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Physiological functions of mitophagy

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Mitochondria are vitally important organelles within our cells. In addition to being the key energy provider, they perform numerous other essential roles ranging from calcium homeostasis to iron metabolism. Therefore, these mitochondrial functions are dependent on the quality and number of mitochondria, which needs to be dynamic in response to a cell's changing needs. Mitochondrial numbers themselves are controlled by mitochondrial biogenesis and turnover. Multiple pathways exist that result in the turnover of mitochondria, but the focus of this review will be on mitophagy (the autophagy of mitochondria). Here, we will touch on the basic mechanisms of mitophagy and how this has been translated from cell-based studies to complex mammalian systems. We will then examine the tasks that mitophagy serves in vivo. While mitochondrial quality control is a critical function of mitophagy, we will also discuss the recent roles that mitophagy plays in metabolic remodeling.

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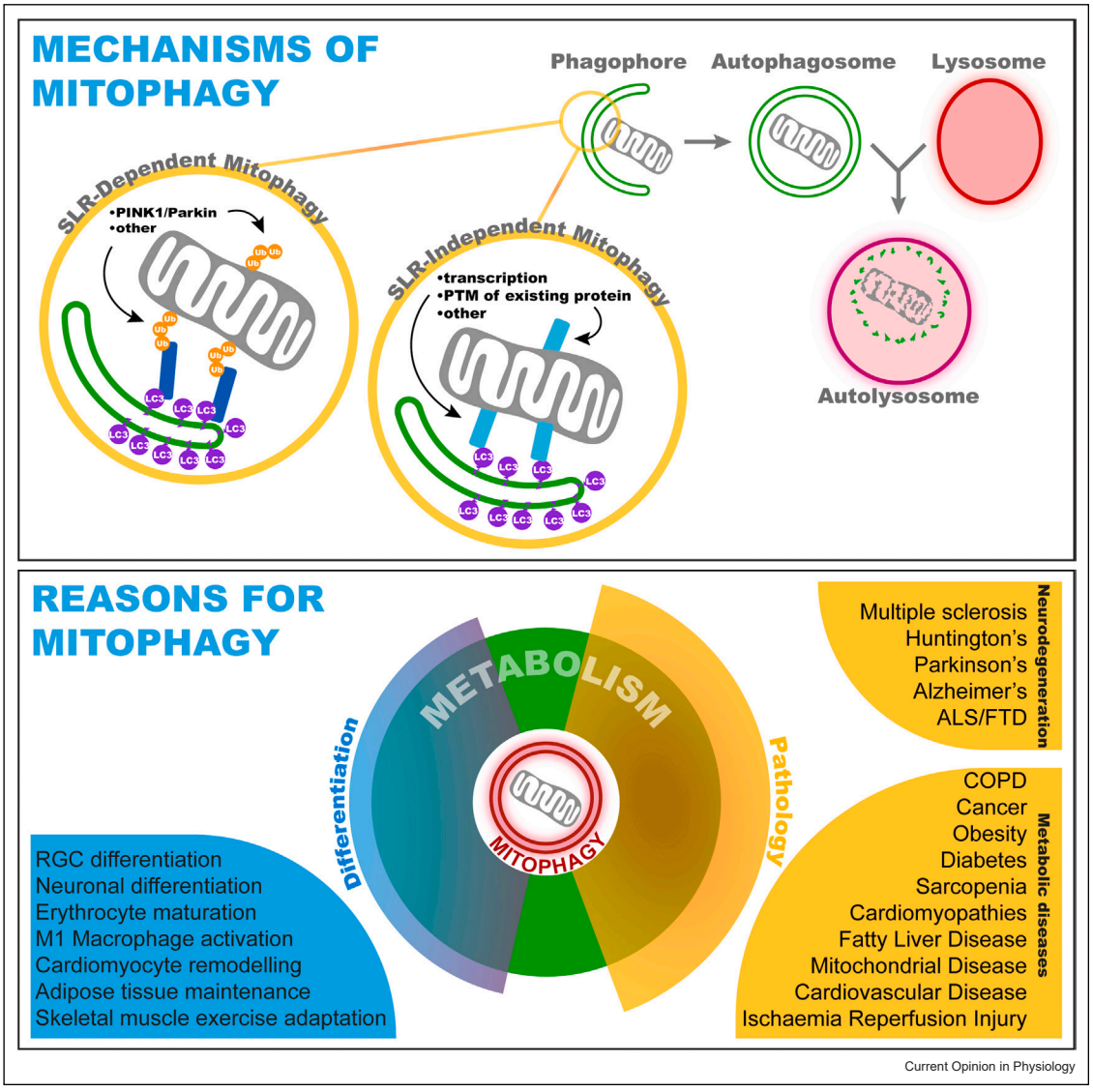
Introduction

Macroautophagy is a membrane-driven lysosomal degradation pathway. It involves the capture and sequestration of cytosolic components within an organelle termed an autophagosome, which forms *de novo* in response to various cellular signals. Once formed, autophagosomes fuse with lysosomes resulting in the degradation and recycling of the sequestered components [1]. In its simplest sense, autophagy is a degradation pathway, however, it plays important and diverse cellular roles, including a protective mechanism to eliminate toxic or potentially harmful components, a nutrient-recycling pathway, or a mediator of cellular remodeling that occurs during differentiation. Given this, it is no surprise that autophagy is essential for vertebrate life [2].

A particular area of autophagy research concerns how specific cargo, or cellular components, are targeted by the autophagy machinery and here we will focus on mitochondria, the autophagy of which is termed mitophagy. While a detailed description of the molecular mechanisms that regulate mitophagy is beyond the scope of this mini-review, there appears to be two main types of mitochondrial targeting. The most studied pathway requires the family of sequestosome-like receptors (SLRs), which are multidomain proteins that can simultaneously bind ubiquitylated proteins on the surface of mitochondria and components of the autophagy-initiating machinery. In this way, it is thought that following the 'tagging' of a mitochondrion with ubiquitin, the SLRs recruit the autophagy machinery to initiate autophagosome engulfment. The second type of mitochondrial targeting proceeds in a similar manner but bypasses the need for SLRs and extensive mitochondrial ubiquitylation, as a resident mitochondrial receptor protein (or even the lipid cardiolipin) can interact directly with the autophagy machinery. In most cases, this occurs upon upregulation of the receptor and/or its post-translational modification. It can also occur upon relocalization of the receptor from inside the mitochondrion to the outer mitochondrial membrane. These processes are summarized in Figure 1, but for more information on the mechanistic details, the reader is referred to these recent reviews [3,4].

As mentioned, SLR-dependent mitophagy has been at the forefront of mechanistic work into mitophagy, largely in part to seminal discoveries showing that PINK1 [5–8], a mitochondrial protein kinase, becomes stabilized upon mitochondrial depolarization where it leads to recruitment and activation of Parkin, an E3 ligase [9]. An elegant mechanism has emerged, summarized here [4], whereby stabilized PINK1 activates Parkin via phosphorylation of both ubiquitin and Parkin itself, leading to ubiquitylation at the mitochondrial surface and recruitment of SLRs. Given that PINK1 and Parkin are mutated in some forms of familial

Figure 1



Physiological functions of mitophagy. Top panel: Basic overview of mitophagy highlighting the two major mechanisms of mitochondrial targeting. In SLR-dependent mitophagy, activation of the PTEN-inducible kinase 1 (PINK1)/Parkin pathway (or other E3 ligases) leads to ubiquitylation of outer mitochondrial membrane proteins. These then bind the cytosolic SLRs (shown in dark blue), which in turn recruit the autophagy machinery, including binding to proteins such as LC3 present in the growing phagophore membrane. In SLR-independent mitophagy, mitochondrial receptor proteins (shown in light blue) are upregulated at the outer membrane, or are post-translationally modified (PTM), to enable them to interact with LC3 and related proteins on the phagophore. The phagophore grows around the mitochondrion and seals to form a mitochondrion-containing autophagosome. This then fuses with a lysosome to form the degradative autolysosome. Bottom panel: Schematic and overview of the roles mammalian mitophagy has been implicated in using physiological models. Metabolism is central to these roles that have been divided into differentiation and pathology. For information on disease implications of mitophagy please see [2]. ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; COPD, chronic obstructive pulmonary disease.

Parkinson's disease (PD), this provided a potential explanation of how a failure to remove faulty mitochondria could lead to the pathology observed in the disease. However, given that key mechanistic work has been carried out in cell lines under harsh conditions, it was not clear how prevalent this type of mitophagy is under physiological conditions.

Mitophagy under physiological conditions

Looking at mitophagy physiologically has proved challenging, especially in mammals. This is in large part due

to the difficulty in easily ruling out other degradation pathways and the fact mitochondria are in close contact with forming autophagosomes, regardless of whether they become engulfed or not [10]. The introduction of fluorescent mitophagy reporter mice, such as the mt-Keima [11] or *mito*-QC [12] mice, has revolutionized this aspect of the field. These mouse models, though expressing distinct mitophagy reporters, work on a similar principle: mitochondria are tagged with a fluorescent reporter with properties that change when the mitochondria move from the cytosol to the acidic environment of the lysosome (normally visualized as a change in color). These models revealed that mitophagy really is a physiological process, with significant evidence of occurrence in most tissues analyzed. These models have also allowed us to examine some fundamental aspects of mitophagy in vivo. Mitophagy is simply not just dependent on the mitochondrial content of the cell. For example, striking mitophagy is seen in the kidney cortex, in the proximal tubules. These structures contain many mitochondria that provide Adenosine triphosphate (ATP) for large-scale salt and protein reabsorption. However, adjacent to these are distal tubules that contain more mitochondria yet display comparatively much mitophagy [12]. Likewise, just because a cell is undergoing significant autophagy in general, this does not necessarily mean it will also be undergoing mitophagy. An example of this was illustrated in the eye, using *mito*-QC mice and another closely related general macroautophagy reporter line [13]. Lens epithelial cells display a large amount of autophagy, but almost no mitophagy. In contrast, a significant amount of autophagy occurring in the photoreceptor cells of the retina is accounted for by mitophagy. Taken together, this suggests that specific signaling is required for mitophagy. Given the prevalent nature of mitophagy in vivo, the next major challenge is to determine the nature of this signaling, and the role mitophagy is playing in these instances. Surprisingly, given the large body of cell-based work, it appears that the PINK1/Parkin pathway plays a minimal role in mitophagy under basal conditions. Loss of PINK1 or Parkin inactivation in *mito*-QC mice failed to significantly change the level of basal mitophagy in multiple tissues [14], a fact that is conserved as the same situation is observed in flies expressing either mt-Keima or *mito*-QC [15], or zebrafish expressing mt-Keima [16]. We do note that in flies, Parkin-dependent turnover of mitochondrial proteins is certainly evident [17,18], and as they age, Parkin-dependent mitophagy is observed [19]. Regardless, it appears likely that the PINK1/Parkin pathway is activated under distinct physiological stressors and while the identity of these is not yet clear, insights from the literature are discussed below. Thus, the nature of all the tissue mitophagy occurring under normal physiological conditions remains somewhat enigmatic. Given that SLR and ubiquitin-driven mitophagy pathways are emerging that work independently of PINK1 and Parkin, such as that exemplified by the ivermectin pathway [20], it is likely that these basal instances are regulated by multiple SLR-dependent and -independent mechanisms.

What then is the physiological role of all this mitophagy? Though there are potentially many, in this mini-review, we will focus on the role of mammalian mitophagy in differentiation and disease, with a particular emphasis on metabolism. Given the metabolic nature of mitochondria, it is no surprise that mitophagy can influence, or be influenced by, the metabolic context of the cell. An overview of mitophagy roles is summarized in Figure 1, a few recent examples of which are highlighted below.

Pathology

Mitophagy is primarily believed to perform a protective function by eliminating damaged and dysfunctional mitochondria that if left to persist could become harmful to the cell. Given this, impaired mitophagy has been shown to be at the core of several pathological conditions, ranging from neurodegenerative to metabolic diseases (summarized in Figure 1).

As previously discussed, loss of function of the PD related PINK1 and Parkin can impair mitophagy in cells, thus providing a compelling hypothesis as to how this disease may progress in vivo, especially given the highly energetic status of the dopaminergic neurons that degenerate in this disease. This hypothesis was further strengthened by work showing that the most common mutation in PD, LRRK2 G2019S, also impairs mitophagy, albeit in a PINK1-independent way, in clinically relevant cells within the mouse brain [21]. In terms of neurodegeneration, a growing body of work now suggests that impaired mitophagy is not exclusive to PD, with evidence suggesting its role may be more widespread with links to Alzheimer's, Huntington's, and amyotrophic lateral sclerosis. For more details here, please see [22,23].

However, it is not yet clear as to whether impaired mitophagy is a key driver of neurodegenerative pathology, or other aspects of mitochondria such as their transport to and from synapses. This is perhaps brought into context by recent work examining the role of Parkin in early tauopathy [24]. Here, phospho-microtubule associated protein tau (MAPT)/Tau activation of Parkin at synapses resulted in the ubiquitylation and degradation of Mitochondrial Rho GTPase 1 (MIRO1), a mitochondrially localized adapter that mediates the anterograde transport of mitochondria. Loss of MIRO1 resulted in increased retrograde transport and hence depletion of mitochondria at the synapse, which manifested as synaptic failure and cognitive decline. Strikingly, this phenotype could be rescued by overexpression of MIRO1, suggesting that the number of mitochondria at synapses may also be relevant rather

than just their turnover per se. It is also important to note that PINK1 and Parkin have also been implicated in an alternate mitochondrial degradation pathway, that of mitochondrial-derived vesicles (MDVs), which bud off from mitochondria and fuse with lysosomes independently of autophagosome engulfment [25,26]. Though not the focus of this review, this pathway has been found to lead to increased mitochondrial antigen presentation and PD-like symptoms in mice lacking PINK1 [27,28].

While there are potentially many mechanisms whereby dysfunctional mitochondria can become harmful, an emerging area suggests inflammation as a key downstream consequence of a failure to clear damaged mitochondria [29]. In particular, release of mitochondrial DNA from damaged mitochondria can trigger inflammation through the cyclic guanosine monophosphate–adenosine monophosphate (GMP–AMP) synthase–stimulator of interferon genes (STING) pathway [30]. Indeed, Klein and colleagues measured interleukin-6 levels (as a readout for the STING pathway activation) in a large cohort of PD patients and found it was a reliable biomarker for patients carrying biallelic *PINK1*/*Parkin* mutations [31].

Inflammation is also a known risk factor for various metabolic disorders, such as diabetes. Increased glucose levels and insulin resistance can lead to mitochondrial dysfunction and production of ROS. The prediction is that increased mitophagy will be beneficial in curbing this disease and recent work supports this hypothesis. For example, proinflammatory cytokines increased ROS production and mitophagy in pancreatic β cells. Importantly, β-cell-specific loss of the protein CLEC16A (previously linked to type-1 diabetes susceptibility and shown to regulate β-cell mitophagy [32]) prevented mitophagy induction in mice upon inflammatory stress, which led to mitochondrial dysfunction and cell death [33].

Differentiation

Given that mitochondria have diverse roles within the cell, it is perhaps not surprising that mitophagy has the potential to affect cells in multiple ways. Given this, mitophagy is emerging not just as a quality control pathway but also as a mechanism that can bring about change within a cell. The best examples of this come from studies showing that mitophagy can play a crucial role in the development and maturation of several cell types. Indeed, basal mitophagy levels are, for example, enhanced during the elimination of sperm-derived mitochondria after fertilization of the egg, erythrocyte development, perinatal cardiac metabolic maturation, and retinal ganglion cell (RGC) differentiation in mammals. During erythropoiesis, colony-forming unit erythroid cells need to undergo a series of programmed processes that lead to the formation of mature enucleated and organelle-free red blood cells [34]. The reason these cells need to lose mitochondria is clear: to increase oxygen storage, by minimizing oxygen consumption by the organelle and maximizing space for hemoglobin. Here mitochondria are cleared, in large part, via mitophagy. A critical step in this mitophagy involves upregulation of the outer mitochondrial membrane protein BCL2 Interacting Protein 3 Like (BNIP3L)/NIX, an autophagy receptor that interacts directly with the autophagy machinery to mediate an SLR-independent form of mitophagy [35,36]. A loss of NIX in mice leads to the presence of mitochondria in mature red blood cells and anemia.

BNIP3L/NIX-dependent mitophagy is not limited to erythropoiesis and appears to play key roles in differentiation processes that are associated with metabolic shifts. An important study showed that programmed mitophagy can drive metabolic changes required for differentiation [37,38]. Boya and colleagues demonstrated that upregulation of NIX-dependent mitophagy, during RGC differentiation, forced increased glycolytic metabolism. This increase was required for early-stage differentiation and a loss of NIX in the retina resulted in a significant reduction of mature RGCs. This may be a common feature in neuronal differentiation, as in addition to neurons of the eye, a similar phenomenon was also observed during the differentiation of induced pluripotent stem cells (iPSCs) to dopaminergic-like neurons [39]. Though the exact role of the increased glycolysis is not known, it is possible that this fuels rapid cell growth in a situation similar to that observed during the Warburg effect for cancer cell growth.

Conversely, mitophagy can also be regulated to promote remodeling toward oxidative metabolism. During the first three weeks after birth, the mitochondrial network in the heart undergoes a significant change to adjust to the change in nutrient availability and ATP demand, with a change from carbohydrate-derived to fatty acid-derived substrate preference [40]. The replacement of fetal mitochondria by mature adult mitochondria was initially shown to be under PINK1/Parkin regulation [41]. However, other SLR-independent mitophagy pathways, such as those driven by NIX or FUN14 Domain Containing 1 (FUNDC1), may also play a role at an earlier developmental stage [42,43]. Again, it is not entirely clear how mitophagy aids in the switch from relying on glycolysis to β-oxidation to accommodate for the increase in ATP demand. It is possible that it becomes more favorable to generate new substrate-optimized adult mitochondria rather than modify the fetal mitochondria already present. In this case, mitophagy aids in the removal of the less-efficient fetal-derived mitochondria.

Another metabolic tissue where mitophagy has been implicated in differentiation is adipose tissue, the major fat repository in the body. There are two main types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). The main function of WAT is to store fat, while that of BAT is to oxidize triglycerides to produce heat. Importantly, under certain conditions of stress, such as chronic cold exposure, white adipocytes can take on properties of brown adipocytes to become beige adipocytes (the so-called browning of WAT). Of relevance here, loss of the core autophagy proteins ATG5 or ATG7 blocked differentiation of mouse embryonic fibroblasts to WAT and mice with tissue-specific loss of autophagy had a reduced WAT tissue mass, with the mutant white adipose cells being much smaller in size yet containing more mitochondria [44,45]. This implies that mitophagy promotes the formation of WAT. In relation to this, mitophagy has also been linked to beige-to-white adipocyte differentiation. Treatment of mice with a β_3-adrenergic receptor agonist leads to increased beige adipocytes. Removal of the agonist results in the beige-to-white adipocyte transition. Using mt-Keima mice, Lu et al [46] showed that Parkin-dependent mitophagy was not only induced but was also required for this transition. Likewise, using different methods, Cairó et al [47] also showed Parkin dependence for this process. It remains to be seen whether the function of this mitophagy is analogous to that mentioned above in the context cardiomyocyte mitochondrial substrate preference, but a switch to carbohydrate-derived substrates for oxidative phosphorylation would certainly favor the increased triglyceride storage associated with WAT (and vice versa for BAT).

Conclusions

Though we have only just skimmed the surface of published work on physiological aspects of mammalian mitophagy, it is clear that this is emerging as a pathway that can influence cell and organismal fate, be this through a protective quality control mechanism, or a metabolic differentiation process. Although certain molecular elements of these diverse pathways have been identified, many remain to be uncovered. Importantly, it is likely that mitophagy is only part of a response driving cellular change and how mitophagy is integrated with other cellular degradation pathways is a key aspect for future work.

CRediT authorship contribution statement

All authors were equally involved in the Conceptualization and writing of the draft. IGG provided overall supervision. Authorship order was decided by the 'Lab Olympics' (speed and accuracy in pipetting, weighing, and racking tips).

Conflict of interest statement

IGG is a consultant for Mitobridge Inc.

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