After the banquet
Mitochondrial biogenesis, mitophagy, and cell survival

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Mitochondria are highly dynamic organelles of crucial importance to the proper functioning of neuronal, cardiac and other cell types dependent upon aerobic efficiency. Mitochondrial dysfunction has been implicated in numerous human conditions, to include cancer, metabolic diseases, neurodegeneration, diabetes, and aging. In recent years, mitochondrial turnover by macroautophagy (mitophagy) has captured the limelight, due in part to discoveries that genes linked to Parkinson disease regulate this quality control process. A rapidly growing literature is clarifying effector mechanisms that underlie the process of mitophagy; however, factors that regulate positive or negative cellular outcomes have been less studied. Here, we review the literature on two major pathways that together may determine cellular adaptation vs. cell death in response to mitochondrial dysfunction. Mitochondrial biogenesis and mitophagy represent two opposing, but coordinated processes that determine mitochondrial content, structure, and function. Recent data indicate that the capacity to undergo mitochondrial biogenesis, which is dysregulated in disease states, may play a key role in determining cell survival following mitophagy-inducing injuries. The current literature on major pathways that regulate mitophagy and mitochondrial biogenesis is summarized, and mechanisms by which the interplay of these two processes may determine cell fate are discussed. We conclude that in primary neurons and other mitochondrially dependent cells, disruptions in any phase of the mitochondrial recycling process can contribute to cellular dysfunction and disease. Given the emerging importance of crosstalk among regulators of mitochondrial function, autophagy, and biogenesis, signaling pathways that coordinate these processes may contribute to therapeutic strategies that target or regulate mitochondrial turnover and regeneration.

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Introduction

In addition to ATP production, mitochondria regulate calcium homeostasis, heme and steroid biosynthesis, and cell survival/death decisions.[1,2] For most differentiated tissues, the proper control of mitochondrial content, distribution and activity is key to maintaining normal cellular functions, while mitochondrial metabolism is often dispensable in rapidly growing neoplastic or stem cells.[3] The mitochondrial proteome is also strikingly different between tissue types.[4,5] For these reasons, there are likely to be significant cell-type specific differences, as well as common pathways, underlying the regulation of mitochondrial structure, function, and content, as well as the fate of cells exhibiting increased mitochondrial autophagy. These factors add complexity to the study of mitophagy regulation, particularly in disease states.

The mitochondrial "lifecycle" begins with the coordinated synthesis of nuclear DNA (nDNA) and mitochondrial DNA (mtDNA)-encoded proteins, together with membrane biosynthesis and the proper targeting and folding of respiratory chain subunits. These processes are grouped under the term "mitochondrial biogenesis," although the dynamics of the system preclude facile identification of newly made mitochondria. In contrast, the clearance of intact mitochondrial segments from the cytoplasm is readily visualized through the process of macroautophagy. Coordination between these two processes must be required for the proper regulation of mitochondrial quality and quantity, although mechanisms that underlie such coordination remain relatively understudied. The importance of cross-regulation is further highlighted by recent studies indicating that disruption of the anabolic-catabolic balance between mitochondrial biogenesis and mitophagy could delay post-injury recovery and contribute to cell death.[6-9] Thus, additional studies aimed at this interface may prove fruitful for our understanding of both healthy and disease states.

In the following sections, we review the major regulatory pathways that have been defined for mitophagy and mitochondrial biogenesis, and discuss how these processes may interact to regulate cell fate decisions. Autophagic stress elicited from
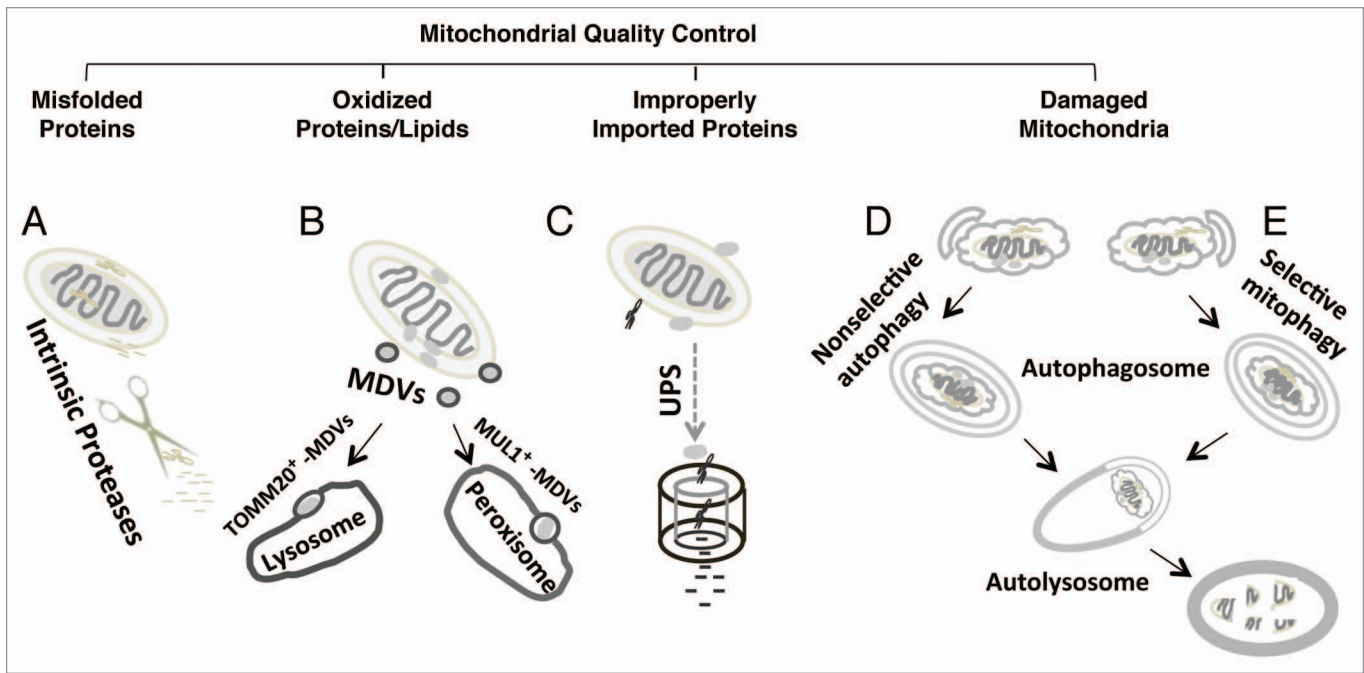
Figure 1. Major clearance pathways engaged in mitochondrial quality control. (**A**) Intrinsic mitochondrial proteases target and degrade unfolded proteins in the matrix and intermembrane space. (**B**) Under conditions of oxidative stress, mitochondria-derived vesicles (MDV) deliver oxidized proteins and lipids for lysosomal and peroxisomal degradation. (**C**) The ubiquitin-proteasome system (UPS) is involved in clearance of damaged outer mitochondrial membrane proteins or improperly targeted nDNA-encoded mitochondrial proteins. Damaged mitochondria may be removed as a consequence of generalized increases in autophagy (**D**) or through specific cargo targeting mechanisms that result in selective mitophagy (**E**). Selective mitophagy also functions to sequester unneeded mitochondria under certain physiological conditions (e.g., maturation of reticuloctyes).

an imbalance between autophagy induction and the successful degradation and reutilization of degraded components can convert a fundamentally adaptive response into a detrimental outcome.[10] Similarly, we propose that the efficiency with which a cell can regenerate mitochondria declines with aging and disease; the ability to balance increased mitochondrial degradation with increased biogenesis may determine the outcome of mitophagy in neurons and other mitochondrially-dependent cells.

Mitophagy and Mitochondrial Quality Control

The degradation of misfolded, oxidized or otherwise damaged mitochondrial components plays a key role in mitochondrial quality control (**Fig. 1**). It has been suggested that the mitochondrion employs its own intrinsic proteases (e.g., LONP1, PARL, and HTRA2/OMI) to degrade unfolded proteins inside the matrix and intermembrane space.[11] In response to oxidative stress, mitochondria-derived vesicles (MDVs) expressing either TOMM20/TOM20 or MUL1/MAPL are formed containing cargoes destined for lysosomal or peroxisomal delivery, respectively.[12,13] Intriguingly, this process does not require mitochondrial depolarization and is independent of the autophagy proteins ATG5 and microtubule-associated protein 1 light chain 3 (MAP1LC3), key mediators of macroautophagy.[13] The proteasome is involved in clearance of damaged or misdirected outer mitochondrial membrane proteins and proteins that fail to be successfully imported.[14,15] Mitochondrial dynamics—fission,

fusion, transport—also play key roles in regulating mitochondrial function and repair, functioning to segregate or exchange damaged mitochondrial components.[16,17] Nevertheless, when mitochondria are subject to severe injury, it is generally accepted that mitophagy is the major mechanism for clearance of the damaged organelles. Programmed or developmental loss of mitochondria, as observed during erythrocyte or lens cell maturation, also occurs through mitophagy. It stands to reason that if mitochondrial degradation is not balanced by a coordinated upregulation of mitochondrial biogenesis, a net loss of mitochondria will occur.

Three major types of autophagic pathways have been characterized: (1) macroautophagy, (2) microautophagy, and (3) chaperone-mediated autophagy (CMA). Macroautophagy (referred to hereafter as autophagy) is a tightly regulated degradation pathway involving the generation of a specialized organelle to target cytoplasmic components to the lysosome. In this manner, autophagy acts as a gatekeeper of cellular homeostasis. Increasing evidence has documented that autophagy plays a pivotal role in numerous biological and physiological processes, including mammalian development and differentiation,[18,19] aging,[20,21] and immunity.[22,23] Aberrations in autophagy are described in neurodegenerative,[24-26] cardiovascular[27] and immunological diseases,[28] and in cancer development.[29]

The process of autophagy involves several steps: induction (nucleation), autophagosome formation (sequestration), maturation to form autolysosomes (fusion), and enzymatic hydrolysis (degradation).[30,31] In addition, from a disease perspective, we propose that the impact of autophagy cannot be fully understood

without consideration of whether or not the liberated molecules are successfully reutilized in biosynthetic pathways, which may become dysfunctional under many pathological conditions.[9,32]

Among different regulatory mechanisms, nutrient starvation is linked to changes in AMP-activated protein kinase (PRKAA2/AMPK) and MTOR signaling, which regulate the phosphorylation states of ULK1/2, the mammalian homolog of yeast ATG1. The details of such regulation have been reviewed elsewhere.[33,34] In addition, noncanonical BECN1/Beclin 1-independent forms of autophagy or mitophagy have been described in response to the complex I inhibitor MPP⁺, resveratrol, mutant leucine-rich repeat kinase 2 (LRRK2) or UV irradiation of individual mitochondria.[35-38] Involvement of these alternative pathways has been implicated in cell fate decisions.

The yeast Atg8 protein and its mammalian homologs are key mediators of autophagosome formation. Atg8 is a cytosolic protein that, upon induction of autophagy, is covalently conjugated to autophagic membranes as they form from a phagophore-assembly site.[39] A portion of Atg8 is recovered from the completed autophagosome by enzymatic cleavage, but a portion remains inside until degraded in the vacuole (the yeast analog of the lysosome).[40,41] MAP1LC3, one of the mammalian Atg8 orthologs,[42] is similarly regulated through ubiquitin-like conjugation catalyzed by mammalian ATG7 and ATG3, and by delipidation reactions involving mammalian ATG4.[43] Thus, lipid-conjugated MAP1LC3 (MAP1LC3-II) is commonly used as a marker of autophagic structures.

MAP1LC3 is regulated by direct phosphorylation of its N-terminal helical region by protein kinase A (PKA), which suppresses its autophagic function.[44] Moreover, MAP1LC3 helices regulate selective autophagy through interaction with cargo adaptor proteins such as SQSTM1 (sequestosome 1/p62),[45] neighbor of BRCA1 (NBR1),[46] the BCL2-related protein BNIP3L/NIX,[47] and the autophagy linked FYVE protein (WDFY3/ALFY).[48]

Role of MAP1LC3-interacting region (LIR) proteins

The BH3 domain-containing BCL2 family members BNIP3 and BNIP3L/NIX were originally identified as intrinsic mitochondrial proapoptotic factors. Later studies suggested both proteins may serve as "receptors" for mitophagy by interacting with key components of the general autophagy machinery. During the course of normal development of the erythroid lineage, the entire cohort of mitochondria is eliminated in mature erythrocytes. BNIP3L is necessary for the sequestration of mitochondria into autophagosomes for selective clearance through a process that is independent of the intrinsic proapoptotic pathway.[49,50] Knockout *Bnip3l*⁻/⁻ mice develop anemia due to reduced life span of erythrocytes that exhibit mitochondrial retention. However, BNIP3L is not required for engagement of the autophagy machinery, implicating a role primarily in cargo recognition. The signaling mechanism involves BNIP3L-dependent loss of mitochondrial membrane potential ($\Delta\Psi_m$) during erythroid maturation, since the uncoupling agent FCCP can reverse the effects of BNIP3L deficiency.[51] BNIP3L-mediated mitophagy is also implicated in the removal of depolarized mitochondria under pathological conditions. In the carbonyl cyanide m-chlorophenyl hydrazone (CCCP) model of mitochondrial injury, the efficient removal of mitochondria is dependent upon two BNIP3L-related events: (1) the reactive oxygen species (ROS)-mediated inhibition of MTOR to induce the general autophagy machinery, and (2) the mitochondrial translocation of PARK2/Parkin and SQSTM1.[52] Thus, in contrast to findings in developmental mitophagy, BNIP3L participates in both induction of autophagy and cargo targeting in this pathological model.

The role for BNIP3 in mitophagic regulation was first described in the ceramide-induced autophagic death of malignant glioma cells.[53] Another study using an adult myocyte in vitro model showed that BNIP3 can induce dynamin 1-like (DNM1L/Drp1) mitochondrial translocation and mitochondrial fission, which promotes a PARK2-dependent mitophagy.[54] Due to the structural similarity of BNIP3 and BNIP3L, it has been proposed that they can regulate autophagy through binding to BCL2 and/or BCL2L1, disrupting the interaction between BCL2 or BCL2L1 and BECN1 to allow the latter to activate the class III phosphatidylinositol 3-kinase PIK3C3/VPS34.[55-57]

Interestingly, BNIP3L contains a LIR domain that is able to physically interact with MAP1LC3 and GABARAP proteins, thereby recruiting the autophagic machinery.[47] Similarly, BNIP3 binds MAP1LC3 to mediate reticulophagy and mitophagy.[58] The list of MAP1LC3 interacting proteins that can mediate the selective sequestration of mitochondria within autophagosomes includes other structurally unrelated proteins such as an outer-membrane protein, FUNDC1, which operates in hypoxic fibroblasts.[59] Mitochondrial lipids that show altered distribution with injury may also facilitate mitophagy through direct interactions with MAP1LC3 (Chu CT, Bayir H, Kagan V, unpublished data). These studies indicate that several changes to the mitochondrial surface may cooperatively or independently serve to enrich for mitochondrial cargo.

The CCCP-PINK1-PARK2 pathway

A major pathway for injury-induced mitophagy, reported initially by the Youle group,[60] has become one of the most widely studied pathways, possibly due to involvement of gene products linked to recessive forms of Parkinson disease. These are PARK2/Parkin, whose mutations represent the most common cause of juvenile onset autosomal recessive parkinsonism,[61] and PTEN-induced kinase 1 (PINK1), which is a mitochondrially targeted kinase implicated in the regulation of mitochondrial quality control.[62,63]

PARK2 is a RING domain containing E3 ubiquitin ligase that can be activated through auto-ubiquitination.[64,65] Under conditions of mitochondrial depolarization induced by mitochondrial uncoupling reagents such as CCCP, PARK2 translocates to mitochondria and mediates mitochondrial degradation.[60,66] Mitochondrial proteins such as BCL2,[67] MFN1/2,[68] and VDAC1[69] are among the substrates of PARK2; although the importance of these ubiquitination reactions for mitophagy remains controversial. It was reported that PARK2 regulates mitophagy by initially engaging the proteasome,[70] whereas other studies suggest that the degradation of mitochondrial outer membrane proteins (TOMM20, TOMM40L, TOMM70A, and SYNJ2BP/OMP25) occurs through a proteasome-dependent, but mitophagy-independent pathway.[15] In any case, the E3

ubiquitin ligase activity of PARK2 is essential for depolarization-induced mitochondrial degradation.

PINK1 shows protective effects against mitochondrial injury induced by neurotoxin challenge, while disease-associated PINK1 mutants or loss of function modeled using RNAi knockdown result in ROS-mediated mitochondrial injury.[63,71] RNAi studies implicate endogenous PINK1 in the suppression of autophagy,[63,72-74] whereas other studies report that dual overexpression of PINK1 and PARK2 promotes mitophagy in the CCCP model.[60,75,76] PINK1 overexpression also suppresses 6-OHDA-mediated mitophagy, possibly by reducing fission or enhancing fusion.[63] The disparate effects of PINK1 in suppressing or promoting mitophagy may reflect differences in subcellular compartmentalization or post-translational modifications of downstream mediators. Recent studies suggest that PARK2 may be auto-ubiquitinated through a PINK1-dependent self-association mechanism in the cytosol.[77,78] These studies disagree, however, on the effect of PARK2 ubiquitination on its participation in mitophagy.

We hypothesize that changes in PINK1 proteolytic processing and/or its subcellular localization regulate whether it serves to stabilize a functional cellular mitochondrial network or regulate its destruction through fission or mitophagy. The effects of PINK1 in promoting autophagy or CCCP-mediated mitophagy require expression of full-length PINK1,[79,80] while the predominant form of PINK1 in normal cells is processed.[81] Under stressed conditions, mitochondrial membrane depolarization prevents mitochondrial import and processing of PINK1, resulting in accumulation of unprocessed PINK1 on the outer mitochondrial membrane to recruit PARK2.[82] This is consistent with studies suggesting that PINK1 acts as an upstream regulator of PARK2,[75,83,84] but the ability of PARK2 overexpression to compensate for PINK1 deficiency[63,83] indicates that PINK1 may not be strictly required for the neuroprotective effects of PARK2 overexpression, even those requiring an intact autophagy machinery.[63]

While the CCCP-PINK1-PARK2 pathway robustly and reproducibly induces nearly complete clearance of mitochondria in transformed cells through proteasomal and lysosomal mechanisms, its biological relevance is less clear. Most studies do not address the viability of the cells either acutely or in longer time frames. In PINK1-deficient cells, mitophagy promotes cell survival, as RNAi knockdown of ATG7 exacerbates cell death.[63] However, HeLa cells overexpressing PARK2 are unable to survive in galactose after CCCP-treatment due to mitochondrial loss, while HeLa cells that lack PARK2 are able to survive.[60] Interestingly, in some studies, neurons either do not exhibit CCCP-induced mitophagy,[85,77] or show delayed, diminished responses compared with HeLa cells.[66] These suggest the possibility of cell-type specific modulatory mechanisms.

Mitogen-activated protein kinase/extracellular signal-regulated kinase

The mitogen-activated protein kinases MAPK1/ERK2 and MAPK3/ERK1 play ubiquitous roles in cell proliferation, differentiation, survival, and death. Nonetheless, the requirement for MAPK1/3 activation in selective autophagy has also been demonstrated.[35,86,87] We previously found that human brain tissues with Parkinson and other Lewy body diseases display abnormal phospho-MAPK1/3 accumulation in aberrant mitochondria, some of which were inside autophagosomes.[88,89] In subsequent in vitro studies, we demonstrated that transfected forms of active, but not kinase-deficient, MAPK1 spontaneously translocate to mitochondria to induce mitophagy, even in the absence of external injury.[90] Inhibiting MAPK1/3 activation with U0126 markedly reduces mitophagy and selective mitochondrial protein degradation in response to mitochondrial toxins.[35,90] Inhibiting MAPK1/3 activation also restores mitochondrial morphology and interconnectivity, blocks the loss of complex I subunits, and reverses the decrease of aerobic respiratory capacities in a chronic model of MPP+ toxicity.[9]

In terms of cellular outcomes, mitophagy associated with sustained MAPK1/3 activation tends to promote cell death.[35,90] This may reflect noncanonical autophagy induction mechanisms,[35,91] or some other factor, such as concurrent suppression of mitochondrial biogenesis.[9]

Mitochondrial Biogenesis in Health and Disease

Mitochondria consist of over 500 different proteins, with significant variations in composition by organism and tissue type. Most mitochondrial proteins are encoded by nuclear genes and synthesized on cytosolic ribosomes, whereas mtDNA encodes 13 essential respiratory chain complex subunits. Precise coordination and crosstalk between the nuclear and mitochondrial genomes would be expected in mediating appropriate responses to changes in physiological status as well as pathological stresses. However, our understanding of this cross-regulation is largely restricted to how nuclear factors promote the synthesis of proteins required for mitochondrial biogenesis. With the exception of apoptotic signaling, much less is known of mechanisms by which mitochondria communicate back to the nucleus.

Mitochondrial biogenesis is a complex process that includes mtDNA transcription and translation, translation of nDNA-encoded transcripts, membrane recruitment, protein import and assembly of the oxidative phosphorylation complexes.[92] Mitochondrial biogenesis is tightly controlled by hormone- or growth factor-initiated intracellular signaling pathways and the resultant activation of nuclear transcription factors.[93] Among these, peroxisome proliferator-activated receptor gamma, coactivator 1 α (PPARGC1A/PGC-1α), nuclear respiratory factors (NRF1, NFE2L2/NRF2) and transcription factor A, mitochondrial (TFAM) are the major players. Numerous factors including hormones, second messengers (calcium, endothelial nitric oxide synthase eNOS, cAMP), and kinase pathways (PKA, MAPK, PRKAA2) act to regulate the process at different levels, by regulating PPARGC1A expression, protein localization or post-translational modifications (**Fig. 2**).

The regulation of PPARGC1A function

PPARGC1A, a master regulator of mitochondrial biogenesis, belongs to a family of transcriptional coactivators that includes PPARGC1B and the peroxisome proliferator-activated receptor gamma, coactivator-related 1 (PPRC1).[94] PPARGC1A is ubiquitously expressed and is capable of driving virtually all aspects of mitochondrial biogenesis, including transcription of respiratory

Figure 2. The regulation of mitochondrial biogenesis by the PPARGC1A-NRF1-TFAM pathway. PPARGCA is activated in response to environmental (cold), physiological [exercise or caloric restriction (CR)] or pathological stimuli (oxidative stress). One major pathway involves PKA phosphorylation of CREB that in turn activates PPARGC1A and multiple transcription factors (NRFs, YY1, ERRs, etc.) to result in the synthesis of both nDNA-encoded mitochondrial proteins and mitochondrial transcriptional regulators such as TFAM. TFAM in turn functions to stabilize mtDNA and promote the synthesis of mtDNA-encoded subunits of the electron transport chain (Ox-Phos/ETC). cAMP-associated phospho-activation and/or deacetylation by SIRT1 increases the activity of PPARGC1A. PPARGC1A can also traffic to mitochondria, where it interacts with TFAM at the mtDNA D-loop. Several major signaling pathways such as MAPK1/3, MYC, MAPK12, and PARK2 are also implicated in modulating mitochondrial biogenesis at different levels. In addition, the PRKAA2, PINK1-PARK2, PKA, and MAPK1/3 pathways also regulate mitophagy, potentially serving to coordinate overall changes in mitochondrial content.
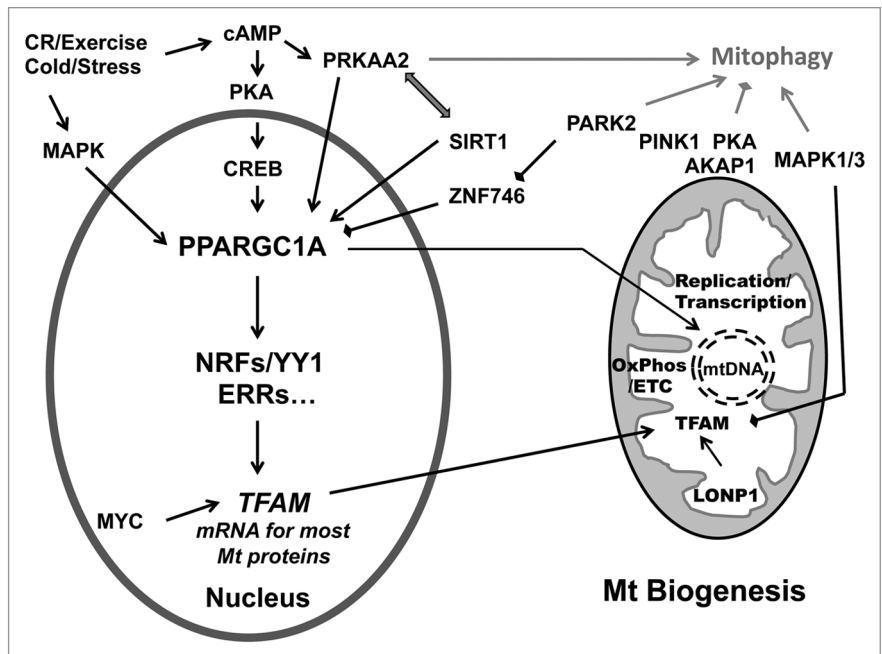
chain and fatty acid oxidation genes, increasing mitochondrial mass, and augmenting mitochondrial respiratory capacity. As an adaptive response to physiological changes such as exercise or caloric restriction, or to pathological stimuli such as oxidative stress, PPARGC1A levels are upregulated, activating transcriptional factors such as nuclear respiratory factors (NRFs), estrogen-related receptors (ERRs), YY1 transcription factor, forkhead box O1 (FOXO1), and myocyte enhancer factors (MEF2/Myef2).[95,96]

The activity of PPARGC1A is related to its expression level, subcellular localization, and post-transcriptional modifications.[97-99] PPARGC1A is predominantly cytoplasmic, but, upon phosphorylation, it is retained in the nucleus to upregulate mitochondrial biogenesis.[98] The nuclear accumulation of PPARGC1A can also be initiated by deacetylation.[97,98] Thus, there are many points of signaling crosstalk for this master regulator of mitochondrial biogenesis.

Recent studies show that PPARGC1A is also localized in the mitochondrial compartment,[9,99,100] where it interacts with TFAM at the mtDNA D-loop.[100] In response to exercise, both nuclear and mitochondrial pools of PPARGC1A serve to promote mitochondrial biogenesis,[101] while decreased mitochondrial PPARGC1A levels may contribute to impaired mitochondrial biogenesis in response to chronic MPP+ intoxication.[9] This transcription factor, therefore, represents one possible mediator of coordinated mtDNA and nDNA transcriptional responses, although its precise role in the mitochondria remains to be elucidated.

There are several major signaling pathways that function upstream to regulate the activation and bioavailability of PPARGC1A. PRKAA2/AMPK functions to upregulate PPARGC1A activity[102,103] by sensing changes in the AMP/ATP ratio.[104] In skeletal muscle, PRKAA2 phosphorylates PPARGC1A at threonine 177 and serine 538, initiating its gene-regulatory functions.[105] SIRT1, an NAD+-dependent deacetylase

implicated in longevity and stress responses, also participates in PRKAA2-related pathways.[106] PRKAA2 enhances SIRT1 activity by increasing intracellular NAD+ levels.[107] SIRT1 deacetylates PPARGC1A to promote its nuclear translocation.[97] Alternatively, SIRT1 can activate PRKAA2 via deacetylation, and activation of the PRKAA2 kinase STK11/LKB1, further increasing phosphorylation of PPARGC1A.[108] In contrast, acetylation of PPARGC1A by the K(lysine) acetyltransferase 2 (KAT2/GCN5) represses its activity,[109] in response to excess calories and the steroid nuclear receptor coactivator 3 (NCOA3/SRC3).[110]

The cAMP responsive element binding protein (CREB) is another potent inducer of PPARGC1A expression. In response to environmental stimuli, increases in cAMP levels activate PKA. Phosphorylation of CREB activates a downstream cascade of transcriptional complexes involving PPARGC1A, NRF1 and NFE2L2, and TFAM.[111] In Huntington disease, mutant HTT/huntingtin inhibits expression of PPARGC1A by interfering with the CREB-TAF4-dependent transcriptional pathway.[112] As both PRKAA2 and PKA pathways function to regulate autophagy, these pathways may function to coordinate mitochondrial degradation-biogenesis responses (**Fig. 2**).

Different branches of the MAPK family show multiple effects on mitochondrial biogenesis. Exercise-induced activation of MAPK12 (p38γ) in mice serves to increase PPARGC1A promoter activity, whereas overexpression of dominant negative MAPK12 attenuates mitochondrial biogenesis.[113] Phosphorylation of PPARGC1A by MAPK12 may act by enhancing its ability to promote binding of NRF1 to the cytochrome *c* promoter and of NFE2L2 to the cytochrome oxidase subunit promoter,[114,115] or by disrupting its interaction with MYBBP1A [MYB binding protein (P160) 1a] in myoblasts.[116]

The MAPK1/3 signaling pathway regulates PPARGC1A activity in a context- or cell-type dependent manner. In Schwann

cells, insulin-like growth factor increases mitochondrial DNA replication and mitochondrial biogenesis,[117] and acetyl-L-carnitine upregulates PPARGC1A and NRF1 levels in hypoxic hippocampal neurons,[118] both through MAPK1/3-dependent mechanisms. However, in other studies, it is the inhibition of MAPK1/3 signaling that enhances PPARGC1A expression, promoting mitochondrial biogenesis in amyloid β injected rats.[119] MAPK1/3-dependent decreases in the mitochondrial pool of PPARGC1A level are observed in a chronic model of MPP+ toxicity; inhibiting MAPK1/3 activation restores mitochondrial levels of both PPARGC1A and TFAM, corrects a deficit in mitochondrial protein translation and results in enhanced mitochondrial function.[9]

While many of the pathways discussed above center on PPARGC1 transcription or post-translational activation, other pathways regulate its bioavailability through degradation. For example, glycogen synthase kinase 3 β (GSK3B) is a kinase, implicated in several models of cell death that negatively regulates PPARGC1A by promoting its proteasomal degradation.[97]

The NRF transcription factors

The nuclear respiratory factors, NRF1 and NFE2L2/NRF2, were the first nuclear transcription factors implicated in the expression of multiple mitochondrial proteins in vertebrates. NRF1, initially identified through its binding to the cytochrome *c* promoter, functions as a positive regulator of transcription.[120] NRF1 binds to gene promoters encoding respiratory subunits, as well as the mitochondrial transcription factors TFAM and TFBs to regulate mitochondrial transcription and ribosome assembly.[121] NFE2L2 was identified based on its specific binding to essential *cis*-acting elements in the cytochrome oxidase subunit IV (COXIV) promoter,[122] and subsequently shown to associate with all 10 nDNA-encoded cytochrome oxidase subunits.[123] Inhibition of NFE2L2 by expression of a dominant negative NFE2L2 allele or using siRNA reduces nDNA-encoded COX subunit expression.[124] In addition to the effect on COX promoters, NFE2L2, in cooperation with NRF1, regulates mitochondrial transcription through effects on the expression of TFAM, TFB1M, and TFB2M.[125]

PPARGC1A controls the expression of NRF1 and NFE2L2,[126] and their activities are in turn regulated by post-translational modifications. NRF1 exists in a dephosphorylated state in serum-starved cells and is phosphorylated upon addition of serum.[127] Serine phosphorylation within its N-terminal domain enhances its DNA binding[127] and *trans*-activation function.[128] In rat hepatoma cells, ROS elicit phosphorylation of NRF1 by AKT1, enhancing its nuclear translocation and increasing TFAM expression.[129] In human breast cancer MCF-7 cells treated with sodium butyrate, NRF1 is acetylated by EP300-CREBBP, which enhances DNA binding.[130]

Mitochondrial transcription factor A

TFAM is a key regulator of mtDNA replication and transcription in vivo, which is essential for mitochondrial biogenesis and embryonic development.[122,131] TFAM was first identified as a high mobility group box protein that stimulates transcription through specific binding to recognition sites in mtDNA.[132] TFAM protein levels are associated with mtDNA copy number. Heterozygous

Tfam+/− knockout mice exhibit reduced mtDNA copy number and respiratory chain deficiencies in heart, while homozygous knockout abolishes oxidative phosphorylation.[131] On the other hand, overexpressing human TFAM stimulates mitochondrial biogenesis and ATP synthesis, and prevents MPTP/MPP+-induced neuronal degeneration.[9,133,134]

In addition to PPARGC1A and NRF proteins, MYC/c-Myc can directly bind to the TFAM promoter, leading to its transcriptional upregulation in lymphocytes.[135] Overexpression of MYC leads to increased mitochondrial biogenesis.[136]

LONP1 is a protease in the eukaryotic mitochondrial matrix that regulates TFAM stability. RNAi knockdown of LONP1 increases TFAM levels and mtDNA copy numbers, while overexpressing LONP1 has the opposite effects;[137] RNAi knockdown of LONP1 also partially prevents the MPP+-induced depletion of TFAM.[9] Interestingly, recent studies suggest that TFAM may also play a role in the nucleus,[138,139] although the relationship to mitochondrial gene transcription remains unknown.

Mitochondrial biogenesis in aged muscle and cardiovascular diseases

Reduced mitochondrial mass and mitochondrial protein quantity are common findings in aging. The decrease in cellular capacity for mitochondrial biogenesis is associated with reduced levels of PRKAA2 and PPARGC1A in skeletal muscle.[95,102,140] Exercise training can increase PPARGC1A levels, attenuating age-associated decreases in mitochondrial mass as assayed by measuring citrate synthase or cytochrome *c* oxidase in young and old rat muscles.[141] The effect of exercise on indices of mitochondrial biogenesis has been confirmed in human studies.[142,143] Pharmacologically activating PRKAA2 results in improvement of aging-induced cardiomyocyte contractile deficits.[144] However, other studies show that exercise training in aged animals fails to increase PPARGC1A levels and does not enhance mitochondrial biogenesis.[145] Old rats also show impaired mitochondrial biogenesis in response to chronic activation of PRKAA2 with β-guanidinopropionic acid.[102] It is possible that impaired nuclear import, as observed in models of oxidative injury,[32] or dysregulation of downstream pathways may limit efficacy of PPARGC1A-targeted therapies in aged or diseased settings.

Treadmill training has been reported to reduce infarct volume and improve post-ischemic recovery of brain function, in association with increased indices of mitochondrial biogenesis.[146,147] Other strategies to target mitochondrial biogenesis have also been described in hypoxic/ischemic injury. Selenite treatment increases protein levels of PPARGC1A and NRF1 to restore mitochondrial functional activities, ameliorating cerebral infarct volume.[148] In this animal model, selenite pretreatment also attenuates ischemia-induced activation of BECN1 and MAP1LC3-II to inhibit autophagy. Levo-triiodothyronine significantly increases the expression of PPARGC1A and TFAM in the peri-infarct zone, resulting in enhanced markers of mitochondrial biogenesis in a rat myocardial infarction model. The treatment reduces infarct-scar size, and increases angiogenesis and cell survival.[149]

Mitochondrial biogenesis in cancers

Markers of mitochondrial biogenesis are usually decreased in tumors.[150-153] Decreased expression of PPARGC1A and TFAM

is found in lung cancers.[151] Application of the PPAR agonists bezafibrate[150] or resveratrol[151] increases the levels of PPARGC1A, TFAM, oxidative phosphorylation components and mtDNA in cultured cervical carcinoma, osteosarcoma and breast cancer cells, decreasing their growth rates and invasive potential.[150] Likewise, overexpression of PPARGC1A drives mitochondrial biogenesis while inducing apoptosis in the human intestinal cancer cells.[152,153] These observations may relate to the known propensity of cancer cells to downregulate mitochondrial respiration in preference to aerobic glycolysis.

However, in other tumor types such as Bowen disease[154] or endometrial carcinoma,[155,156] increased mitochondrial biogenesis is linked to growth of tumors. An increase in mtDNA content and mitochondrial biogenesis is also associated with activation of PPARGC1A in type I endometrial cancer.[155,156] Thus, the potential role for manipulating mitochondrial biogenesis remains unclear in neoplasia.

Mitochondrial biogenesis in neurogenerative diseases

In contrast to cancers, there is more evidence to support a possible therapeutic role for modulating mitochondrial biogenesis and mitochondrial turnover in neurodegenerative diseases such as Huntington, Alzheimer, and Parkinson diseases.[112,133,157-162]

Decreased mitochondrial function is a common feature for several neurodegenerative diseases. These include significant reductions in the enzymatic activities of mitochondrial oxidative phosphorylation complexes accompanied by decreased expression of PPARGC1A and its downstream targeted proteins in Huntington,[163-165] Alzheimer,[157,166-168] and Parkinson patients.[169,170]

Mutant HTT suppresses PPARGC1A expression, whereas crossbreeding of *Ppargc1a* knockout (KO) mice with HD knockin (KI) mice leads to increased neurodegeneration of striatal neurons and motor abnormalities in the HD mice.[112] Overexpressing PPARGC1A or pharmacologically activating PPARGC1A can partially reverse the toxic effects of mutant HTT in cultured striatal neurons, increasing the number of mitochondria, and improving survival in mouse models of HD.[112,161] Interestingly, PPARGC1A can also upregulate the autophagy-lysosome pathway through activation of transcription factor EB (TFEB) to promote the clearance of HTT aggregates.[171] In Alzheimer disease, overexpression of PPARGC1A improves mitochondrial biogenesis and function in APPswe M17 cells,[157] protects against amyloidogenic Aβ accumulation and promotes cell survival.[168,172,176] Recombinant TFAM restores mitochondrial gene expression in cybrid models of optic neuropathy.[173]

A meta-analysis of gene expression studies indicates that loss of PPARGC1A is a major factor in Parkinson disease.[170] PPARGC1A-deficient mice are much more susceptible to MPTP toxicity,[174] while overexpression of TFAM or PPARGC1A can prevent neuronal cell damage induced by MPTP, oxidative stress, mutant SNCA/α-synuclein or the pesticide rotenone.[134,170,174,175] However, another study shows that a persistent high level of PPARGC1A expression causes selective loss of dopaminergic neurons, and reverses its protective effects in a model of SNCA overexpression.[176] These studies suggest that tight control of PPARGC1A levels in a physiological range is crucial for its neuroprotection.

Proposed Interplay of Mitochondrial Biogenesis and Mitophagy in Determining Cell Fate

Both mitochondrial autophagy and mitochondrial biogenesis are complex, regulated pathways. The balance of mitochondrial biogenesis and degradation responses regulates the content of mitochondria within cells. Under normal situations in which the complete cycle of degradation and regeneration is intact, factors that tip the balance between these processes most likely reflect developmental changes in the demand for mitochondrial function. Under pathological conditions, however, we propose that imbalanced responses in either direction can contribute to cellular degeneration and susceptibility to cell death (**Fig. 3**).

Decreased mitochondrial content or function, often accompanied by reduced levels of PPARGC1A or NRF1, are commonly observed with aging[145,177] and in neurodegenerative diseases, cancer, cardiovascular or liver diseases.[151,178,179] At the same time, oxidative or other forms of damage related to either genetic or environmental factors serve to promote mitophagic turnover of mitochondria.[35,60,63,90] Our recent data suggests that the ability of neuronal cells to undergo mitochondrial biogenesis may dictate whether or not the mitophagic response is successful in compensating for chronic, low level impairment of complex I function.[9] We propose that the clearance of marginally functional mitochondria at more rapid rates than regeneration of functional mitochondria is maladaptive in mitochondrially dependent cell types. In this context, blunting or slowing the mitophagic response while enhancing mitochondrial biogenesis may prove effective.

On the other hand, a deficiency in autophagy as observed in other disease models can lead to accumulation of damaged or less efficient mitochondria.[180-182] ROS are liberated as a byproduct of oxidative phosphorylation, particularly in damaged or marginally functional mitochondria. Moreover, depolarized mitochondria are unable to effectively buffer cytoplasmic calcium, and may undergo the mitochondrial permeability transition to release cytochrome *c* and other pro-apoptotic mediators. While loss of mitochondrial function would be expected to trigger compensatory mitochondrial biogenesis, this short-term solution may ultimately lead to larger reservoirs for release of ROS or apoptotic mediators from further accumulation of marginal mitochondria. So how then is feedback between the processes of mitophagy and mitochondrial biogenesis regulated?

Pathways that regulate both mitophagy and mitochondrial biogenesis

Several signaling pathways are implicated in both mitophagy and mitochondrial biogenesis, and are likely to play important roles in coordinating these processes.

PKA is a kinase that functions upstream of both PPARGC1A and autophagy, promoting biogenesis,[111] while suppressing autophagy/mitophagy through phosphorylation of MAP1LC3.[44,74] As PKA phosphorylation of DNM1L/DRP1 inhibits its fission-promoting activity,[183] PKA may downregulate mitophagy through that mechanism as well. Whereas PKA is able to promote mammalian mitochondrial mass through more than one mechanism, in yeast, activation of PKA impairs the receptor activity of
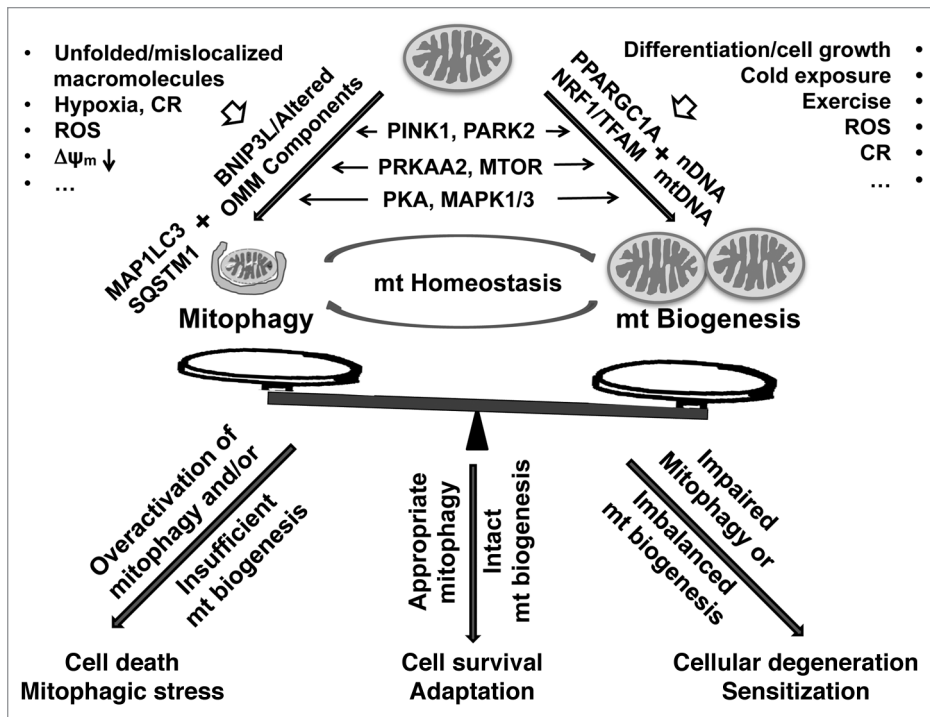
Figure 3. The balance of mitophagy and mitochondrial biogenesis determines cellular adaptation to physiological and pathological stressors. Developmental or pathological stimuli trigger changes on the mitochondrial surface that signal their elimination by the autophagy machinery (top left). Simultaneously, overlapping triggers (e.g., reactive oxygen species [ROS] or caloric restriction [CR]) or activation of shared regulatory pathways (e.g., PRKAA2 or PARK2) function to regulate mitochondrial biogenesis (top right). Individual kinase pathways (MAPK1/3, MTOR, PKA) may show opposing effects on mitophagy and mitochondrial biogenesis to result in either a net decrease or increase in mitochondrial mass. However, restoration of mitochondrial homeostasis under conditions of increased mitochondrial damage would require simultaneous upregulation of mitophagy and mitochondrial biogenesis. This may occur through cellular integration of multiple competing pathways, or involve localized kinase signaling that triggers mitophagy, while biogenesis is triggered elsewhere in the cell. We propose that balanced mitochondrial recycling, as mediated by appropriately coregulated signals for mitophagy and mitochondrial biogenesis, is required for maintaining mitochondrial homeostasis and normal cellular function and survival. However, overactivation of mitophagy relative to the capacity for mitochondrial biogenesis would lead to a net loss of mitochondria, contributing to "mitophagic" cell death in cell types dependent upon mitochondrial function (lower left). Conversely, impaired mitochondrial clearance or excessive/sustained inputs to drive mitochondrial biogenesis also results in imbalanced responses, resulting in increased oxygen consumption and sensitization to stressors (lower right).

mitochondrial translation; however, it inhibits mitophagy, modestly reducing cell death.[35] In contrast, in a low dose, chronic MPP+ model, inhibiting MAPK1/3 activation not only blunts the autophagy/mitophagy response, but also restores the capacity for mitochondrial biogenesis, resulting in restoration of normal mitochondrial structure and function.[9] The protection by U0126 exceeds that induced by *ATG7* RNAi, indicating that survival is dependent upon both reducing mitophagy and restoring normal levels of mitochondrial translation.

As discussed above, PINK1 has been implicated in the regulation of mitochondrial dynamics and autophagy/mitophagy, albeit in a complex, context-dependent manner. Loss of PINK1 also results in decreased mtDNA levels as well as decreased mitochondrial ATP synthesis and activity of complex IV of the electron transport chain in human dopaminergic SH-SY5Y cells, suggesting a possible impairment in mitochondrial biogenesis.[187] Likewise, mouse PINK1 deficiency affects mtDNA copy number, protein levels of biogenesis factors, fission/fusion proteins and bioenergetics in *pink1*−/− mouse hearts, affecting post-natal myocardial development and function.[188] PINK1 is also markedly reduced in end-stage human heart failure. While a definitive link between PINK1 and mitochondrial biogenesis remains to be established, these findings suggest that manipulating PINK1 expression may provide potential therapeutic strategies for some forms of cardiac disease.

Tom70 and inhibits the biogenesis of the channel protein Tom40, which affects mitochondrial protein import.[184,185] The inappropriate activation of one of the yeast PKA catalytic subunits, Tpk3 promotes the production of dysfunctional, ROS-producing mitochondria and causes cell death.[186] It is apparent that the effects of PKA on mitochondrial clearance and biogenesis are context dependent. In mammals, the data suggest that PKA tilts the balance to favor increased mitochondrial mass.

In contrast to PKA, which upregulates mitochondria, the MAPK1/3 pathway serves to downregulate mitochondria through opposing effects on mitophagy and mitochondrial biogenesis. Activation of MAPK1/3 stimulates autophagy/mitophagy in Parkinson models,[35,90] potently inhibiting mitochondrial biogenesis,[9] and promoting cell death. Interestingly, at high concentrations of MPP+, blocking MAPK1/3 does not improve

PARK2 not only plays an important role in CCCP-induced mitochondrial degradation, but also is involved in the regulation of mitochondrial biogenesis. PARK2 is associated with TFAM, enhances TFAM-mediated mitochondrial transcription and promotes mitochondrial biogenesis.[189] Disease-associated PARK2 mutations abolish its interaction with TFAM and mtDNA.[189,190] ZNF746/PARIS, a substrate of PARK2 represses the expression of PPARGC1A and its target gene, NRF1.[191] *Park2* knockout leads to a ZNF746-related loss of dopaminergic neurons, which is reversed by PPARGC1A overexpression.[191] Thus, PARK2 appears to promote mitochondrial health by enhancing both the mitophagy and biogenesis phases of recycling.

Mitochondrial biogenesis and autophagy/mitophagy are also regulated in a coordinated manner[192] by PRKAA2 and PPARGC1A. In response to nutrient starvation or the

mitochondrial uncoupler CCCP, the activation of PRKAA2 suppresses the MTOR pathway to elicit autophagy/mitophagy responses.[33,193] At the same time, PRKAA2 initiates mitochondrial biogenesis via SIRT1-dependent deacetylation of PPARGC1A[107] or upregulation of PPARGC1A expression.[102,103] Likewise, PPARGC1A also regulates both biogenesis and degradation through transcriptional mechanisms. In a Huntington disease mouse model, overexpression of PPARGC1A not only enhances mitochondrial biogenesis, but also upregulates autophagy-lysosome function via induction of TFEB to eliminate HTT aggregates.[194]

Given the central role of PRKAA2 in sensing the bioenergetics status of the cell to modulate both autophagy and PPARGC1A, it is not surprising that either genetic or pharmacological upregulation of PRKAA2 may represent promising therapeutic strategies for several pathological conditions. Injection with AICAR (5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside), an agonist of PRKAA2, induces autophagy and facilitates the elimination of defective mitochondria, which is associated with improvements in a Duchenne muscular dystrophy mouse model.[195] Acetylcholine provides cardioprotection against hypoxia/reoxygenation injury in a cellular model through a PRKAA2-PPARGC1A-associated mechanism that increases mitochondrial density, mass, mitochondrial DNA copy number, and ATP synthesis.[196]

From these examples, it is clear that crosstalk between autophagy/mitophagy and mitochondrial biogenesis is critical for mitochondrial homeostasis. The accumulation of defective mitochondria and lysosomes in aged myocytes suggests that inefficient autophagy is associated with the development of aging-related disorders in the heart,[197] while enhancing autophagy gene expression can extend the life span of aging flies.[198] Recessive mutations in PINK1 and PARK2 are hypothesized to contribute to defective targeting of damaged mitochondria,[80] and enhanced mitophagy is neuroprotective in PINK1 knockdown cells.[90] The rapid removal of dysfunctional or damaged mitochondria would serve to prevent accumulation of oxidized lipids, proteins, and DNA, limiting the risk of apoptosis.[199] However, overactivation of autophagy/mitophagy without appropriate levels of compensatory mitochondrial biogenesis may also contribute to deficiencies in mitochondrial function and cell death,[35,90,200] or to the degeneration of dendrites in neurons.[201] Replenishment of new mitochondria through mitochondrial biogenesis accelerates recovery of mitochondrial and cellular functions after oxidative stress.[202] Since decreased mitochondrial biogenesis is implicated in aging, cardiovascular diseases, diabetes, and neurodegenerative diseases, therapeutic strategies involving the nonselective stimulation of autophagy may need to consider potential bystander effects on mitochondria.

Conclusions

In summary, mitochondrial quality control includes several tiers: damage prevention, dynamic remodeling and localized repair, mitophagy, and coordinated mitochondrial biogenesis.[62] Mitochondrial biogenesis and mitophagy are two key processes, whose balanced induction may be necessary for cellular adaptation and recovery from stress and injury (**Fig. 3**). We propose that disruption of this balance leads to cellular degeneration or cell death. Understanding the underlying mechanisms that contribute to imbalanced recycling responses and delineating methods to manipulate these two processes are essential for developing new strategies for the treatment of certain human diseases.

Although mitophagy is involved in numerous physiological and pathological conditions, the machineries controlling mitophagy in aging and disease contexts are only beginning to be understood. It appears that the role of mitophagy, like that of autophagy in general, comprises a double-edged sword, emerging as a protective mechanism in response to mild to moderate stress, but leading to cell death when excessively activated. As cell growth, atrophy, and health are dependent upon shifting the balance of anabolic and catabolic processes, we propose that the nebulous concept of "excessive" mitophagy may be defined by the biosynthetic capacities of the aged, injured or diseased cell. In many disease models, promoting mitochondrial biogenesis has been beneficial, although an excess of mitochondrial biogenesis may result in increased oxygen consumption and oxidative stress if not balanced by other quality control mechanisms. Thus, a challenge for the future involves delineating mechanisms that underlie the coordinated regulation of mitochondrial function, autophagy, and biogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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