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REVIEW

Mitochondrial network remodeling: an important feature of myogenesis and skeletal muscle regeneration

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Abstract

The remodeling of the mitochondrial network is a critical process in maintaining cellular homeostasis and is intimately related to mitochondrial function. The interplay between the formation of new mitochondria (biogenesis) and the removal of damaged mitochondria (mitophagy) provide a means for the repopulation of the mitochondrial network. Additionally, mitochondrial fission and fusion serve as a bridge between biogenesis and mitophagy. In recent years, the importance of these processes has been characterised in multiple tissue- and cell-types, and under various conditions. In skeletal muscle, the robust remodeling of the mitochondrial network is observed, particularly after injury where large portions of the tissue/cell structures are damaged. The significance of mitochondrial remodeling in regulating skeletal muscle regeneration has been widely studied, with alterations in mitochondrial remodeling processes leading to incomplete regeneration and impaired skeletal muscle function. Needless to say, important questions related to mitochondrial remodeling and skeletal muscle regeneration still remain unanswered and require further investigation. Therefore, this review will discuss the known molecular mechanisms of mitochondrial network remodeling, as well as integrate these mechanisms and discuss their relevance in myogenesis and regenerating skeletal muscle.

Keywords Mitochondria · Mitophagy · Biogenesis · Fission · Fusion · Skeletal muscle · Skeletal muscle stem cells · Regeneration

Introduction

Mitochondria are organelles that are vital for energy production, cell survival, and stress regulation. Mitochondria are capable of manipulating both their morphology and function in response to various cellular stimuli. The synthesis of de novo mitochondria, termed biogenesis, is accompanied by increased respiration, metabolic processes, and ATP production, while autophagic degradation of mitochondria (mitophagy) is needed to remove damaged or unnecessary mitochondria (Fig. 1). The balance between biogenesis and mitophagy is important in modulating cell survival and cell fate in various physiological and pathological states [1–8]. The elongation (fusion) and division (fission) of mitochondria serve as a bridge between biogenesis and mitophagy. For instance, mitochondrial fusion prevents mitophagy while fission is an important preceding step needed for mitophagy. Furthermore, mitochondrial fusion can promote the survival of damaged mitochondria through complementation of mitochondrial DNA (mtDNA), whereas fission can remove damaged parts of the mitochondrial network, thereby preventing the entire network from sustaining major damage [3]. In stem cell populations, the switch from a quiescent to an activated state is often (if not always) accompanied by remodeling of the mitochondrial network in order to prime the cell for the increased metabolic demand associated with activation [9]. Mitochondrial turnover is also important in initiating the differentiation program of stem cells to reconstruct damaged tissues. Skeletal muscle is one of the tissues that is highly reliant upon optimal mitochondrial function, given its high metabolic activity. Additionally, skeletal muscle tissue sustains damage due to daily wear and tear, and from numerous disease states, with its repair being intimately dependent upon the turnover of mitochondria within resident skeletal muscle stem cells (satellite cells) [10, 11]. Needless to say, the study of mitochondrial dynamics and turnover in regulating skeletal muscle stem cell function

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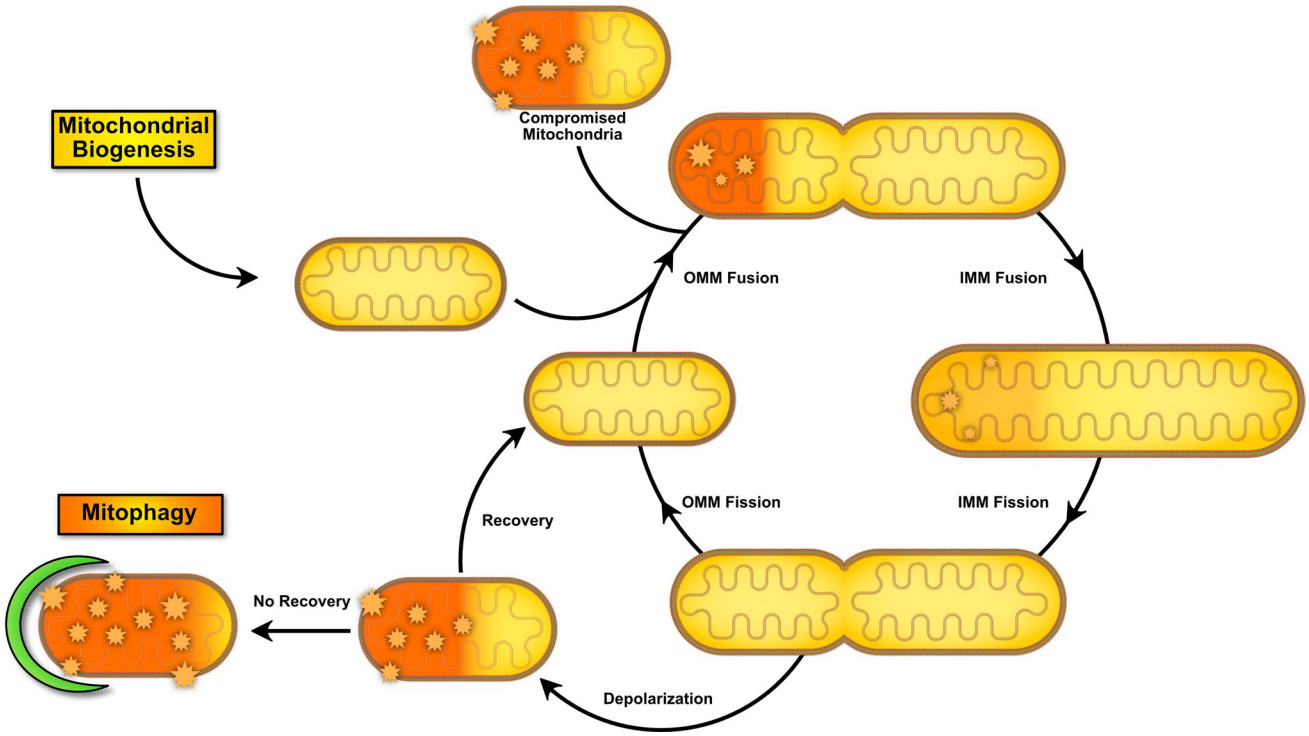

Fig. 1 Mitochondria life cycle and contribution of dynamic processes in bridging the gap between biogenesis and mitophagy processes. Biogenesis results in the formation of de novo mitochondria that can fuse together to form a reticular network. Healthy mitochondria may also fuse with damaged/compromised mitochondria to allow for complementation of material (substrates, mitochondrial DNA, etc.). In response to numerous stressors ultimately causing depolarization, a portion of the mitochondrial network can split and undergo mitophagy or, in cases where recovery takes place, they can fuse back to the existing network

and skeletal muscle tissue regeneration is still in its infancy. However, recent studies have shown the importance of these processes in maintaining skeletal muscle stem cell and skeletal muscle tissue function. Thus, this review will shed light on the molecular mechanisms of mitochondrial dynamics/turnover, their regulation through two major classes of sensors, and their known relevance in skeletal muscle stem cell differentiation and skeletal muscle tissue regeneration.

Mitochondrial biogenesis

Mitochondrial biogenesis is a highly regulated process that is dependent upon the synchronous interaction between mitochondrial and nuclear factors. Over the past two decades, the peroxisome proliferator-activated receptor (PPAR)-gamma coactivator-1 (PPARGC1) family of transcriptional coactivators has emerged as central regulators of mitochondrial biogenesis and metabolism [12]. The PPARGC1 family consists of three members, PPARGC1A, PPARGC1B, and PPARG related coactivator 1 (PPRC1) [13]. These factors interact with transcription factors and nuclear receptors that ultimately enrich the cell with the machinery needed for metabolism [14–16]. PPARGC1A, commonly called PGC1α, has previously been thought to be a necessary mediator of biogenesis [17]; however, growing evidence suggests that there are other factors that are also involved. PPARGC1B, metabolites, and other dietary factors are among the few evolving elements that have been explored to play a role in PPARGC1A-independent mitochondrial biogenesis [18–23]. This section will highlight PPARGC1A-dependent and -independent mechanisms of mitochondrial biogenesis (Fig. 2).

Mechanism of PPARGC1A-dependent Mitochondrial Biogenesis

PPARGC1A is a co-transcriptional regulatory factor that is highly inducible under various physiological conditions including exercise, starvation, cold, and hypoxic stress [15]. These conditions alter energy levels (i.e., increased AMP:ATP ratio) and/or increase stress signaling cascades to trigger mitochondrial biogenesis. To meet the demands of the cell/tissue in these conditions and promote survival, several interconnected pathways are activated that ultimately result in increased levels of PPARGC1A [24, 25]. PPARGC1A can produce an adaptive response by working

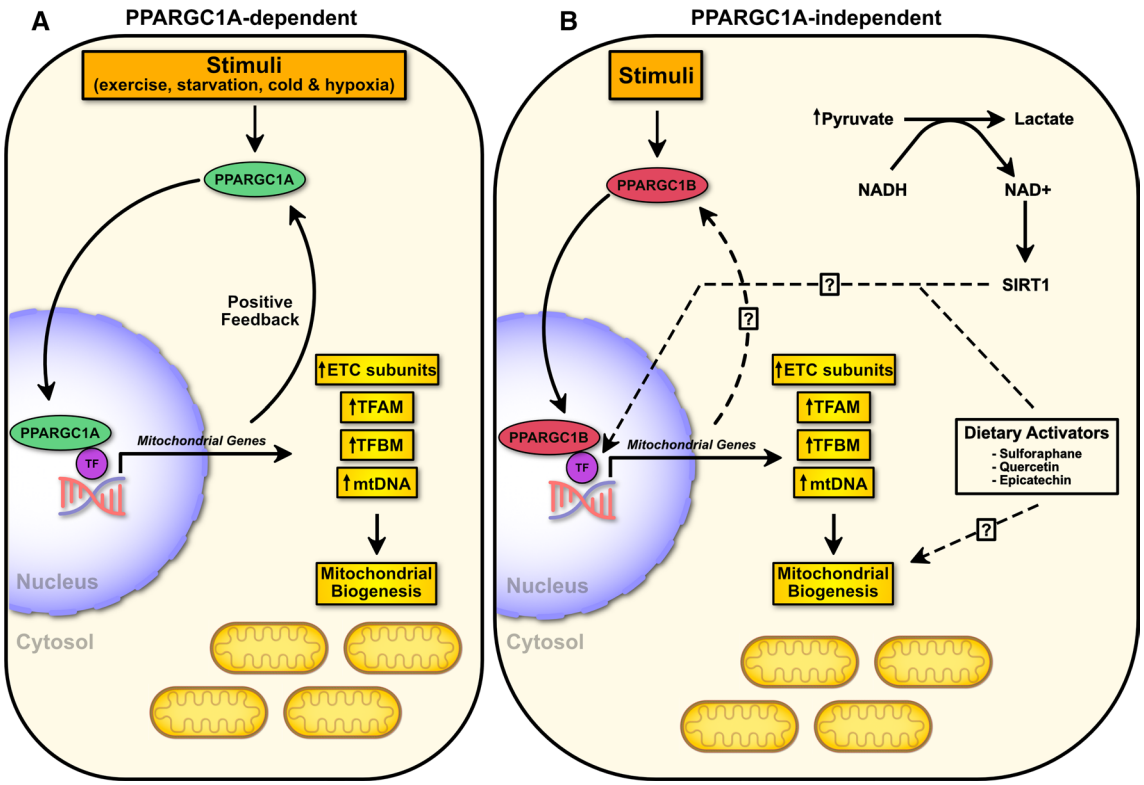

Fig. 2 Mitochondrial biogenesis overview. **a** PPARGC1A-dependent mitochondrial biogenesis occurs in response to multiple stimuli leading to the induction of transcriptional coactivator PPARGC1A. This leads to subsequent transcription of mitochondrial biogenesis genes including those of the electron transport chain (ETC), TFAM and TFBM, and mitochondrial DNA (mtDNA). **b** Mitochondrial biogenesis can also occur independent of PPARGC1A. Transcriptional coactivator PPARGC1B, pyruvate, and dietary activators are among the factors that can induce mitochondrial biogenesis. *TF* transcription factor

alongside several transcription factors to promote the transcription of genes involved in metabolism and mitochondrial biogenesis [24, 25].

The canonical transduction of PPARGC1A leads to its binding and coactivation of nuclear respiratory factors (NRFs) and estrogen-related receptors (ESRRs). NRFs are key components in regulating mitochondrial biogenesis, with NRF1 and nuclear factor erythroid 2 like 2 (NFE2L2 or NRF2) being the major targets of PPARGC1A. The significance of these nuclear factors has been established in developmental studies where the knockout of either of these factors results in embryonic lethality [26, 27]. Although homologous, NRF1 and NFE2L2 have slightly different downstream targets. NRF1 forms homodimers on DNA to target a broad range of genes related to oxidative phosphorylation (OXPHOS), mitochondrial membrane transport, detoxification (i.e., glutathione pathway), heme biogenesis, and mitochondrial DNA replication [28]. In contrast, NFE2L2 or GA-binding protein (GABP) seems to be mitochondrial specific with similar targets including mitochondrial transcription factor A (TFAM), mitochondrial transcription factor B (TFBM), and respiratory proteins [29]. The activity of NRF1 has also been shown to be methylation-dependent [30], whereas NFE2L2 requires deacetylated by sirtuin-7 (SIRT7) to form heterotetramers on DNA to enhance transcriptional activity [31].

Compared to NRFs, the physiological function of ESRRs in mitochondrial biogenesis is less studied in its relationship with PPARGC1A. PPARGC1A can target, bind, and activate ESRRA to regulate the expression of genes involved in OXPHOS, fatty acid oxidation, mitochondrial membrane transport, and mitochondrial DNA replication [32, 33]. Interestingly, in skeletal muscle PPARGC1 and ESRR induced regulator, muscle 1 (PERM1) can serve as a positive mediator of mitochondrial biogenesis [34–36]. PERM1 is transcribed by PPARGC1A and ERRA transcription factors and serves as a feed-forward mechanism that elevates the transcription of PPARGC1A, and thus, enhance mitochondrial biogenesis and oxidative capacity [36]. Similar homologues to PERM1 have yet to be identified in other tissues. Nonetheless, the inhibition of ESRRA impairs the ability of PPARGC1A to induce the expression of these genes, and reduces mitochondrial biogenesis as evidenced by a lower mtDNA:nDNA ratio. Interestingly, forced activation of ESRRA was able to induce mitochondrial biogenesis in the absence of PPARGC1A, although not to the

same extent [32, 33]. Nonetheless, this suggests that there are likely other mechanisms in place capable of triggering the synthesis of important mitochondrial machinery in the absence of PPARGC1A.

Mechanism of PPARGC1A-independent Mitochondrial Biogenesis

Indeed, PPARGC1A plays a major role in biogenesis; however, the existence of redundant pathways contradicts the idea of a single master regulator. In fact, PPARGC1B has been shown to exhibit similar properties to PPARGC1A and was thought to be an important regulator of mitochondrial biogenesis [34, 35]. Similar to PPARGC1A, PPARGC1B is able to partner with NRF1 and ESRRA to enhance the expression of mitochondrial transcription factors and trigger robust mitochondrial biogenesis [18, 20, 22]. In double knockout models of *Ppargc1a* and *Ppargc1b*, skeletal muscle has significantly diminished mitochondrial function, and mtDNA:nDNA content compared to knockout of either alone [36]. It should be noted that the function of PPARGC1B may be tissue-specific since *Ppargc1b* knockout reduces mitochondrial content in the slow-twitch soleus muscle, and the heart, but not in adipose tissue [37]. Furthermore, *Ppargc1b* knockout impairs lipid metabolism in the liver, resulting in hepatic steatosis [37]. Thus, PPARGC1B is an important molecule that has a similar function to PPARGC1A and is a chief candidate for further investigation.

Cell studies have identified pyruvate as an important substrate regulating mitochondrial biogenesis in a PPARGC1A-independent manner [21, 23]. Pyruvate treatment is able to increase mitochondrial content as measured by MitoTracker, cytochrome *c* (CYCS), and electron transport chain (ETC) protein content in PPARGC1A knockdown C2C12 cells and primary myoblasts from *Ppargc1a* knockout mice [23]. Although the mechanism of pyruvate-induced biogenesis remains unidentified, the authors propose that excess pyruvate can reduce to lactate and produce nicotinamide adenine dinucleotide (NAD^+) and SIRT1-mediated biogenesis. A follow-up study demonstrated that pyruvate treatment in C2C12 cells increases PPRC1 and respiratory proteins as a potential compensatory mechanism for the loss of PPARGC1A [21].

Some studies suggest that PPARGC1A is dispensable, particularly when it comes to exercise-induced mitochondrial biogenesis [19, 35]. The emerging roles of NFE2L2, estrogen-related receptor gamma (ESRRG), peroxisome proliferator-activated receptor delta (PPARD), and dietary activators (sulforaphane, quercetin, and epicatechin) have been elegantly highlighted in the context of exercise and skeletal muscle [19]. These factors can interact with members of the PPARGC1 family or with other less defined co-transcriptional regulators to promote the transcription of important mitochondrial genes, including NRF1, TFAM, and OXPHOS-related genes [19].

Mitochondrial fission and fusion

Mitochondria are highly dynamic organelles that continuously undergo cycles of fission and fusion. These processes are fundamental in maintaining mitochondrial morphology and function, and thus, play a central role in maintaining cellular health. On one hand, mitochondrial fission is required during cell division to allow equal distribution of mitochondria in each daughter cell [38]. Mitochondrial fission also enables the efficient removal of damaged mitochondria via selective autophagy (mitophagy) or participates in the induction of cell death [39, 40]. On the other hand, mitochondrial fusion is needed for mtDNA inheritance and helps mitigate stress by mixing contents from partially damaged and healthy mitochondria in a complementary fashion [41, 42]. Mitochondrial fusion is also required during cell differentiation, particularly in stem cell populations, and prevents the autophagic breakdown of mitochondria [9]. Defects in fission/fusion machinery has severe implications and leads to several diseases, particularly in tissues with high energy demands such as the brain, heart, and skeletal muscle. Given the central role of the mitochondria in energy production, metabolism, etc. greater emphasis has been placed on understanding the balance of fission and fusion over the past two decades. This section will underline the mechanism and regulators of mitochondrial fission and fusion (Fig. 3).

Mechanism of mitochondrial fission and fusion

The basis of mitochondrial fission is the constriction and scission of the mitochondrial membrane, resulting in two mitochondria [43, 44]. This mechanism is made possible by a dynamin-like GTPases protein, called dynamin 1-like (DNM1L or DRP1). DNM1L is traditionally found in the cytosol and translocates to the mitochondria in response to several upstream regulators, as explained later. DNM1L migration to the mitochondria is accompanied by its interaction with adaptor proteins found on the outer mitochondrial membrane (OMM). These OMM adaptor proteins include mitochondrial fission 1 (FIS1), mitochondrial fission factor (MFF), and mitochondrial dynamics protein of 49/51 kDa (MID49/51) [43, 44]. For example, the loss of these adaptor proteins, particularly MID49/51, reduce mitochondrial fission, while favouring mitochondrial fusion, and promote resistance to apoptotic stimuli [45]. Nonetheless, once bound to the adaptors, DNM1L oligomerizes around the mitochondria and utilizes GTP hydrolysis to induce a conformational change resulting in the constriction of the

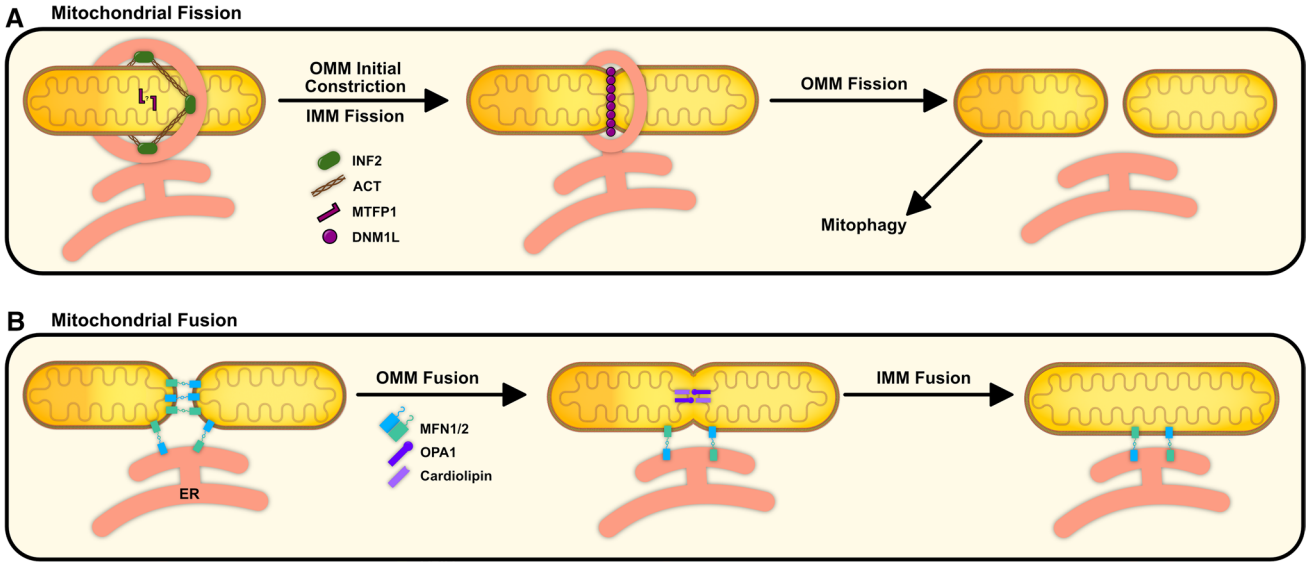

Fig. 3 Overview of mitochondrial dynamics. **a** Mitochondrial fission is mediated by ER-mito interplay involving an initial OMM constriction via INF2-mediated ACT polymerization and IMM fission by MTFP1. DNM1L is then recruited to OMM adaptor proteins to complete the final constriction and scission of the mitochondria. **b** Mitochondrial fusion is mediated by the interaction of MFN1/2 found on the OMM, followed by OPA1 interaction with cardiolipin on the IMM. These events can take place at ER-mito contact sites

OMM and division of the mitochondria [46, 47]. In contrast to the OMM, the constriction of the inner mitochondrial membrane (IMM) has yet to be fully addressed. Overexpression of IMM protein mitochondrial fission process 1 (MTFP1) has been found to elevate mitochondrial fission whereas depletion of MTFP1 results in hyperfusion [48, 49]. The untethering of the mitochondrial membranes may also facilitate IMM fission [50]. One study found that an influx of calcium ions into the mitochondrial matrix can lead to neutralization of tethering by inner membrane mitochondrial protein (IMMT), resulting in a separation of the IMM from the OMM [50]. Taken together, it is well understood that DNM1L mediates fission through its interaction with adaptor proteins found on the OMM, whereas the mechanism of IMM fission has yet to be fully determined.

Mitochondrial fusion is mediated by three major dynamin-like GTPase proteins: mitofusin 1 (MFN1), MFN2, and optic-atrophy 1 (OPA1). The location of these proteins on the mitochondria dictates their function with MFN1/2 being found on the OMM while OPA1 is found on the IMM. MFN1 forms homomultimers or heteromultimers with MFN2 and undergo oligomerization to fuse the OMM [51]. GTP hydrolysis induces a conformational change in MFN1/2 oligomers, pulling and fusing two OMMs [52]. Upon OMM fusion, the long isoform of OPA1 (L-OPA1) mediates the fusion of the IMM through heteromultimer interaction with cardiolipin, once more through the hydrolysis of GTP [53]. The function of OPA1 extends beyond just mitochondrial fusion alone. The enzymatic conversion of L-OPA1 to its short isoform (S-OPA1) via overlapping with the m-AAA protease 1 (OMA1) or YME1-like 1 (YME1L1) peptidase has also been shown to aid in the dissociation of the IMM, favouring fission over fusion [50]. In addition to regulating IMM fusion, OPA1 is a necessary protein in stabilizing mtDNA and maintaining cristae morphogenesis in both long and short configuration [54, 55].

Other important players of mitochondrial dynamics

Indeed, DNM1L, OPA1, MFN1/2 and their related proteins are major mediators of mitochondrial dynamics; however, other mediators have also been shown to play an important role in this process. The endoplasmic reticulum (ER), and lipid molecules are important in priming or enhancing the fission and fusion processes.

ER-mitochondria (ER-mito) contacts have several biological functions including tethering, lipid metabolism, calcium signaling, and in recent years, recognized to mediate mitochondrial dynamics (reviewed elsewhere [56, 57]). ER and mitochondria can form junctions together with the interaction of mitochondrial MFN2 [58]. At these junctions, MFN2 is ubiquitinated at Lys192 by membrane-associated ring-CH type finger 5 (MARCHF5), triggering its oligomerization and providing a platform for ER-mito tethering [58]. These ER-mito sites define the location for not only mitochondrial fission [59–61] but also fusion events [62]. In fact, the majority of mitochondrial fission and fusion events occur at ER-mito contact sites [62]. The constriction of the mitochondria by the ER has been proposed to occur in two sequential phases. First, ER inverted formin 2 (INF2) protein

can mediate the initial constriction around the OMM via actin (ACT) polymerization and myosin II (MYH2) mediated contraction [59–61]. This initial constriction is followed by the recruitment of DNM1L and induction of the second constriction to finally divide the mitochondria [59, 60]. A subpopulation of fission proteins (DNM1L, MFF, and FIS1) have also been identified on the ER and were shown to be involved in priming mitochondria for division. Of these proteins, ER-localized MFF was found to function as a platform to allow the recruitment and oligomerization of DNM1L prior to its transfer onto the mitochondria [59]. This mechanism coupled with INF2-mediated ACT polymerization are proposed to be major initiation steps for fission. Furthermore, ER-mito contacts have been shown to play a role in rescuing depolarized mitochondria through a "kiss-and-run" or transient fusion mechanism. This transient fusion event has been proposed to allow the exchange of proteins, metabolites, and ions between healthy and compromised mitochondria [62]. Nonetheless, further investigation is necessary to determine the mechanism(s) involved in sensing and rescuing mitochondria in this manner.

Changes in lipid composition of the OMM/IMM can guide and even enhance mitochondrial fission and is increasingly being studied (reviewed elsewhere [63]). Ceramide, cardiolipin, and phosphatidic acid are among some of the molecules responsible for manipulating DNM1L/OPA1 and thereby regulating mitochondrial dynamics. Ceramide synthesis within cardiomyocytes promotes DNM1L activation, mitochondrial fission, and apoptosis [64]. The inhibition of ceramide synthesis reduced apoptosis and mitochondrial fission, although it is unclear whether the reduction in apoptosis is a direct result of the inhibition of fission [65]. Similarly, cardiolipin can promote mitochondrial fission but also promote fusion depending on its localization. OMM localized cardiolipin enhances DNM1L-mediated fission by enhancing its GTPase activity [66–71]. In contrast, IMM cardiolipin promotes fusion via its interaction with OPA1 [53]. Cardiolipin can be cleaved by mitochondrial-surface phospholipase D (PLD6) to produce phosphatidic acid [72, 73], which has the opposite function on mitochondrial fission. Phosphatidic acid suppresses fission by sequestering DNM1L on the OMM [74, 75], while also promoting fusion events by enhancing MFN1/2 protein interactions [73].

Mitochondrial degradation

Mitochondria undergo dynamic changes to their structure to promote cellular survival as an initial response to cellular stress. In instances of high stress leading to mitochondrial damage and dysfunction, the efficient removal of damaged mitochondria is required to protect against cell death [76]. Several quality control mechanisms, including misfolded protein degradation (AAA protease-mediated) [80–82], vesicular transport of select proteins to the lysosome [79, 80], and autophagic removal of damaged mitochondria (mitophagy) have been identified to help mitigate cellular damage and maintain homeostasis. Of these factors, mitophagy plays the largest role and is present at a crossroad between cell survival and death [1, 3]. Furthermore, the failure of mitophagy has been implicated in various pathological conditions [81–84]. Emerging evidence supports the notion that mitochondria can undergo mitophagy through various mechanisms. These redundant pathways further demonstrate the evolutionary importance of the removal of damaged mitochondria. This section will highlight the various mechanisms of mitophagy (Fig. 4).

PINK1/PRKN-mediated mitophagy

The most studied mechanism of mitophagy is orchestrated by two proteins: the Ser/Thr kinase, PTEN-induced kinase 1 (PINK1), and the E3-ubitquitin ligase parkin (PRKN) [85, 86]. In mammalian cells, PINK1 serves as a molecular sensor of mitochondrial depolarization [85, 86]. PINK1 targets translocase of outer mitochondrial membrane (TOMM) protein to form a stable complex, enabling its mitochondrial targeting sequence (MTS) and transmembrane (TM) domains to extend into the mitochondrial matrix [85, 86]. In healthy cells, the extension of PINK1 into the matrix enables the breakdown of the MTS domain by mitochondrial processing peptidase (MPP) [87]. Upon this initial cleavage of PINK1, the IMM protein presenilin-associated rhomboid-like (PARL) removes the TM segment, resulting in the dissociation of PINK1 from TOMM [87–91]. The remaining double cleaved PINK1 is broken down within the cytosol via the N-end rule pathway [92] (Fig. 4a). In damaged cells containing compromised (depolarized) mitochondria, PINK1 once again associates with TOMM; however, the MTS domain is unable to extend to the mitochondrial matrix [93, 94]. As a result, the MTS domain is not cleaved by MPP, and concomitantly the TM domain also escapes PARL mediated processing [93, 94], resulting in the accumulation of PINK1 on the OMM. As PINK1 accumulates on the OMM, it becomes highly active after dimerization and autophosphorylation at Ser228 and Ser402 [95], and recruits PRKN to the OMM [94, 96] (Fig. 4b).

PRKN is a unique molecule that is able to autoregulate its own activity. Specifically, the ubiquitin-like (UBL) domain of PRKN ensures a closed conformation of the molecule under resting physiological conditions [97]. PINK1 phosphorylates PRKN at Ser65 to induce a conformation change to an "open" state to initiate the activation and recruitment of PRKN [97–100]. Furthermore, PINK1 accumulation on the OMM leads to the phosphorylation of cytosolic ubiquitin at Ser65 which interacts with phosphorylated PRKN

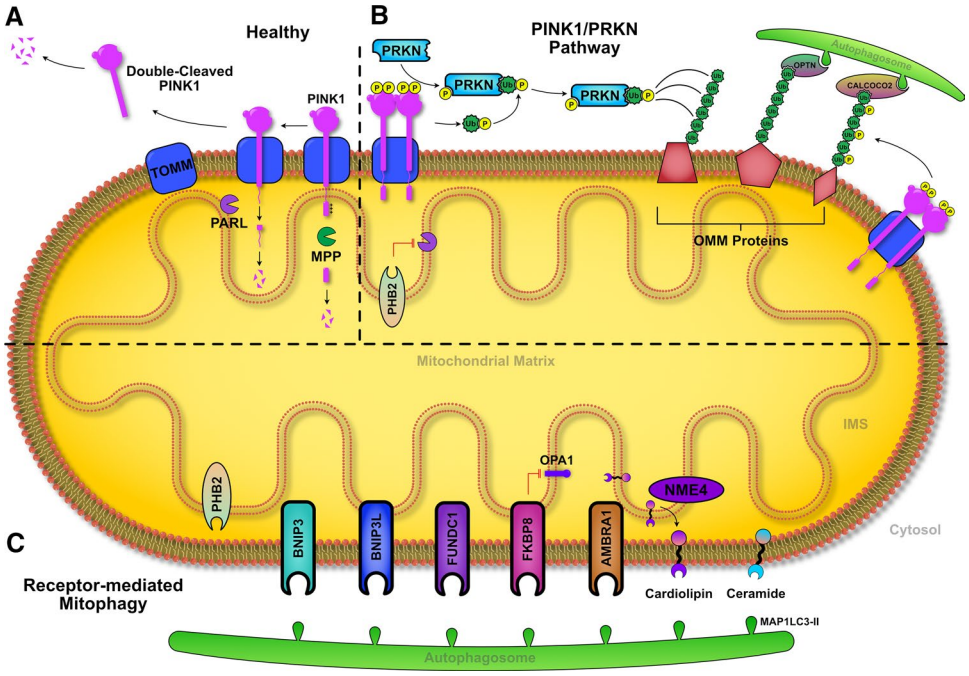

Fig. 4 Mechanism of mitophagy. **a** Under normal conditions, PINK1 is partially imported, cleaved by MPP and PARL enzymes, and released into the cytosol to undergo degradation. **b** Following depolarized, PINK1 can accumulate on the OMM, activating PRKN directly and indirectly (Ub-mediated). The maximally activated PRKN can ubiquitinate OMM proteins, leading to recognition via cargo proteins (OPTN and CALCOCO2), and subsequent degradation through autophagy. **c** OMM receptor proteins and lipids can also mediate mitophagy independent of PINK1/PRKN through direct interaction with MAP1LC3-II found on the autophagosome

[101–103]. In fact, the addition of a phosphorylated ubiquitin plays an essential role in activating PRKN and inducing mitophagy even in the absence of PINK1-mediated PRKN phosphorylation [100, 103]. The maximally activated PRKN can ubiquitinate multiple proteins on the OMM including MFN1/2, FIS1, TBC1 domain family member 15 (TBC1D15), voltage-dependent anion channels (VDACs), among others [104, 105]. The elongation of ubiquitin chains on the OMM by PRKN, coupled with their phosphorylation by PINK1 at Ser65, provides a feed-forward amplification mechanism that activates and recruits additional PRKN molecules to the OMM [106, 107]. This amplification results in greater recognition of damaged mitochondria and progression of mitophagy [106, 107].

The ubiquitination of OMM proteins allows for their recognition by the autophagic machinery through the interaction of adaptor proteins. Several adaptor proteins have been shown to interact with ubiquitinated OMM proteins including optineurin (OPTN), calcium binding and coiled-coil domain 2 (CALCOCO2), TAX1 binding protein 1 (TAX1BP1), neighbor of BRCA1 gene 1 (NBR1), and sequestosome 1 (SQSTM1). These proteins have a ubiquitin-binding domain and a microtube-associated protein 1 light chain 3 (MAP1LC3) interacting region (LIR) motif that work together to enable the recognition, efficient recruitment of the autophagosome, and degradation of mitochondria [108–110]. Interestingly, OPTN and CALCOCO2 can be recruited in the absence of PRKN, although their contribution may be limited [109]. The contribution of TAX1BP1 is also relatively low, while NBR1 and SQSTM1 have been shown to be dispensable for mitophagy [108, 109].

Mitophagy through multifunctional receptors

Although the PINK1/PRKN pathway of mitophagy is the most studied, other mechanisms exist and the contribution of these PRKN-independent mechanisms may be more important in certain types of cells or tissues. Hypoxia-inducible proteins, OMM spanning proteins, IMM spanning proteins, and lipids are some of the players involved in recruiting the autophagic machinery to induce mitophagy (Fig. 4c).

B-cell lymphoma 2 (BCL2) interacting protein 3 (BNIP3) and sister protein BNIP3-like (BNIP3L or NIX) are situated at the OMM upon depolarization stimuli and have been characterized under hypoxic conditions and for their role in apoptosis [111]. These proteins have also been shown to promote autophagy by competitively replacing BCL2 and BCL2 like 1 (BCL2L1) from Beclin-1 (BECN1), leading to the formation of the autophagosomal machinery, while combined ablation of BNIP3 and BNIP3L significantly reduces hypoxia-induced autophagy [112]. BNIP3 and BNIP3L also contain a LIR motif that can directly interact with MAP1LC3 to induce mitophagy [113–116]. The interaction between MAP1LC3 and BNIP3/BNIP3L is weak under normal growth conditions [114, 117], and is enhanced once BNIP3/BNIP3L are phosphorylated at the LIR motif [117, 118]. Furthermore, BNIP3 has been shown to anchor and inhibit the breakdown of OMM bound PINK1, thus increasing full-length PINK1 accumulation and concomitant PINK1/PRKN-mediated mitophagy [119]. On the other hand, BNIP3L has been shown to improve mitochondrial turnover in Parkinson's disease patient cells and compensate for lack of functional PINK1/PRKN [120].

Furthermore, BNIP3L does not influence PINK1/PRKN-mediated mitophagy but seems to be an important factor in mediating mitophagy in the absence of PINK1/PRKN.

FUN14 domain-containing 1 (FUNDC1) is another OMM protein that is expressed under hypoxic conditions. FUNDC1 can function independent of PINK1/PRKN and is highly dependent upon its phosphorylation state. Phosphorylation of Tyr18 and Ser13 inhibits the interaction of the FUNDC1 LIR motif with MAP1LC3 [121, 122], whereas Unc-51 like autophagy activating kinase 1 (ULK1)-mediated phosphorylation at Ser17 enhances FUNDC1 and MAP1LC3 association [123]. Under hypoxic conditions, phosphoglycerate mutase 5 (PGAM5) localizes at the mitochondria and dephosphorylates FUNDC1 at Ser13, and thus, promotes mitophagy [121]. Ubiquitination of FUNDC1 by a mitochondrial E3 ligase, MARCHF5, in response to hypoxia, ultimately leads to the degradation of FUNDC1 and reduces mitophagy [124]. Furthermore, hypoxia can induce FUNDC1 accumulation at ER-mito contacts [125]. The association of FUNDC1 with calnexin mediates mitochondrial fission and mitophagy, while the loss of this interaction circumvents mitophagic degradation through hyperfusion [125]. Together, the balance of phosphorylation states, ubiquitination, and regulation of fission provides precise control over FUNDC1-mediated mitophagy under hypoxic conditions.

FK506 binding protein 8 (FKBP8) is among the mitophagy receptors that is involved in apoptotic processes while also regulating cell size through the modulation of the mechanistic target of rapamycin kinase (MTOR) [126]. The precise contribution of FKBP8 to mitophagy is not entirely understood. In overexpression experiments, FKBP8 shows a strong affinity for MAP1LC3A and recruits MAP1LC3A to induce mitophagy in a manner that is independent of PRKN [127]. Interestingly, FKBP8 is not degraded during mitophagy [128]. Instead, FKBP8 can avoid degradation by translocating to the ER [128]. Further, FKBP8 can promote mitochondrial fission and subsequent mitophagy under hypoxic stress in a PRKN-independent manner [129]. Interestingly, FKBP8-induced fission was independent of DNM1L and BNIP3/BNIP3L [129]. Instead, FKBP8 interacts with OPA1 on the IMM, likely inhibiting its partnering with cardiolipin, and thus favouring fission [129]. Nonetheless, further examination of this protein is needed to better elucidate this mechanism.

Autophagy and BECN1 regulator 1 (AMBRA1) is an autophagy protein that has recently been shown to participate in mitophagy similar to other mitophagy receptors. A pool of AMBRA1 can localize on the mitochondria and interact with MAP1LC3 through its LIR motif [130]. In cells overexpressing mitochondria specific AMBRA1, almost all mitochondria are degraded [130]. This occurs in cells that do not express PRKN, and cells with PRKN-knockdown [130, 131]. Interestingly, a small pool of AMBRA1 is capable of binding to BCL2 under normal conditions, and after autophagy induction, AMBRA1 dissociates from BCL2 to bind to BECN1 to progress autophagy [130]. Thus, the multifunctionality of AMBRA1 warrants further study into its role in mitophagy.

Prohibitin 2 (PHB2) is the first IMM receptor to be identified for its role in receptor-mediated mitophagy. Upon proteasomal rupture of the OMM, the LIR motif of PHB2 interacts with MAP1LC3 to induce mitophagy that is independent of PRKN [132]. PHB2 has also been shown to participate in PINK1/PRKN-mediated mitophagy. The depletion of PHB2 on depolarized mitochondria destabilizes PINK1 on the OMM, and thus, prevents recruitment of PRKN [133]. In contrast, the overexpression of PHB2 recruits PRKN and promotes PRKN-mediated mitophagy [133]. In depolarized mitochondria, PHB2 interacts with PARL protease, preventing it from cleaving PGAM5 and PINK1 [133]. The ablation of PHB2 permits PARL-mediated cleavage of PGAM5, which is involved in stabilizing PINK1 on the OMM [133]. Moreover, the lack of PHB2 and full-length PGAM5 destabilizes PINK1 and inhibits mitophagy.

Lipids such as cardiolipin and ceramide have also been implicated as important molecules involved in mitophagy. The translocation of cardiolipin from the IMM to the OMM is mediated by NME/NM23 nucleoside diphosphate kinase 4 (NME4) in response to mitophagic signals [134, 135]. The externalized cardiolipin can freely interact with MAP1LC3 and promote mitophagy [134]. Similarly, ceramide, which is already present on the OMM, can bind MAP1LC3B-II and induce lethal mitophagy [136]. Ablation of the ceramide-binding site on MAP1LC3B prevents endogenous ceramide-mediated mitophagy [136]. The precise mechanism by which ceramide recruits autophagic machinery has yet to be determined.

Interplay between mitochondrial biogenesis, fission/fusion, and mitophagy

Mitochondria are highly adaptive organelles capable of modulating their morphology and function in response to various cellular stresses. The innate ability of these organelles to adapt is essential for normal cellular function and survival. Furthermore, the de novo formation, dynamic shift in structure, and subsequent removal of damaged mitochondria come together as a major quality control mechanism for this organelle. Alterations in any of these mechanisms can have severe implications on cellular function, potentially leading to disease states [2, 4–8]. Cellular energy/nutrient and stress sensors work together to maintain mitochondrial function through biogenesis, fission/fusion, and mitophagy.

There is considerable overlap between energy/nutrient and stress sensors, yet they are still able to maintain a fine-tuned response. This section will discuss major energy/nutrient, and stress sensors in the context of mitochondrial biogenesis, dynamics, and mitophagy (Fig. 5).

Role of energy/nutrient sensors

AMP-activated protein kinase (AMPK) is a major energy sensor in cells that is activated under low energy states, particularly when the ratio of AMP:ATP rises [137, 138]. The activation of AMPK is important in tissues with high energy demands, including the brain, heart, and skeletal muscle. To counter the reduced energy levels within cells, AMPK functions by directly phosphorylating various targets involved in energy metabolism [139–141]. AMPK-mediated phosphorylation of PPARGC1A activates the co-transcription factor, which upregulates genes responsible for ATP production and mitochondrial biogenesis, as discussed earlier. AMPK has also been shown to phosphorylate various epigenetic regulators including DNA methyltransferase 1 (DNMT1), RB binding protein 7 (RBBP7), and histone acetyltransferase 1 (HAT1) in vitro [142]. Phosphorylation of these proteins results in increased acetylation and reduced methylation of histones, ultimately favouring the transcription of PPARGC1A and related biogenesis genes [142]. This epigenetic control may function as a priming step for the accumulation of PPARGC1A prior to its phosphorylation by AMPK.

AMPK is also necessary for mitochondrial fragmentation under starvation conditions [143, 144]. Activated AMPK triggers the phosphorylation of adaptor protein MFF that enhances the recruitment of DNM1L to the OMM, thus, promoting mitochondrial fission [144]. The use of AMPK-mimetic, AICAR, on non-phosphorylatable MFF mutant cells does not lead to mitochondrial fission. Conversely, mutant cells containing constitutively phosphorylated AMPK sites on MFF have greater fragmentation [144]. This landmark study suggests that the phosphorylation of MFF by AMPK is needed for mitochondrial fission. Given that

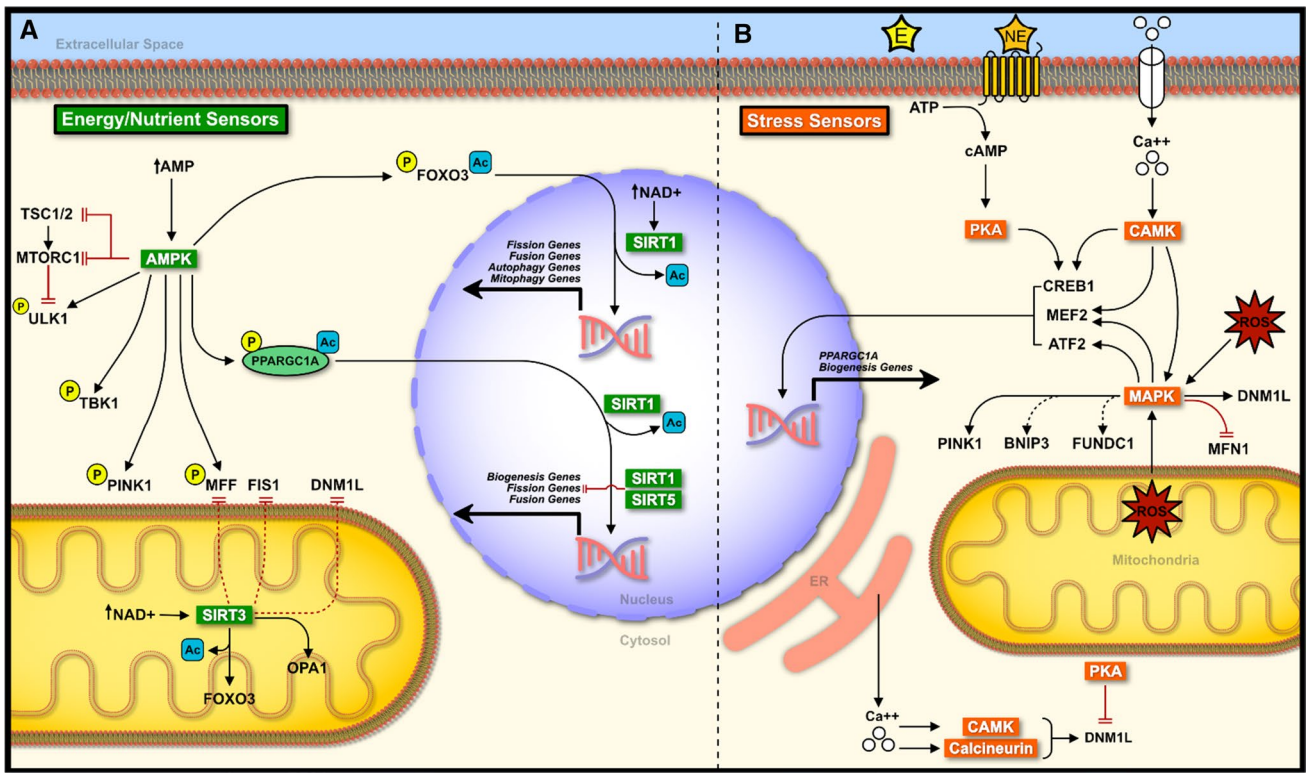

Fig. 5 Interplay between mitochondrial biogenesis, dynamics, and mitophagy. **a** Under low energy conditions, AMPK phosphorylates multiple targets to promote the turnover of mitochondria through the promotion of mitochondrial biogenesis, fission, and subsequent mitophagy. Low energy conditions can also stimulate the activity of SIRTs resulting in the deacetylation of target proteins and transcription factors. SIRTs promote biogenesis, and mitophagy, while inhibiting fission events. Together AMPK and SIRTs provide a fine-tuned response under low energy conditions. **b** A number of stress sensors work together to promote mitochondrial homeostasis. PKA, CAMK, calcineurin, and MAPK all promote biogenesis and mitophagy. CAMK, calcineurin, and MAPK also promote fission whereas PKA inhibits fission through the modulation of DNM1L function. Thus, these stress sensors display a similar fine-tuned response to that of AMPK-SIRT. Solid black lines indicate direct activation. Solid red lines indicate direct inhibition. Dotted lines indicate indirect activation (black) or inhibition (red). *E* epinephrine, *NE* norepinephrine

AMPK also activates autophagy, these authors also demonstrated that AMPK-mediated mitochondrial fission preceded mitophagy events [144].

AMPK also phosphorylates several target proteins required for the synthesis of autophagic machinery. AMPK can inactivate the nutrient sensor MTOR complex 1 (MTORC1) directly through the phosphorylation of regulatory-associated protein of MTOR (RAPTOR) [145], or indirectly via phosphorylation of upstream tuberous sclerosis 1/2 (TSC1/2) [146]. Inactivation of MTORC1 and AMPK-mediated phosphorylation of forkhead box O3 (FOXO3) enables its translocation to the nucleus and enhances its transcriptional activity [147]. FOXO3 regulates several autophagy (ULK1, BECN1, MAP1LC3, etc.) and mitophagy (BNIP3 and BNIP3L) factors [148, 149]. AMPK also directly phosphorylates ULK1 at Ser555, enabling it to translocate to the mitochondria and initiate autophagosome formation [150]. Furthermore, AMPK isoform AMPKα2 was found to phosphorylate PINK1 at Ser495 to enhance the recruitment of PRKN and concomitant mitophagy [151]. AMPK-mediated mitophagy can also occur independent of PRKN. For example, phosphorylation of TANK binding kinase 1 (TBK1) at Ser172 via ULK1 can promote recognition and engulfment of damaged mitochondria in a PINK1/PRKN-independent manner [152]. This is possible through TBK1-mediated phosphorylation of autophagy receptors including OPTN, CALCOCO2, and SQSTM1, which serves to enhance their binding capacity [152, 153].

Sirtuins (SIRTs) are a class of nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases that are responsible for a plethora of biological functions [154]. SIRT1 and SIRT3 have been widely investigated with regards to mitochondrial biogenesis. SIRT1 localizes in the nucleus while SIRT3 localizes exclusively in the mitochondria. Similar to AMPK, SIRTs become active during low energy states when the NAD^+:NADH ratio shifts toward higher levels of NAD^+. Knockdown of SIRT1 or SIRT3 in cells results in reduced fatty acid oxidation/oxidative metabolism, reduced PPARGC1A deacetylation, and elevated reactive oxygen species (ROS) generation with no change in mtDNA:nDNA [155–157]. *Sirt1* knockout mice display lower *Ppargc1a* mRNA [158]; however, it remains unknown whether this leads to reduced mitochondrial content (i.e., mtDNA:nDNA). The overexpression of SIRT1 and SIRT3 is able to increase mitochondrial content, likely through the activation of PPARGC1A [156, 159, 160]. Interestingly, SIRT1 but not SIRT3 overexpression is able to increase mitochondrial oxidative function through increased transcription of PPARGC1A [158, 159].

The role of SIRTs in mitochondrial dynamics is to promote cell survival primarily through the inhibition of mitochondrial fission/fragmentation. The activation of SIRT1 via melatonin or SRT1720 treatment invokes a reduction in DNM1L and MFF levels [161–163]. This is accomplished through the activation of PPARGC1A and inhibition of c-Jun N-terminal kinase (JNK) signaling [161–163]. Interestingly, SIRT1 can prime ACT polymerization around mitochondria and in conjunction with AMPK, can lead to mitochondrial fragmentation [164]. Similarly, SIRT3 promotes mitochondrial fusion. SIRT3 overexpression reduces DNM1L, MFF, and/or FIS1 through the inhibition of suppressor of ras val 2 (SRV2), normalization of AMPK-mediated fission, and suppression of JNK signaling [165–167], while also promoting OPA1-mediated fusion [168]. SIRT3 overexpression may also potentiate the fine tuning of fission/fusion events through the deacetylation and activation of FOXO3, resulting in elevated DNM1L, FIS1, and MFN1 [169]. *Sirt3* knockout also leads to inflammation as a result of reduced mitochondrial fusion [170]. Furthermore, SIRT5 can play an auxiliary role in inhibiting mitochondrial fission through the reduction of FIS1 and MID51, which would otherwise lead to fragmentation and mitophagy [171].

Similar to AMPK, SIRTs can promote autophagy and mitophagy under low energy/starvation conditions. Multiple SIRTs can bind and deacetylate FOXO [169, 172–175]. Nicotinamide or resveratrol treatment promote mitophagy through the activation of SIRT1/3, leading to the activation of FOXO3 and subsequent PINK1/PRKN signaling [176, 177]. SIRT1 also impairs PRKN translocation to the mitochondria and delays mitophagy [178]. Furthermore, SIRT3 increases the transcription of genes involved in PINK1/PRKN and BNIP3/BNIP3L-mediated mitophagy through the deacetylation of FOXO3. *Sirt3* knockout reduced FOXO3 deacetylation and subsequent *Prkn* expression in cardiac cells of diabetic animals, whereas overexpression of SIRT3 leads to greater FOXO3 transcriptional activity, greater *Prkn* expression, and activates mitophagy [175]. Upregulated SIRT3-mediated deacetylation of FOXO3 also promotes receptor-mediated mitophagy through the transcription of *Bnip3* and *Bnip3l* under oxidative stress conditions [169]. In other words, SIRT3 has a crossover role in modulating oxidative stress conditions. This has become apparent given that SIRT3 activates mitogen-activated protein kinase 1/3 (MAPK1/3)-cAMP response element-binding protein 1 (CREB1), leading to elevated BNIP3 and mitophagy [174].

In summary, the energy sensors AMPK and SIRTs play similar roles with respect to mitochondrial turnover such that they promote biogenesis and mitophagy to clear away damaged mitochondria and repopulate the cell with healthy mitochondria. Where these sensors differ is with respect to modulating mitochondrial dynamics. AMPK promotes mitochondrial fission, whereas SIRTs normalize AMPK signaling and may promote mitochondrial fusion [165–167]. It may be possible that these sensors work together to

fine-tune the dynamic response of mitochondria under various conditions.

Role of stress sensors

Stress-mediated MAPK signaling plays a part in PPARGC1A activation, particularly in skeletal muscle cells and tissue. Exercise is one of many stressors that can activate MAPK signaling , and thus, increases the expression of *Ppargc1a* [179]. Exercise-induced activation of MAPK is partially a result of the formation of reactive oxygen species (ROS) and elevated cytosolic calcium ion concentrations [180, 181]. Exercise increases levels of phosphorylated MAPK in the nucleus where it can interact and form a complex with myocyte enhancer factor-2 (MEF2), thereby activating MEF2, and increasing the transcription of *Ppargc1a* [182, 183]. MAPK can also phosphorylate activating transcription factor 2 (ATF2), another factor known to enhance *Ppargc1a* transcription [179–181]. The chemical inhibition or dominant-negative mutant of ATF2 significantly reduces *Ppargc1a* mRNA expression in vitro, while chemical- or exercise-induced activation of MAPK leads to increased PPARGC1A promoter activity [179].

MAPK1/3 have been suggested to be important in mitochondrial dynamics through the manipulation of DNM1L and MFN1 activity. In cancer cells, the phosphorylation of Ser616 on DNM1L by MAPK1/3 increases mitochondrial fission and promotes tumor growth [184], while knockout of *Dnm1l* inhibits MAPK1/3 mediated mitochondrial fission [184]. In non-cancer cells, Ca^{2+} influx results in MAPK1/3 activation and subsequent mitochondrial fission through the phosphorylation of Ser616 on DNM1L [185]. Furthermore, MAPK1/3 phosphorylates MFN1 at Thr562 in neuronal cells, inhibiting its function, and thus inhibiting mitochondrial fusion while subsequently increasing fission, and susceptibility to apoptotic stimuli [186]. Taken together, it is possible that under cellular stress the MAPK1/3-mediated DNM1L activation and MFN1 inhibition favours mitochondrial fission and may be an important preceding step in cell death signaling.

MAPK signaling also plays an important role in mitophagy. Early evidence pointed at the localization of MAPK1 at the mitochondria to promote mitophagy in neuronal cells treated with a neurotoxin [187]. MAPK1 and MAPK14 knockdown inhibits mitophagy during starvation and hypoxic conditions while only marginally inhibiting autophagy as a whole [188]. The mechanism of MAPK mediated mitophagy has yet to be fully elucidated; however, there is evidence that MAPK1/3 is an important molecule responsible for the stabilization of PINK1; enabling PINK1/PRKN-mediated mitophagy to occur [189]. Some evidence also suggests that MAPK1/3 signaling can promote PINK1/PRKN-independent mitophagy through the activation of BNIP3 and FUNDC1 [174, 190]; however, more work is needed to fully understand this mechanism.

Calcium signaling is another essential activator of PPARGC1A-dependent mitochondrial biogenesis and mitochondrial fission. Stimulation of skeletal muscle causes the release of stored calcium ions (Ca^{2+}) that activates calcineurin, and calcium/calmodulin-dependent protein kinase IV (CAMK4). Calcineurin interacts with myocyte enhancer factors (MEFs) family of transcription factors that subsequently aid in the transcription of *Ppargc1a* [191]. PPARGC1A can coactivate MEF transcription in a positive feedback loop, and thus, further increase its own expression [191]. Likewise, the overexpression of active calcineurin in skeletal muscle can increase PPARGC1A protein levels [192]. In contrast, CAMK4 phosphorylates and activates CREB1, a transcription factor that induces *Ppargc1a* [191, 193]. Thus, CAMK4 may be working synergistically alongside calcineurin to increase *Ppargc1a* transcription [193]. Together, calcium-mediated mitochondrial biogenesis can work through MEF and CREB1 to ultimately increase *Ppargc1a* expression [191, 193, 194].

Calcium signaling within cells controls mitochondrial dynamics by triggering calcineurin and CAMK2. In both cases the elevation in cytosolic calcium, which occurs during depolarization events, results in the activation of calcineurin and CAMK2. Activation of calcineurin dephosphorylates DNM1L, promoting its translocation to the mitochondria [195–197]. This was demonstrated by a dominant-negative mutant of calcineurin that effectively blocked mitochondrial fission during depolarization. Calcineurin was found to dephosphorylate DNM1L at Ser637 and Ser656 [195–197]. On the other hand, CAMK2 enhances the activity of DNM1L via Ser616 phosphorylation [198, 199], while inhibition of CAMK2 reduces phosphorylation of DNM1L at Ser616 and inhibits mitochondrial fission following ionizing radiation treatment [198]. Similarly, the chronic downstream activation of CAMK2 by isoproterenol (β-adrenergic receptor agonist) administration increases Ser616 phosphorylation of DNM1L in WT cells but not in dominant-negative DNM1L mutant cells [199]. Further research is needed to identify whether calcineurin-mediated dephosphorylation or CAMK2-mediated phosphorylation events occur to mitochondrial fusion proteins (MFN1/2 and OPA1).

Aside from the role of calcium in mediating mitochondrial fission as a priming step for mitophagy, calcium signaling can also promote mitophagy directly through its interaction with PINK1 and PRKN. Depolarization of the mitochondria promotes intracellular flux of calcium resulting in increased *Pink1* mRNA and PINK1 protein expression; potentially as a protective mechanism against increased cytosolic calcium [200]. Another study demonstrated that the OMM protein ras homolog family member T1 (RHOT1) can function as a calcium-sensitive platform for the docking

of PRKN during mitophagy [201]. Furthermore, mitochondrial depolarization can recruit calcium-activated CAMK1 to the OMM to promote PINK1/PRKN-mediated mitophagy [202]. To date, the interaction between calcium signaling and OMM mitophagy receptors (BNIP, BNIP3L, FUNDC1, etc.) is not well understood.

Cyclic AMP (cAMP) is another upstream signal that regulates mitochondrial biogenesis. The activation of cAMP can be mediated by various hormonal signals including epinephrine/norepinephrine, glucagon, thyroid hormone, among others [203–208]. It is worth noting that hormonal cAMP signaling can also reduce mitophagy in instances when mitophagy is overactive (i.e., insulin resistance), and thus, it may be important in fine-tuning mitochondrial degradation. cAMP binds and activates protein kinase A (PKA), which then phosphorylates CREB1. Phosphorylated CREB1 can translocate to the nucleus and ultimately promote PPARGC1A, along with other biogenesis promoting proteins [203, 204, 206, 208].

Cytosolic PKA and OMM bound PKA have been established to inhibit DNM1L activity [196, 209, 210]. PKA phosphorylates DNM1L at Ser656 [196] and Ser637 [209], thereby reducing its GTPase activity and preventing its translocation to the mitochondria. This subsequently results in reduced mitochondrial fragmentation, and likely promotes cell survival [196]. Moreover, a balancing act between PKA and calcineurin has been identified, whereby PKA phosphorylates and calcineurin dephosphorylates Ser656 and Ser637 on DNM1L [195–197]. This cycling between phosphorylation states of DNM1L provides fine control over fission activation and inhibition within cells.

cAMP signaling has also been implicated in PINK1/PRKN-mediated and receptor-mediated mitophagy. Under normal conditions, mitochondrial scaffolding protein A-kinase anchoring protein 1 (AKAP1) recruits PKA to the OMM to phosphorylate DNM1L at Ser637 to inhibit its function, and prevent subsequent mitophagy [211]. Following depolarization, PINK1 recruitment to the OMM displaces PKA from AKAP1, enabling DNM1L-mediated fission and mitophagy [211]. Furthermore, CREB1 signaling alongside MAPK1/3 elevates BNIP3 and FUNDC1 to promote mitophagy [174, 190]. Interestingly, activation of PKA results in BNIP3L phosphorylation and dissociates BNIP3L from the OMM, thereby preventing excessive mitophagy, which can lead to insulin resistance [212].

In summary, cellular stress signaling including ROS, Ca^{2+}, and hormones have considerable interplay with respect to their roles in regulating biogenesis, fission/fusion, and mitophagy. Together these cascades formulate a stress response to promote gross mitochondrial remodeling through increased biogenesis, fission, and mitophagy in an attempt to promote cellular function and survival.

Mitochondrial interplay during skeletal muscle regeneration

Skeletal muscle undergoes continuous cycles of degeneration and regeneration in response to everyday contractile activity or traumatic injury. In order for skeletal muscle to resume normal function, an elaborately coordinated response from different cell types spanning across multiple phases must take place. These phases can be generalized into one of three categories: (1) degeneration/inflammation, (2) myogenesis, and (3) remodeling [213–217]. The first phase occurs immediately following damage and is spearheaded by the infiltration of neutrophils. These cells clear debris through phagocytosis and release chemotactic molecules to attract macrophages, which take over the bulk of the degradation of damaged skeletal muscle tissue [218]. The initial presence of the classical pro-inflammatory phagocytic M1 macrophage and the efficient transition to the alternative anti-inflammatory non-phagocytic M2 macrophage is crucial for the second phase of the regeneration process, myogenesis [216, 218]. Macrophages signal quiescent skeletal muscle stem cells, called satellite cells, triggering their activation into myoblasts. This is accompanied by proliferation, migration, differentiation, and fusion of myoblasts to form de novo skeletal muscle fibres (myofibres) or fusion directly to existing damaged skeletal muscle fibres [213–216]. Throughout these phases, the gross remodeling of the extracellular matrix (ECM) takes place, which involves the removal of old ECM, followed by the deposition of new ECM proteins [214, 219]. These ECM proteins provide the new myofibres with appropriate scaffolding material to mature and resume normal function.

Complete skeletal muscle regeneration can range from 14 to 28 days or more depending on the type/severity of damage and health of the cells involved [220–222]. The multiple steps satellite cells undergo to form myofibres requires extensive intracellular remodeling of the mitochondria. In fact, absence of mitochondrial remodeling has been repeatedly shown to reduce the differentiation capacity of cultured myoblasts [1, 223–228] and diminish the regenerative capacity of skeletal muscle tissue [10, 11, 229, 230]. The mitochondria within skeletal muscle are categorically defined based on their localization within the myofibre. Subsarcolemmal (SS) mitochondrial are located in the periphery of the myofibres and are heavily involved in energy production for transcriptional activities and interact closely with myonuclei [235–237]. On the other hand, intramyofibrillar (IMF) mitochondria are situated at the I-band of the sarcomere and provide energy for muscle contraction [235–237]. Although SS and IMF mitochondria may have divergent physiological roles

and locations within muscle, there is evidence that these populations are linked through the network, and that the architecture of individual mitochondria and the configuration of the network are dependent on the metabolic characteristics of the muscle [238–241]. However, the influence of different populations of mitochondria is unknown in regenerating muscle and during myogenesis. Of note, the dynamic nature of these mitochondria vary considerably between mature skeletal muscle tissue and immature myoblasts [242]. Functional assessment of mitochondrial fusion events revealed that mature myofibres display less frequent fusion events compared to myoblasts [242]. The stable contractile structure (i.e., the myosin-actin complex) of mature skeletal muscle provides a physical barrier that partially limits mitochondrial dynamics compared to immature myoblasts [235–237, 242]. Although mitophagy has been shown to change throughout myoblast differentiation [1, 232], the direct impact of the contractile structure on mitophagic processes is unclear. Nonetheless, upon skeletal muscle damage, there is largescale degradation of these contractile structures [243], which may enable greater mitochondrial network remodeling to occur [242]. The nuances of mitochondrial remodeling are far from being completely understood. This section will highlight the current knowledge of mitochondrial involvement and interplay in satellite cell/myoblast function in vitro and during in vivo skeletal muscle regeneration (Fig. 6).

Mitochondrial fission and mitophagy during myogenesis and skeletal muscle regeneration

Satellite cells and myoblasts are the core of the regeneration process. The differentiation of myoblasts is coupled with metabolic reprogramming that ultimately results in increased OXPHOS and mitochondrial mass to support the newly formed myotubes. One of the features that occurs during the onset of differentiation is mitochondrial fission and

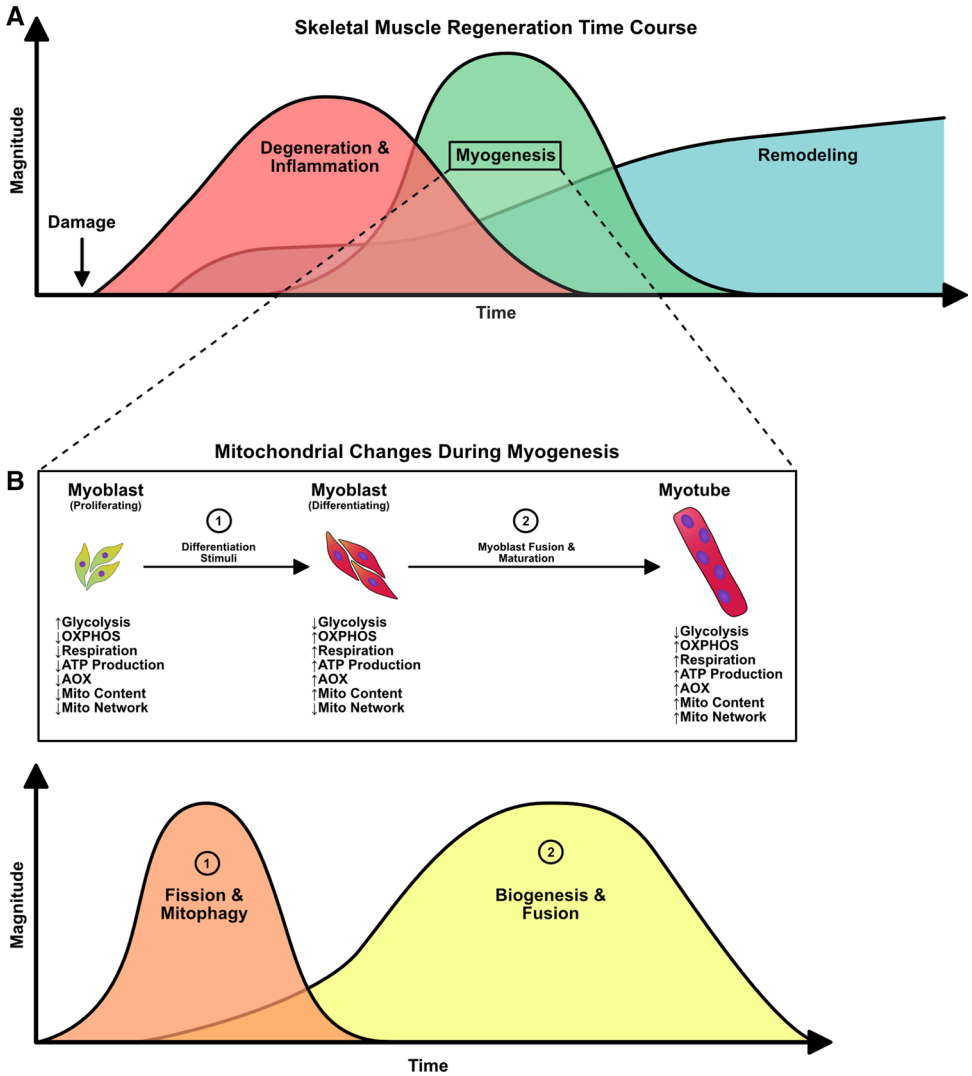

Fig. 6 Mitochondrial alterations during skeletal muscle regeneration. **a** Generalized overview of overlapping stages during skeletal muscle regeneration. **b** Mitochondrial alteration during the "myogenesis" stage, including shift from glycolysis to increased oxidative phosphorylation (OXPHOS) coupled with increased respiration, ATP production, antioxidant (AOX) levels, and mitochondrial content

mitophagy. The mitochondria present in myoblasts are in an immature state, as indicated by their underdeveloped cristae, low levels of β-oxidation, and low overall respiration [232, 244–246]. Upon differentiation stimuli, myoblasts must generate ATP at a higher rate to support the intracellular remodeling that is accompanied by differentiation. In doing so, differentiated myoblasts shift towards a more oxidative phenotype [225, 226]. To undergo this metabolic shift, the existing mitochondria present in myoblasts must be renewed. In C2C12 myoblasts, differentiation stimuli result in an initial yet dramatic increase in DNM1L levels, autophagy, and mitophagy markers [1, 223, 224, 227, 228]. Both the increase in mitochondrial fission and mitophagy have been shown to be essential for differentiation. The chemical inhibition of DNM1L via mdivi-1 treatment has been shown to reduce DNM1L translocation to the mitochondria, thereby reducing fission, and concomitantly leads to impaired differentiation and negligible myotube formation [223]. Likewise, the knockdown of ATG7 or knockout of *Bnip3* in C2C12 myoblasts has been shown to ablate differentiation [1]. In both instances of impaired fission/mitophagy, greater apoptotic activity was noted [1, 223]. Interestingly, ATG7 knockdown and *Bnip3* knockout myoblasts display altered DNM1L and OPA1 levels, suggesting a link between autophagy/mitophagy and mitochondrial dynamics [1]. Nonetheless, these results demonstrate that mitochondrial fission and subsequent mitophagy are important processes that enable the progression of myoblast differentiation.

Studies in skeletal muscle tissue have signified the importance of mitochondrial fission in skeletal muscle growth and maintenance of skeletal muscle mass [247–251]. Skeletal muscle tissue-specific knockout of DNM1L results in reduced mitophagy and causes severe muscle wasting and weakness [248]. However, DNM1L deletion in newborn mice results in no alterations in important myogenic regulatory factors (MRFs) such as myogenic differentiation 1 (MYOD1) or myogenin (MYOG) [248]. In contrast, the overexpression of DNM1L and/or FIS1 causes dysfunction of mitochondrial respiration and reduced mtDNA content as a result of excessive mitophagy [247, 249, 250]. The investigation of this fission/mitophagy phenomena has also been noted in the regeneration skeletal muscle tissue. In vivo myoblast-specific knockout of DNM1L does not alter overall satellite cell content or affect the regeneration program following cardiotoxin (CTX)-induced skeletal muscle damage [247], suggesting that DNM1L does not impair satellite cell function during regeneration [247]. Nonetheless, the investigation into other factors has helped characterize the role of fission during skeletal muscle regeneration. *Fis1* expression dramatically increased between 3 and 5 days following freeze injury which is at approximately the same time that satellite cells are activated [10]. *Fis1* in regenerating skeletal muscle tissue remained slightly above the levels found in undamaged/control tissue for up to 28 days. Consistent with these results, DNM1L is elevated 14 days following cardiotoxin (CTX)-induced skeletal muscle damage [230]. Furthermore, activated ULK1, BNIP3, and MAP1LC3-II were elevated in 14 days post-CTX regenerating skeletal muscle tissue even in animals treated with the autophagy inhibitor, 3-methyladenine (3-MA) [230]. A follow-up study from this same group found an increase in DNM1L, BNIP3, and PINK1/PRKN alongside mitochondrial localization of MAP1LC3B-II in regenerating muscle 7 days post-freeze injury [11]. It would be interesting to investigate whether satellite cells derived from damaged skeletal muscle exhibit a similar response to what is observed in C2C12 myoblasts. Ultimately, this may better elucidate the function of the initial fission/mitophagy processes in satellite cells during skeletal muscle regeneration.

Mitochondrial biogenesis and fusion during myogenesis and skeletal muscle regeneration

As C2C12 myoblasts continue to differentiate and mature into myotubes, so do the mitochondria within the cells. During the differentiation process, myoblasts begin to differentially express MRFs, with MYOD1 and MYOG being two MRFs whose transient expression is required for the progression of myoblast differentiation. In some instances, the elevation of certain MRFs coincides with elevated PPARGC1A, TFAM, cytochrome c oxidase subunit IV (COXIV), and mtDNA [1, 232–234]. Although MYOD1 is expressed early during myoblast differentiation, it has been shown to directly promote the transcription of *Ppargc1b* or enhance *Ppargc1a* expression in the presence of activated SIRT1 [158, 235]. The nuclear localization of PPARGC1A, in particular, follows a similar trend to that of MYOG [228]; however, a direct relationship between the two has not been established. The downregulation of *Ppargc1a* in C2C12 myoblasts increases ROS generation, mitochondrial damage, mitophagy, and results in poor differentiation [232]. Indeed, ROS formation during differentiation may play an important role in promoting mitochondrial biogenesis through MAPK signaling [225]; however, excessive ROS seems to have the opposite effect [232]. This reduction in ROS during the latter half of the differentiation process, as a result of increased antioxidant enzymes [225], may be an important feature for alleviating mitophagy and enabling the repopulation of mitochondria through biogenesis. Moreover, as fission/mitophagy begin to decline and mitochondrial biogenesis machinery increases, so do the levels of fusion protein OPA1 [228]. It is worth noting that the absence of mitophagy during the early stages of myoblast differentiation results in a blunted PPARGC1A response, and decreased mitochondrial protein content [1]. This may emphasize a

greater importance of mitophagy in modulating mitochondrial biogenesis. Nonetheless, mitochondrial biogenesis and fusion lead to increased basal and maximal respiration needed for the highly active myotubes [234].

Similar to C2C12 cell culture experiments, MYOD1 and MYOG are elevated at approximately 3 days post-injury in skeletal muscle tissue and are also synchronous with upregulation of mitochondrial biogenesis genes, including *Ppargc1b*, *Pprc1*, *Nrf1*, *Nfe2l2*, *Esrra*, and *Tfam* [10, 229]. In addition to these critical events, *Mfn1* and *Mfn2* are elevated 3 days following CTX-injury [229], while MFN2 peaks 10 days post-freeze-injury [10]. Although MFN1/2 have well-established roles in maintaining skeletal muscle mass and preventing muscle wasting [44]; the role of MFN1/2 during regeneration has not been explored. In contrast, the role of OPA1 on myogenesis and skeletal muscle regeneration has been characterized. Constitutive skeletal muscle-specific deletion of *Opa1* in neonatal mice resulted in a significant reduction of quiescent and activated satellite cells , with no alteration in apoptosis in these cells, which suggests a link between OPA1 and satellite cell self-renewal [255]. Furthermore, treatment of CTX-injured skeletal muscle with a microRNA against *Opa1* results in a poor skeletal muscle regenerative response, prolonged inflammation, and reduced regenerating myofibre size [256]. These studies suggest that OPA1 may be an important component in satellite cell self-renewal and regeneration; however, additional studies are required to delineate this relationship. Investigation into OPA1 during skeletal muscle regeneration may provide novel insight into its role in maintaining mitochondrial morphology during the different phases of the regeneration process. Nonetheless, the coupling of mitochondrial biogenesis and fusion likely promotes respiration for the regenerating skeletal muscle; however, this has not been assessed. Furthermore, the inhibition of mitochondrial protein synthesis through the administration of Chloramphenicol or the skeletal muscle-specific knockout of *Esrra* has been shown to significantly impair regeneration in freeze- and CTX-injury models, respectively [10, 229]. In these instances, regenerating skeletal muscle displayed smaller fibres, reduced mitochondrial density, increased fibrosis, and diminished oxidative enzyme activity [10, 229]. An interesting feature to note is that when AMPK was forcibly activated 3 days post-CTX-injury via AICAR treatment, a significant impairment in the regenerative response was observed. This suggests that early activation of AMPK beyond physiological levels may not be beneficial to mitochondrial biogenesis or regeneration [229]. Instead, it seems to be more beneficial to allow the skeletal muscle tissue to coordinate its regenerative response to damage without the aid of external compounds that would otherwise promote mitochondrial remodeling. Additionally, it is unknown if mitochondrial biogenesis markers continue to increase as MRFs decline during the second half of the regeneration process (i.e., after satellite cell differentiation and formation of de novo myotube/myofibres), or whether mitochondrial respiration is altered in regenerating myofibres.

Concluding remarks

Accumulating evidence demonstrates that mitochondrial dynamics are intimately involved in regulating mitochondrial remodeling processes. The repopulation of mitochondria is an important step in maintaining cellular function and homeostasis in various cell types, under different stress conditions, and in disease states. Furthermore, dysfunction in these processes has been repeatedly shown to impair cellular function, leading to aberrant changes in cell behaviour. In the case of skeletal muscle stem cells, the precise mechanism and role of these processes has yet to be fully elucidated, and greater emphasis is needed in this regard. Nonetheless, the present data highlights the importance of mitochondrial dynamic and turnover processes in facilitating skeletal muscle regeneration. As this field continues to emerge, it may provide valuable information for the development of inhibitor/activator molecules to enhance skeletal muscle regeneration, particularly in diseased states through the targeting of these various mitochondrial mechanisms.

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