of the RTG pathway, that can also be activated under conditions of energetic stress, is the TOR signaling pathway [73]. In yeast, *Lst8p* has been identified as a positive regulator of TOR kinase complexes [73]. There are two types of TOR kinase complexes: TORC1, which is sensitive to rapamycin, and TORC2, which is not [74]. Both TOR kinase complexes have homologous genes in mammals (mTOR), indicating evolutionarily conserved functions [75, 76]. TORC1 positively regulates a variety of anabolic processes, which include ribosome biogenesis and protein translation; whereas, TORC1 has been demonstrated to inhibit catabolic processes such as autophagy [77]. TORC2 is less study than TORC1 but some works indicated that TORC2 has cell survival functions, proliferation as well as a role in cytoskeleton organization and polarity [78].

SIRT2, a mitochondrial SIRT family member, can also trigger the retrograde response in yeast. The SIRT2 pathway prevents abnormal histone deacetylation and reprograms cellular metabolism, which improves protein homeostasis by regulating protein synthesis [79, 80]. The cellular energetic stress caused by mitochondrial dysfunction can induce the SIRT2 induced retrograde response, which results in alteration of protein transcription involved in metabolic pathways [69]. In mammalian cells it has been observed that during energetic stress, mitochondrial retrograde signaling is facilitated by the inhibition of mTOR activity [81].

In *C. elegans*, it has been demonstrated that mutations in the mitochondrial electron transport chain (ETC) genes can generate mitochondrial stress, which secondarily activates AMPK subunit $\alpha 2$ [82]. Activation of AMPK subunit $\alpha 2$ has compensatory effects on cellular energetics [83]. When mitochondrial stress is created by inhibition of the TCA

cycle, mitochondria can trigger a retrograde response through activation of late-cycle glyoxy genes, such as *gei-7* [84].

In mammalian cells, the retrograde response has been largely related to mTOR and AMPK signaling. Similar to yeast, in mammalian cells the AMPK pathway is activated mainly by an increase in the AMP/ATP ratio [85], promoting the activation of PGC-1 α . PGC-1 α stimulates cellular metabolism and mitochondrial biogenesis [85]. Other cellular stresses, such as glucose deprivation, ischemia, hypoxia, oxidative stress, inhibitors of the tricarboxylic acid cycle, inhibitors of the respiratory chain, inhibitors of the mitochondrial ATP synthase, and hyperosmotic stress, can activate AMPK signaling [86–88]. AMPK is also involved in the mitochondrial quality control system, which regulates mitochondrial dynamics and induces mitophagy [89].

As we mentioned before, the ratio of NAD⁺/NADH in the mitochondria may affect the activity of deacetylases SIRT3, and can also regulate the retrograde response. SIRT3 is expressed in two forms, a ~44-kDa long form and a ~28-kDa short form, that was localized exclusively in mitochondria. In liver it has been seen that the fasting or calorie restriction triggered upregulation of SIRT3, and this promotes mitochondrial biogenesis, fatty acid oxidation, and also activation of the urea cycle and ketogenesis [90]. Sundarezan *et al.* show that during stress, SIRT3 levels are increased not only in mitochondria but also in the nuclei of cardiomyocytes, which contributes to SIRT3 signaling. In addition they identified Ku70, a nuclear protein, as a new target of SIRT3. SIRT3 physically binds to Ku 70 and deacetylates it, and this promotes interaction of Ku70 with the proapoptotic protein Bax. Thus, under stress conditions, increased expression of SIRT3 protects cardiomyocytes, in part by hindering the translocation of Bax to mitochondria [91].

Another of the transcription factors that is involved in the retrograde response is Forkhead box O (FOXO). In mammalian cells, there are four isoforms of FOXO, which can be phosphorylated at different residues by several stress-responsive kinases in the cytosol, promoting translocation of these transcription factors to the nucleus [92, 93]. FOXO allows the transcription of mitochondrial antioxidant enzymes and helps to remove damaged mitochondria by inducing mitophagy. Therefore FOXO maintains cell homeostasis, through crosstalk between mitochondria and nucleus [94].

Another transcription factor that likely participates in retrograde signaling is Signal Transducer and Activator of Transcription 3 (STAT3). The STAT family of nuclear transcription factors is associated with various physiological and pathological functions [95]. Although STAT3 is involved in retrograde signaling as a regulator of nuclear gene expression, it also plays other roles in mitochondrial-nuclear interactions by being a sensor of mitochondrial dysfunction as well as an effector of anterograde signaling. In addition to nuclear and cytosolic STAT3, a small pool of STAT3 has been identified in the mitochondria [95]. The mitochondrial STAT3 functions as a sensor of mitochondrial dysfunction because it is subject to oxidation by ROS, and this appears to result in loss of STAT3 from the mitochondria [96]. Meier *et al.* [96] have also suggested that some of the loss of mitochondrial STAT3 induced by ROS may be due to translocation of STAT3 out of the mitochondria. Cytosolic STAT3 can be phosphorylated in Tyr705 by JAKs activated by

cytokines or growth factors, which triggers translocation of STAT3 to the nucleus for its canonical function of binding to DNA and driving gene transcription. The biological function of nuclear STAT3 is very diverse, depending on cell type, the ligand receptor that initiates the response, and cell maturation stage, fetal versus adult [96].

The translocation of STAT3 into the mitochondria is also subject to regulation [96]. Phosphorylation of Ser727 is essential for STAT3 translocation and its mitochondrial functions (activation of Complex I, II and V of the ETC and interaction with Cyclophilin D to regulate MPTP) [97]. Whether this is due to a transcription effect on the mitochondrial genome or protein-protein interactions is uncertain.

More recently, a G-Protein Pathway Suppressor 2 (GPS2) was identified in mammals as part of retrograde signaling. GPS2 regulates insulin signaling, pro-inflammatory pathways, and lipid metabolism [98–100]; deficiency of GPS2 in mice is embryonic lethal [101], indicating the physiological importance of GPS2. Recent work shows that GPS2 can also directly activate mitochondrial genes encoded in the nucleus. Mitochondrial depolarization activates GPS2 translocation to the nucleus and triggers genes involved in mitochondrial biogenesis [102].

Pathways dependent on ROS

Reactive oxygen species (ROS) are produced constantly by the ETC during aerobic metabolism, and ROS production and scavenging are tightly balanced within the cell. ROS can act as second messengers in numerous cellular processes, known as redox signaling [103]. However, cellular oxidative stress occurs when ROS production exceeds the antioxidant systems. Oxidative stress can inactivate mTOR signaling among other signaling molecules [104]. As discussed earlier, mTOR is a master modulator of protein synthesis from the nuclear genome, and it also controls mitochondrial biogenesis [105]. It was also reported that NF- κ B can be activated by high levels of mitochondrial ROS. NF- κ B is a transcription factor, which promotes cell proliferation and survival [106]. ROS can also induce expression of genes involved in OXPHOS, promoting mitochondrial biogenesis through the signaling of PGC-1 α [107]. Ciron *et al.* demonstrated in a study of neurodegenerative disease that the absence of PGC-1 α in cells results in abnormal mitochondria and fragmented ER. Null mice with disrupted expression of full-length PGC-1 α are more vulnerable to oxidative stress, excitotoxic injury and oligomerization of α -synuclein, a protein which in turn downregulated PGC-1 α expression [108].

Increases in physiological ROS levels that are not detrimental to cell viability, induce a retrograde signal through the activation of transcription factors such as nuclear factor erythroid 2 related factor 2 (NFE2L2; also known as NRF2). NRF2 activation triggers expression of antioxidant genes both in mitochondria and the cytosol [109, 110].

Another ROS-sensitive regulator of the retrograde response is MCLK1 (mitochondrial enzyme necessary for ubiquinone biosynthesis). Studies have shown that reduced activity of MCLK1 affects mitochondrial ETC function, reducing ATP synthesis, and increasing ROS production, and this is considered part of the retrograde response [111, 112]. Recent work

shows that CLK-1 could act as a mitochondrial messenger during oxidative stress. Excessive ROS production allows this transcription factor to translocate into the nucleus to induce a protective mechanism leading to inhibition of the mitochondrial unfolded protein response (mtUPR) and activation of ROS metabolic genes [113]. It has also been observed that the mutation in *Clk-1* inhibits mitochondrial respiration and increases ROS production. These mitochondrial functional changes trigger the activation and stabilization of a transcription factor, hypoxia-inducible factor 1 α , HIF-1 α , which regulates cellular adaptation to low oxygen levels [114].

The accumulation of misfolded proteins in the mitochondria activates the mtUPR [115], which is a form of retrograde mito-nuclear communication that is responsible for quality control of the mitochondrial proteome. However, most recent studies have demonstrated that the mtUPR can trigger peptide release from the mitochondria, which affects nuclear gene transcription [116]. This unique mechanism can synchronize both nuclear and mitochondrial genomes and restore the homeostasis between the two cellular organelles. One study demonstrated in mammalian cells that ClpP cleaves unfolded proteins accumulated in the mitochondrial matrix, releasing peptides from the mitochondria, leading to the activation of various signaling molecules, such as c-Jun N-terminal kinase (JNK), protein kinase RNA-activated (PKR), c-Jun, CHOP-10, and eIF2 α [117]. On the other hand, unfolded proteins can accumulate in the intermembrane space of the mitochondria. The mtUPR can activate the Akt-dependent signaling cascade [118]. The mtUPR generates peptides that can alter mitochondrial function by regulating proteases and chaperones to affect protein stability. Additionally, by activating metabolic genes, the mtUPR alters mitochondrial metabolism [115, 119]. Furthermore, it has been shown that mitochondria can regulate cell function and cellular metabolism by releasing peptides that are encoded by the short open frames (sORFs) in the mitochondria genome [120].

Other molecular signaling cascades, which involve p38MAPK and PMK-1, can be activated by oxidative stress. The stress-inducible signaling pathways, such as p38MAPK and PMK-1 activate the transcription factor skinhead 1 (SKN-1) by phosphorylation. SKN-1 translocate into the nucleus where it induces adaptive mechanisms that protect against oxidative stress, such as increased expression of proteins such as superoxide dismutase and catalase [121].

Nitric Oxide Synthase (NOS) produces another physiologically important signaling molecule, nitric oxide (NO). The reactive molecule NO modulates mitochondrial respiration by S-nitrosation of various electron transport chain subunits [122, 123]. Physiological levels of NO can induce a retrograde response through the alteration of Ψ_m . Retrograde signaling mediated by NO results in modulation of mitochondrial biogenesis through the increased expression of PGC-1 α and NRF1 [124]. The pathological consequences of excessive NO production can stimulate apoptosis [125]. This is due to the excessive production of peroxynitrite from superoxide and NO, which stimulates cytochrome c release and initiates apoptosis [126, 127].

Sp1 is another transcription factor, which is affected by mitochondrial ROS. Similar to STAT3, Sp1 can be oxidized in the mitochondrial matrix, causing loss of activity, which affects mitochondrial homeostasis [128, 129]. The cysteine thiol groups located in the zinc

fingers are affected by ROS. This causes Sp1 to lose its DNA binding capacity, resulting in a decrease in target protein expression [128, 129]. Sp1 can be a potential transcription factor of mitochondrial calcium uptake 1 (MICU1), a regulator of the MCU channel, the major mitochondrial calcium uptake pathway. Therefore, a decrease in Sp1 function can lead to dysregulation of Ca^{2+} in the mitochondria, which that can be considered as a downstream consequence of the retrograde response. It has been shown in the heart of diabetic mice that a decrease in MICU1 expression contributes to myocardial apoptosis and the progression of cardiomyopathy [130]. It has also been found that Sp1 regulates the expression of SERCA2 (a key regulator of Ca^{2+} sarcoplasmic reticulum) in cardiomyocytes [131], which implies that Sp1 can have multiple effects on Ca^{2+} homeostasis in cardiomyocytes. Dysregulation of Sp1 can have multiple consequences leading to Ca^{2+} dysregulation in the heart.

Pathways dependent of Ca^{2+} Signaling

Ca^{2+} homeostasis cells is tightly controlled because Ca^{2+} is involved in many physiologic and pathologic processes. It is known that the mitochondria are crucial organelles, which are affected by changes in cytosolic $[\text{Ca}^{2+}]$ ($[\text{Ca}^{2+}]_c$) and simultaneously have the potential to perturb $[\text{Ca}^{2+}]_c$, if they inappropriately release their stored calcium [132]. An important element in the retrograde response in mammals is Ca^{2+} signaling [133, 134]. This retrograde signal is generated through the alteration in Ψ_m , which the authors termed as mitochondrial stress. The Ca^{2+} dependent retrograde response could also be induced by different stressors that affect mtDNA content or generate mtDNA mutations, and by stressors that target the ETC or OXPHOS directly, or treatment with ionospheres. These stressors can reduce Ψ_m , which ultimately impairs Ca^{2+} uptake into the mitochondria and potentially can release Ca^{2+} into the cytoplasm if matrix $[\text{Ca}^{2+}]$ is high [133, 135]. Luo *et al.*, has demonstrated that the increased $[\text{Ca}^{2+}]_c$ in FCCP-treated cells was correlated with activation of the MAP kinases ERK1 and ERK2 [136]. Furthermore, other studies have shown that ETC inhibition is associated with increased $[\text{Ca}^{2+}]_c$. A sustained elevation in $[\text{Ca}^{2+}]_c$ activates different Ca^{2+} regulated kinases, such as CaMKIV. CaMKIV has been shown to activate CREB by phosphorylation [137], which triggers nuclear translocation and activation of expression of several mitochondrial proteins removal of free Ca^{2+} from the culture media can abolish the activation of nuclear encoded genes, confirming the role of Ca^{2+} in retrograde signaling under these conditions [137].

One of Ca^{2+} sensitive signaling processes involves the activation of Ca^{2+} /calmodulin-responsive calcineurin, which activates NF- κ B and Nuclear Factor of Activated T Cells (NFAT) [138, 139]. Dephosphorylation of $\text{I}\kappa\text{B}\beta$ can activate the NF- κ B signaling cascade by promoting translocation into the nucleus [140]. Calcineurin mediates the dephosphorylation of $\text{I}\kappa\text{B}\beta$, which allows NF- κ B to translocate into the nucleus and stimulate the synthesis of proteins involved in Ca^{2+} uptake and release, such as Ryanodine Receptor I or II (RyR1 or RyR2) [135, 138]. Calcineurin also mediates the dephosphorylation of NFAT, which allows nuclear translocation and expression of genes involved in pathologic hypertrophy [141].

Apart from CAMKIV, Ca^{2+} dependent protein kinase C isoforms, c-Jun N-terminal kinase (JNK) and p38 MAPK are other Ca^{2+} -regulated kinases that can be activated by elevated

$[Ca^{2+}]_c$. These kinases can stimulate several transcription factors, such as CREB, early growth response protein 1 (EGR1), cAMP-dependent transcription factor ATF2, CCAAT/enhancer-binding protein- δ (CEBP δ), and CEBP Homologous Protein (CHOP) [137, 138]. Many of these transcription factors are involved in a mitochondrial stress response pathway similar to the unfolded protein response in the endoplasmic reticulum [142, 143]. The activation of CHOP induces nuclear encoded gene expression [144]. The activity of CHOP is modulated by its association with CEBP β and ATF2. It has been shown that CHOP activation with the association with ATF2 and other members of the family can disrupt Ψ_m [133]. The activation of retrograde signaling through these transcription factors promotes mitochondrial adaptive responses, which affects calcium metabolism, glucose metabolism, insulin signaling, and cell proliferation [145–148].

Role of RNAs in mito-nuclear communication

Bi-directional communication between the nucleus and the mitochondria can also be modulated by several classes of non-coding RNA (ncRNA), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and tRNAs. Emerging research in this field, shows that ncRNA can have direct and indirect impacts on mitochondrial biology [149].

In the following section, we will describe specifically, the key roles of some miRNAs in the coordination of essential cellular processes in the bidirectional signaling pathways established between mitochondria and nucleus.

MicroRNAs in anterograde signaling

Some work has shown that miRNAs can regulate anterograde signals, like miR-181c, which is generated in the nucleus and translocated to the mitochondria, where it can modulate the COX1 mRNA transcription and mt-COX1 expression [150, 151] and it has also been reported that during muscle differentiation miR-1 increases mitochondrial translation [152]. Moreover, miR-7 is a regulator of Voltage-Dependent Anion-selective Channel 1 (VDAC1) and this is reported to regulate the function of the permeability transition pore of the mitochondria [153]. Other microRNA involved in mito-nuclear communication is miR-214 that modulates mitochondrial morphology by down-regulating Mitofusin 2 [154]. In neurons, It has been shown that miR-338 can bind to mRNA of cytochrome c oxidase subunit IV (COX4) and affects not only energy metabolism but also intracellular ROS levels and thereby axonal growth [155].

Other miRNAs implicated in anterograde signaling, which are abundant in cardiac tissue, is the miR-30 family. These microRNAs are involved in mitochondrial dynamics and can regulate fission and fusion via the p53-Drp1 axis [156]. miR-30 targets p53, which decreases its expression, leading to reduction of Drp1, and in this way it suppresses mitochondrial fission, one of the first steps of apoptosis.

MicroRNAs in retrograde signaling

So far, we have described miRNAs involved in the anterograde response because they are the most studied, but more recent studies show regulation of the retrograde response by

miRNAs. One example of the miRNAs that mediate retrograde communications is miR-210. This miRNA is significantly induced in situations of low oxygen tension by HIF-1 α and can directly repress OXPHOS by targeting the nuclear-encoded cytochrome c oxidase assembly protein (COX10) and the iron–sulfur cluster scaffold (ISCU). miR-210 contributes to the change in metabolism under hypoxic conditions [157, 158]. Other examples are miR-23a and miR-23b, which control expression of mitochondrial glutaminase. Both miRNAs function to downregulate glutamine metabolism upon oncogenic activation. Suppression of miR-23a and miR-23b levels, increases ATP synthesis through the TCA cycle and increases expression of mitochondrial glutaminase [159]. It has been shown that the over expression of miR-378 attenuates ischemic injury in heart, by inhibiting the apoptotic program by downregulating caspase-3 protein levels [160].

Finally, miR-663 has been reported to positively regulate expression of OXPHOS subunit genes and the assembly of OXPHOS complexes. Carden *et al.* [154] described the function of this miRNA, which directly regulates nuclear encoded subunits of complex III, validated using luciferase assays. This study suggests that tumor progression involves oxidative stress caused by mitochondrial dysfunction, leading to a decrease in the miR-663 expression that reduces the expression of complex III ETC genes, destabilizes the super complexes, and reduces OXPHOS enzymatic activities, and these changes together contribute to tumorigenesis [161].

These papers all provide increasing evidence indicating that miRNAs modulate mitochondrial function and thereby contribute to signals that trigger adaptive cellular responses and/or nuclear-dependent programming of mitochondrial activities.

Other RNAs in interorganelle signaling

Along with mRNA, tRNAs are generated in the nucleus but must be efficiently delivered from the nucleus to the cytoplasm for protein synthesis, in a step termed “primary tRNA nuclear export”. Nevertheless, this traffic is not unidirectional, the tRNAs can be imported back to the nucleus by the “tRNA retrograde nuclear import” step which is conserved from budding yeast to vertebrate cells and has been hijacked by viruses, such as HIV. This bidirectional travel serves numerous functions ranging from tRNA modification, to tRNA quality control, to regulation of translation, and to HIV replication [162, 163]. Although there is not yet much evidence linking this to the retrograde response, we cannot rule out some participation. Similarly, although the mitochondria generate some of their own tRNAs, there is a requirement for tRNA import into the mitochondria for protein synthesis within the mitochondrial matrix [164]. Whether this process could be a participant in anterograde signaling remains to be determined.

Nuclear-Mitochondrial Communication in Muscle Physiology and Pathophysiology

Mitochondria provide the most efficient means for cellular energy generation, and different cell types have different amounts of mitochondria, generally proportional to the energy requirements. Muscle cells, which includes cardiac muscle, require a reliable source of

energy. Therefore, the bioenergetics of the mitochondria in the muscle cells could be different from the other cell types. But in muscle cells the nuclear-mitochondrial communication is also essential, similar to other cell types, which we have discussed earlier in this article. In muscle cells the same signaling pathways generally have very similar functions in nuclear-mitochondrial communication. However, there are some differences in the involvement of these common signaling pathways in muscle cells compared to other cell types. Herein, we will discuss the similarities of the nuclear-mitochondrial communication in mammalian muscle cells with other cell types we have discussed earlier as described in Table 1. Additionally, we will highlight the differences in nuclear-mitochondrial communication between mammalian muscle cells and other cell types, including yeast, as illustrated in Figure 1.

Anterograde signal

In skeletal muscle, PGC-1 α/β , NRF-1, NRF-2, and TFAM play very similar roles, as we have discussed earlier in other cell types with regard to anterograde signals [165–168]. Like other organs, such as brown adipose tissue, heart, and kidney, with large numbers of mitochondria, in slow-twitch skeletal muscle, there is a very high expression of PGC-1 α [169–171], and, in skeletal muscle, PGC-1 α expression can be induced further. Physiological states, like short-term exercise, fasting, can upregulate PGC-1 α expression in skeletal muscle [166, 169, 172–176]. Like other cell types, PGC-1 α/β activate(s) ERRs and PPAR δ in muscle cells. The down-stream function of ERR- α is also very similar in muscle cells stimulation of oxidative phosphorylation, fatty acid oxidation, and TCA cycle, and also regulation of mitochondrial fusion/fission [177, 178]. Interestingly, in skeletal muscle, especially in slow twitch fiber type, the activation of PPAR δ , can upregulate genes that are associated with fatty acid oxidation [179, 180]. Additionally, in skeletal muscle it has been shown that YY1 is an essential protein for PGC-1 α function. The loss of YY1 expression causes exercise intolerance and ultrastructural signs of mitochondrial myopathy in mice [181].

The mTOR complex is a key regulator of skeletal muscle mass [182]. In this tissue, it has been shown that activation of the mTOR complex can directly stimulate mitochondrial respiration [183]. In another study, it has been demonstrated that mTOR binds to the transcription factor YY1, and recruits PGC1 α , in skeletal muscle. This mTOR-YY1-PGC-1 α complex then activates mitochondrial gene expression. The authors have used the mTOR inhibitor rapamycin, and showed a dissociation of PGC-1 α from the mTOR-YY1 complex, which thereby decreases mitochondrial gene expression [184, 185]. On the other hand, Williams *et al.*, showed that in skeletal muscle, it is ERR and not the Akt/mTOR pathway, which influences PGC-1 α/β mediated mitochondrial biogenesis [186].

As in other cell types, SIRT1 has been shown to associate with PGC-1 α in muscle. SIRT1 can deacetylate PGC-1 α , and therefore SIRT1 can be considered a regulator of PGC-1 α . The deacetylated PGC-1 α can alter mitochondrial number and function [187, 188]. Although SIRT1 has nuclear functions, other SIRTs, such as SIRT3 and SIRT4, are present in the mitochondria and can regulate mitochondrial metabolism, such as fatty acid oxidation, by deacetylation and by ADP-ribosylation of mitochondrial enzymes [189, 190]. Interestingly,

SIRT4 knockdown increases SIRT1 expression in the nucleus, indicating another form of mito-nuclear communication [189].

MEF2, as we mentioned before, is another muscle-enriched transcription factor. MEF2 plays an important role in intracellular calcium homeostasis by targeting histone deacetylase (HDAC) and also is a regulator of troponin I type1, PGC-1 α and subunits of complex I of the ETC [54–56].

Retrograde signal

Retrograde mito-nuclear communication has been primarily studied in pathological or stress conditions in muscle cells. For example, during oxidative stress, it has been shown that ROS can affect DNA methyltransferases (DNMTs), and SIRT1. This process has been found to be detrimental as this leads to DNA hypermethylation of nuclear genes, and as a consequence, this epigenetic regulation downregulates the affected genes [191]. During aging, there is a ROS-induced progressive decline in mitochondrial function that perturbs cellular homeostasis. Additionally, Gomes *et al.* [192] has shown that during aging, SIRT1 can be activated by the decrease in NAD⁺ in muscle cells. Activated SIRT1 can inhibit PGC-1 α / β mediated mitochondrial biogenesis.

An important role of FOXO has been demonstrated in skeletal muscle mitochondria, which impacts nuclear gene expression as well as protein degradation. The role of FOXO was described in muscle atrophy, due to its role in upregulation of F-bx (MAFbx)/atrogin-1 mediated protein degradation [193]. It has also been shown that the overexpression of FOXO1 and/or FOXO3 decreases muscle mass [194]. Furthermore, deletion of FOXO1/3 isoforms can prevent the decline of muscle mass and force [195]. Additionally, FOXO plays a role in the regulation of energy metabolism [196]. FOXO1/3 are regulators of lipid metabolism during starvation and exercise [197, 198]. In skeletal muscle myotubes, specifically the C2C12 cell line, overexpression of FOXO1 alters oxidative metabolism by increasing expression of fatty acid protein lipase CD36 and lipoprotein lipase [197, 199]. Another recent study shows FOXO1 plays an important role in glucose metabolism and regulation of inflammatory markers, in skeletal muscle [200].

One of the effects of obesity and type 2 diabetes in muscle cells is mitochondrial dysfunction, which may be related to incomplete beta oxidation of fatty acids, resulting in lipid deposition [201–203]. Prasad *et al.* has proposed that the mitochondrial beta oxidation intermediates, such as long, medium and short acylcarnitines, may act as a retrograde signal to the nucleus, which downregulates several nuclear-encoded mitochondrial genes that include *Nrf-1*, *Nrf-2*, *Pgc-1 α* , and *Tfam* [204].

During endurance training, skeletal muscle can be exposed to low concentrations of oxygen, which stabilizes HIF-1 [205, 206]. HIF-1 α is the primary transcriptional response factor for hypoxic adaptation and can be considered part of the retrograde response of the muscle, which upregulates glycolysis and angiogenesis in response to tissue hypoxia [206]. Data also support a role for HIF-2 α in skeletal muscle [205]. HIF-2 α induces transcription of genes in

slow-twitch oxidative muscle fibers, which has been shown to be necessary for the PGC-1 α -induced switch to more oxidative metabolism [205, 207].

A role for calcium in retrograde mito-nuclear communication has been suggested by an *in vitro* study of Biswas *et al.*, who showed in myotubes, lower mitochondrial membrane potential leads to increased cytosolic $[Ca^{2+}]_c$. The increase in $[Ca^{2+}]_c$ triggers cell reprogramming and one of those changes is upregulation of the nuclear-encoded mitochondrial gene cytochrome c oxidase Vb. Upregulation of cytochrome c oxidase Vb plays an important role in mitochondrial membrane biogenesis [133]. Pioneering work from Avadhani's group [138, 208] showed that mitochondrial membrane depolarization leads to increased $[Ca^{2+}]_c$ and triggers NFAT in the mitochondria. This ultimately results in mitochondrial ATF2 translocation into the nucleus in C2C12 myotubes. There are several transcription factors, such as JNK1 and CaMKIV, that are activated by phosphorylation mediated by the rise in $[Ca^{2+}]_c$. On the other hand, in response to mitochondrial dysfunction, calcineurin can activate CREB1, NF- κ B, p53, MEF-2, PGC-1 α , and hnRNPA2 by dephosphorylation [137, 138, 209–211].

Sp1, Sp3, and STAT3 are transcription factors that are present in many tissues including muscle. Transient activation of these factors plays fundamental roles in maintenance of cellular homeostasis [212–214], but prolonged activation of STAT3 has been shown to stimulate protein degradation [214]. These transcription factors contain many cysteine residues that can be oxidized by ROS. By this mechanism, ROS can be a regulator of the retrograde response.

Anterograde Mito-Nuclear communication mediated by miRNA

Currently, there is abundant evidence of functional miRNAs generated from the nuclear genome, but no functional miRNAs have yet been described to originate from the mitochondrial genome. Therefore, we will focus on miRNAs as mediators of anterograde mito-nuclear communication. As described in Figure 1, miRNAs play an important role in nuclear to mitochondrial communication in muscle cells. Most of the miRNAs are present in the RNA-induced silencing complex (RISC) in the cytoplasm, where they regulate directly or indirectly protein synthesis, including proteins that will be imported into the mitochondria that are essential for mitochondrial metabolism and function. For example miR-494 regulates mitochondrial biogenesis by targeting the expression of TFAM and Foxj3 [215]. miR-696 regulates the levels of PGC-1 α in muscle cells [216]. Several other studies have shown in human skeletal muscle and C2C12 myoblasts that miR-31 can inhibit the expression of HDAC4 and NRF1. This is one of the possible mechanisms by which miR-31 can regulate skeletal muscle regeneration by altering mitochondrial biogenesis [217, 218]. miR-128 has been reported to be highly expressed in skeletal muscle. miR-128 can target the 3'UTR of Sp1 mRNA; Sp1 plays a critical role in mito-nuclear communication. Overexpression of miR-128 can inhibit muscle satellite cell proliferation and differentiation by downregulating Sp1 expression [219]. miR-542–3p has been reported to induce mitochondrial ribosomal stress in human quadriceps muscle; this microRNA may target components of the mitochondrial ribosome including mitochondrial ribosomal protein (MRP) S2, S10, S18C, S25, S26, and S27 [220].

Skeletal muscles contain several sub-types of myofibers, which differ in contractile and metabolic properties. Therefore, miRNAs can have different functions or targets in different fiber types [217, 221]. Wada *et al.* [210] show that miR-23a affects mitochondrial content, muscle fiber composition, and muscle adaptations. In this study, the authors have observed that PGC-1 α and COX4, were significantly decreased in the slow soleus muscle, but not the fast plantaris muscle of mice.

As an example of another mechanism of miRNA action, in cardiomyocytes, miR-181c has been proposed for the first time to primarily function in the mitochondrial compartment [150, 222]. miR-181c is encoded in the nucleus, matures in the cytoplasm, and then finally translocate into the mitochondria [222]. Most importantly, miR-181c is functional inside the mitochondria. miR-181c targets the 3'-end of the mitochondrial mt-COX1 mRNA [150, 222]. This attenuates the expression of mt-COX1, which results in excessive ROS production, and that ultimately leads to heart failure *in vivo* if overexpressed for several weeks [150]. This provides evidence that a nuclear encoded miRNA, miR-181c, can alter a mitochondrial encoded gene, mt-COX1, by direct interaction with its mRNA. It has also been demonstrated that miR-181c can target KRAS mRNA in the cytoplasm of gastrointestinal cancer cells; no mitochondrial targets were reported [223, 224]. Therefore, it appears that miR-181c translocation into the mitochondrial compartment can be a tissue specific event.

More recently, Zhang *et al.* postulated a mechanism by which miR-1 could form a functional complex with Argonaute 2 (AGO2) in the absence of GW182 to translocate into the mitochondria, in C2C12 myotubes [152, 225]. The translocation of miR-1 into the mitochondria happens during myogenesis. Additionally, Shepherd *et al.* [226], demonstrated that another functional complex containing miR-378 and AGO2 translocate into the mitochondria with the help of Polynucleotide Phosphorylase (PNPase). The mechanism responsible for translocation of miRNA into the mitochondrial matrix is not fully understood [227]. However, the effect of a miRNA inside mitochondria has been studied extensively. For example, after entering the mitochondrial matrix, miR-1/AGO2 is reported to target mitochondrial transcripts such as *mt-Cox1*, *mt-Nd1*, *mt-Cytb*, *mt-Cox3* and *mt-Atp8* in skeletal muscle cells [152], although the mechanism is unconventional. In cardiomyocytes, miR-378 targets and downregulates mt-ATP6. ATP6 is a component of the F0 subunit of the mitochondrial ATP synthase, and the reduction in this subunit by miR-378 translocation into the mitochondria plays an important role in diabetes induced cardiomyopathy [225]. Another miRNA, miR-21, has been reported to directly target *mt-Cytb* to positively modulate *mt-Cytb* translation in mitochondria in H9c2 cells [228]. In silico analysis has identified putative, canonical target sites on several mitochondrial transcripts for miR-133a and members of the let-7 family [218].

In addition to the data suggesting a mechanistic link between specific miRNA and mitochondrial function described above, endurance training and aging can change the expression of miRNAs in skeletal muscle, and other studies show changes in mitochondrial function under these conditions. Therefore, other mechanistic links between miRNA and mitochondria may also be important. It has been reported that the levels of several miRNAs

such as, miR-1, miR133a, miR-133b and miR-181a are increased in human skeletal muscle and miR-9, miR-23a, miR-23b, miR31 are decreased after exercise [217, 229].

Concluding Remarks

Mito-nuclear communication is essential for normal cellular function; the perturbation in mito-nuclear communication is often associated with disease. Retrograde signaling is an important aspect of the communication between mitochondria and nucleus. The detailed mechanisms of retrograde signaling, and likely some of the key regulators of this signaling process, are still unknown. But several groups around the world are now interested in this novel aspect of cellular biology, and studies are shedding light on this new field. As this review discussed, the mitochondrial retrograde signaling pathways impact a wide spectrum of cellular activities, both under normal and pathophysiologic conditions. Retrograde responses can adjust the integration of carbohydrate and nitrogen metabolism to maintain a balanced mitochondrial redox state required for functional mitochondria. Mitochondrial retrograde signals can be triggered by various metabolites, such as ATP, acetyl-CoA, NAD⁺, Ca²⁺ and ROS. Better understanding of the interactive mechanisms of mito-nuclear communication may offer new strategies for therapeutic intervention in multiple pathophysiologic conditions.

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Figure 1.

Mitochondria to Nucleus Retrograde and Anterograde Signaling. Mitochondrial stress produced by different triggers that leads, according to the stressor, to imbalances in key metabolites that can trigger nuclear reprogramming. This implies that the nucleus alters expression of genes involved in different pathways to affect homeostasis and lifespan of the mitochondria. The nucleus also encodes miRNAs that play a regulatory role in this process in different compartments.

Table 1.

Skeletal muscle transcript factors and pathways involved in anterograde and retrograde signal.

Anterograde Signal in Skeletal Muscle		
Transcription Factor & Pathway Identified	Significance	Reference
PGC-1α/β	Promotes the development of muscle mass and energy metabolism. Stimulates transcription factors such as NRF, TFAM, ERR and PPAR. Translocates to the mitochondria and regulates expression of mt-genes.	[165–169, 172–176, 188]
NRF 1,2	Regulates expression of ETC components and antioxidant enzymes, and regulates TFAM activity.	[34, 168]
PPARδ	Stimulates the expression of enzymes involved in mitochondrial fatty acid oxidation.	[179, 180]
ERRα, β, γ	Regulates the TCA cycle, OXPHOS, and fatty acid oxidation.	[177, 178]
TFAM	Regulates mitochondrial DNA transcription and replication.	[34]
YY1	Functions as a co-activator of PGC-1 α and mitochondrial gene expression.	[181]
mTOR	Activates mitochondrial gene expression.	[182–185]
SIRT1	Regulates the transcription of PGC-1 α gene by deacetylation.	[187, 189]
SIRT3,4	Regulates mitochondrial metabolism, such as fatty acid oxidation, by deacetylation and by ADP-ribosylation of mitochondrial enzymes.	[48, 189, 190]
Sp1,3	Regulates genes such as PGC-1 α , ERRs and Growth factor receptor 1	[212, 213]
MEF2	Regulates genes such as GLUT4, troponin I, PGC- α and ND6.	[54–56]
STAT3	Contributes to anterograde signaling by translocating into the mitochondria, where it serves as part of the ROS response.	[214]
Retrograde signal in Skeletal Muscle		
Transcription Factor or Signaling Molecules & Pathway Identified	Significance	Reference
ROS	Increased ROS causes DNA damage, modification of protein, mitochondrial dysfunction.	[191, 204]
NAD^{+}	Loss of NAD $^{+}$ activates SIRT1.	[192]
HIF-1,2α	Stimulates genes involved in angiogenesis and glycolysis.	[205, 206]
FOXO1,3	Regulates muscle mass and oxidative metabolism.	[194, 200]
Sp1,3	Loss of Sp1/3 in response to ROS downregulates genes such as PGC-1 α , ERRs and Growth factor receptor 1	[212, 213]
[Ca^{2+}]$_c$	Release of mitochondrial calcium triggers nuclear reprogramming and upregulates cytochrome c oxidase Vb.	[133]
Acylcarnitines	Downregulate nuclear-encoded mitochondrial genes such as <i>Nrf-1</i> , <i>Nrf-2</i> , <i>Pgc-1α</i> and <i>Tfam</i> .	[204]