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Mechanisms of mitochondria and autophagy crosstalk

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Autophagy is a cellular survival pathway that recycles intracellular components to compensate for nutrient depletion and ensures the appropriate degradation of organelles. Mitochondrial number and health are regulated by mitophagy, a process by which excessive or damaged mitochondria are subjected to autophagic degradation. Autophagy is thus a key determinant for mitochondrial health and proper cell function. Mitophagic malfunction has been recently proposed to contribute to progressive neuronal loss in Parkinson disease. In addition to autophagy's significance in mitochondrial integrity, several lines of evidence suggest that mitochondria can also substantially influence the autophagic process. The mitochondria's ability to influence and be influenced by autophagy places both elements (mitochondria and autophagy) in a unique position where defects in one or the other system could increase the risk to various metabolic and autophagic related diseases.

Introduction

Autophagy is a cellular degradation system that is highly conserved among different eukaryotic species. Since the discovery of this pathway over 40 years ago, the identification of autophagy-regulating proteins (ATG) has tremendously increased our understanding of how autophagy functions.[1,2] The orchestrated activation of the pro-autophagic Beclin1/PI3K complex and recruitment of ATG proteins induces the formation of autophagosomes. These double membranous vesicles sequester and degrade cytoplasmic materials. Among the autophagosomal substrates are cytosolic proteins, ribosomes and organelles (such as mitochondria and the ER) as well as bacteria and viruses.[3] The enormous variety of substrates explains the close link between autophagy defects and diverse human diseases, including cancer and neurodegenerative disorders. Seminal studies by Youle and colleagues identified the Parkinson disease-associated proteins Pink1 and Parkin as mediators of the selective degradation of dysfunctional mitochondria by autophagy (termed mitophagy).[4] Disease-associated Parkin mutants caused loss of mitophagy upon mitochondrial damage,[5,6] suggesting that the accumulation of damaged mitochondria could contribute to the mechanism of Parkinson disease.

The selective degradation of mitochondria by autophagy controls mitochondrial number and health. Besides being a substrate for autophagy, accumulating evidence indicates that mitochondria themselves can influence the autophagic process in several ways. To date, mitochondria have been linked to virtually every step of autophagy, including autophagosomal biogenesis and autophagic flux.[7-9] In this short review, we summarize the possible means by which mitochondria and autophagy crosstalk, with an emphasis on the mitochondrial control of autophagy in mammalian cells. The strong interconnection between the mitochondrial and autophagic systems could potentiate the contribution of both systems for neurodegenerative, inflammatory and cancer-related diseases.

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Mitochondria: A Dynamic Organelle

Mitochondria are highly dynamic organelles, with morphologies ranging from small roundish elements to larger interconnected networks. Mitochondrial architecture is not random, rather the opposing processes of fission and fusion specifically determine mitochondrial shape. On the molecular level, mitochondrial morphology is controlled through a family of dynamin-related proteins. Mitofusin 1 and 2 (Mfn1, Mfn2) and optic atrophic protein 1 (Opa1) fuse mitochondria,[10] while fission is mainly regulated by the Dynamin-related protein1 (Drp1) and mitochondrial fission factor (Mff).[11,12]

The dynamic nature of mitochondria allows the adjustment of mitochondrial morphologies to specific cellular processes. For example, before cells enter the energy-costly DNA replication phase (S phase) mitochondria become hyperfused and increase their ATP production.[13] Different cellular pathways can regulate the activity of mitochondria-shaping proteins and adapt mitochondrial architecture to the cell's state.[14] Our best understanding of this regulation relates to Drp1 activity. Multiple posttranslational modifications, including phosphorylation, sumoylation and ubiquitination events, regulate Drp1 activity and thus mitochondrial division.[11,14] Mitochondrial shape is also determined through the activity of fusion proteins. The E3 ligase March5 has been identified to regulate fusion through targeting of Mfn1 and/or Mfn2.[15,16] In addition, fusion is determined through mitochondrial membrane potential, as the activity of the inner membrane fusion protein Opa1 is voltage-dependent.[17-20]

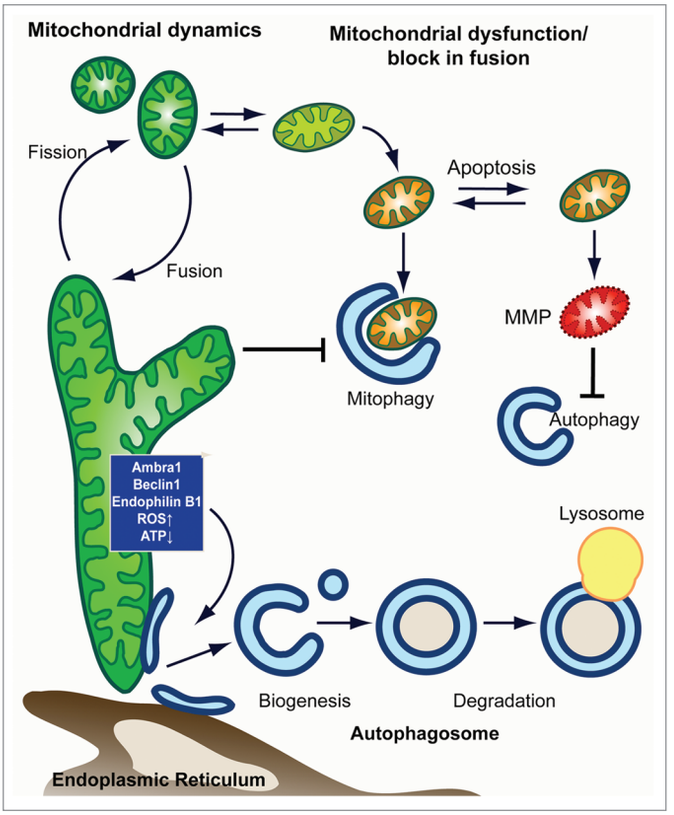

Figure 1. Model for mitochondria-autophagy crosstalk. In this model, we depict the main intersection between in autophagy-mitochondrial crosstalk from the side of (1) autophagy and (2) mitochondria. (1) Autophagy shapes mitochondrial health and number through the selective degradation of mitochondria in a process termed mitophagy. Elimination of damaged mitochondria is facilitated by mitochondrial fission and promotes cell survival. Mitophagic malfunction leads to the accumulation of dysfunctional mitochondria and makes the cell more susceptible to MMP and apoptosis. When cell death is induced, apoptotic executers inactivate pro-autophagic proteins, thus inhibiting autophagy. (2) Autophagic degradation of mitochondria is affected by mitochondrial shape/function, with heavily fused mitochondria being a poor substrate that evades autophagic degradation. Mitochondria, furthermore, are able to control autophagic induction and autophagsomal biogenesis from mitochondria (or other autohagosomal origins such as the ER) through mitochondrial localized proteins and/or metabolic products (such as ROS and ATP).

The specific control of mitochondrial morphology has a significant impact on mitochondrial function and homeostasis. Mitochondrial fusion was suggested as a route for the rapid exchange of metabolites, mitochondrial DNA (mtDNA) and membrane components,[21-27] while fission is thought to facilitate the segregation of mtDNA and isolation of mitochondria from the network to allow their degradation.[28-32] Through this, mitochondrial fission and fusion influences nearly all aspects of mitochondrial function, including respiration, calcium buffering and apoptosis.[33-37]

The dynamic nature of mitochondria is also essential for mitochondrial quality control. Healthy mitochondria go through continuous fission and fusion cycles, which are, in general, timely coupled. In this process, after fusion takes place, it is rapidly followed by a mitochondrial fission event. Mitochondria then spend the vast amount of time in a post-fission state, which they only leave by re-fusing into the mitochondrial network. As mitochondrial fusion is dependent on membrane potential ($\Delta\psi_m$), mitochondrial depolarization will retain mitochondria in a post-fissioned state.[17-20,32] The continuous failure of damaged mitochondria to fuse back into the mitochondrial network eventually leads to mitochondrial elimination through autophagy.[32] Mitochondrial dynamics thereby provides the cell with a powerful mechanism to regulate the number and overall health of mitochondria.

Mitochondria as an Autophagy Substrate

One link between autophagy and mitochondria is the selective elimination of excess or damaged mitochondria, a process called mitophagy. Mitochondria are degraded under a variety of different conditions, including basal mitochondrial quality control,[32] mitochondrial dysfunction[4,32] and during developmental processes, such as during the maturation of immature red blood cells.[38-40] To date, considerable progress has been made in identifying mitophagic adaptors or the degradation of parental mitochondria after fertilization and understanding the overall importance of mitophagy for aging and neurodegenerative diseases.

Mitochondrial depolarization can occur naturally during mitochondrial fission or can be induced through cellular stress pathways, including apoptosis. Upon extensive damage, mitochondrial membranes can be permeabilized through distinct routes, and mitochondrial membrane permeabilization (MMP) constitutes one of the hallmarks of apoptotic or necrotic cell death.[41] However, if the mitochondrial insult is not too severe and only a fraction of the mitochondrial pool is damaged, mitophagic degradation could rescue the cell and prevent cell death.

Damaged mitochondria can be recognized through the voltage-sensitive kinase Pink1. Under normal circumstances, Pink1 is continuously degraded on mitochondria, but upon loss of $\Delta\psi_m$, Pink1 is stabilized on the outer mitochondrial membrane.[42-44] The rapid accumulation of Pink1 on the mitochondrial surface facilitates recruitment of Parkin,[45-49] an E3 ligase to mitochondria, where it ubiquitinates multiple mitochondrial proteins, including the fusion proteins Mfn1/2 and the VDAC1 protein.[6,50-55] The accumulation of ubiquitin-modifications is thought to facilitate the recruitment of the autophagy adaptor p62, eventually leading to the autophagosomal degradation of the damaged mitochondrion.[4-6,56] Mutations in the genes coding for both PINK1 and Parkin were identified in the early-onset forms of Parkinson disease. In cell culture models, disease-associated mutants of Pink1 and Parkin dramatically reduced the recruitment of Parkin to damaged mitochondria and their subsequent degradation.[5,6,43,44,52]

Another protein linked to mitophagy in mammalian cells is NIX. In immature red blood cells, NIX mediates the mitophagic removal of excess mitochondria.[38,39,57] But the elimination of damaged mitochondria seems also be NIX-dependent in some cell lines.[58] In addition to mitophagy-mediators, the loss of

general autophagy regulators, like ATG5 or ATG7, also leads to significant accumulation of damaged mitochondria,[59-65] further supporting the idea that autophagy plays an essential role in mitochondrial quality control to ensure the health of the mitochondrial pool.

Recent studies demonstrated that mitochondria are not only a downstream substrate of mitophagy, but that they are able to actively influence their own fate during starvation-induced autophagy. Two recent studies showed that during starvation, mitochondria react to the depletion of nutrients (especially nitrogen sources) with rapid and extensive mitochondrial tubulation.[66,67] The formation of elongated mitochondrial networks appears to be dependent on the PKA-mediated inactivation of the fission protein Drp1, removing the counterbalancing force to fusion. Interestingly, these mitochondrial networks resulted in sustained mitochondrial ATP production, enhanced cellular survival[66] and, most importantly, prevented the elimination of mitochondria.[66,67] In contrast to this, fusion-incompetent mitochondria were heavily degraded during starvation. This suggests that mitochondrial morphology actively influences mitophagic responses.

The exact mechanism by which mitochondrial fusion prevents mitophagy is still unclear. The mitochondrial size alone could be a determining factor, as the loss of Drp1-activity also decreases mitophagy under basal conditions[32] and upon external mitochondrial damage.[4,53] Alternatively, changes in mitochondrial activity and/or recruitment of mitophagy-adaptors (like Parkin) could be causative for the decreased degradation of fused mitochondria.

Mitochondrial depolarization/fragmentation are two common prerequisites for mitophagy, and mitochondrial fusion can block mitophagy. This intimate link between mitochondrial shape and degradation suggests that both processes could also be coupled on the molecular level. Indeed, two different systems were identified that affect both mitophagy and mitochondrial shape. Parkin has been suggested to regulate mitochondrial fusion in addition to its well-established function as a mitophagy adaptor.[4,68,69] A similar connection has been suggested for the autophagy-regulating proteins ATG12 and ATG3. During the induction of autophagy, ATG12 gets covalently linked to ATG5, thus driving the expansion and formation of the autophagosome. A recent study by Debnath and colleagues identified ATG3 as a further acceptor for ATG12.[70] Lack of the covalent ATG12/3 complex led to mitochondrial fragmentation and loss of mitophagy, partially mimicking the effects of Parkin depletion in mammalian cells. Even though mitochondrial dynamics and mitophagy are linked by several means, it will be important to understand which processes/proteins directly affect mitochondrial dynamics and which effects on mitochondrial shape are only secondary to changes in mitophagy and/or the accumulation of dysfunctional mitochondria.

Mitochondria as Autophagic Membrane Source

To date, the membrane origin(s) of autophagosomes remains under debate. Several organelles have been suggested to contribute lipids for the formation of autophagosomes, including the ER, the Golgi and plasma membrane.[71-73] In a recent study, Hailey et al. added mitochondria to the growing list of potential autophagosomal membrane sources.[8,74] Impressive imaging analysis revealed that during starvation, the membranes of autophagosomes and mitochondria are in continuity, allowing the transfer of a mitochondrial outer membrane marker (GFPcb5^{MitoTM}) into nascent autophagosomes.

Although the question of how and from which organelle(s) autophagosomes originate is not fully clear, several lines of evidence support the role of mitochondria during autophagosomal biogenesis under starvation. In mammals, the autophagy-regulating proteins Beclin1 and Bcl-2 not only localize to the ER and but also to mitochondria. Beclin1 is part of the pro-autophagic class III PI3K complex, which is implicated in the initiation of autophagosomal biogenesis.[75-78] It was believed that the initiation of Beclin1-dependent autophagy is solely regulated on the level of the ER,[79] but studies by Cecconi and colleagues identified Ambra1 (activating molecule in beclin1-regulated autophagy) as a potential contributor of Beclin1-dependent autophagosome formation from mitochondria.[80] Under nutrient-rich conditions, Bcl-2 interacts both with AMBRA1 at the mitochondrial surface and Beclin1 at the ER to inhibit autophagy. But upon starvation, endogenous Ambra1 dissociates from Bcl-2, leading to an increased interaction between Ambra1 with Beclin1 on mitochondria and the ER. The mitochondrial Ambra1/Beclin1 complex could thus drive autophagsomal biogenesis from mitochondrial and ER membranes.

Another protein that could couple mitochondria to autophagosomal biogenesis is Endophilin B1, a membrane-shaping protein with pro-autophagic activity.[81-84] Under normal circumstances, Endophilin B1 cycles between the cytosol and mitochondria and can be enriched on mitochondrial surfaces upon stress.[85] On mitochondria, Endophilin B1 could activate the Beclin1-PI3K complex through binding of the Beclin1 adaptor UVRAG[82] and drive autophagosomal biogenesis using mitochondrial membranes.

Several lines of evidence support mitochondria as a potential autophagosomal membrane source, which raises the question of why specifically starvation-induced autophagy (but not other types of autophagy) uses the mitochondrial membrane.[8] The lipid requirements of autophagy could contribute to this selectivity. Phosphatidyl-ethanolamine, the lipid needed to covalently link ATG8 homologs to autophagosomal membranes, can be produced in two different locales, the ER and mitochondria.[86] PE produced in the mitochondria is synthesized through decarboxylation of Phosphatidylserine, transferred from the ER into mitochondria. In the ER, the Kennedy pathway utilizes DAG and exogenous ethanolamine for the formation of PE. Nutrient depletion could limit the availability of DAG/ethanolamine (produced following growth factor engagement) and affect PE availability in the ER. This would make the mitochondrial membrane the primary site of PE production and, thereby, the site of autophagosomal biogenesis.

Unicellular organisms continuously adapt to fluctuating nutrient availability in their environment, but in mammalian

tissues, nutrient levels are kept rather stable. Even though nutrient availability is tightly regulated, several processes that lead to the starvation of cells or tissues in mammals are known. Newborns proceed through starvation periods shortly after birth, during which autophagy is essential for survival.[87] But starvation-induced autophagy also plays a role in cancer. In the microenvironment of tumors, where access to nutrients and oxygen is restricted, autophagy promotes tumor cell survival.[88] In contrast to its pro-survival role in established tumors, autophagy suppresses tumor development. Dysfunctional mitochondria and protein aggregates are linked to reactive oxygen species (ROS) generation, activation of DNA damage and cell death.[89-92] Degradation of these materials could protect cells against progressive cell damage, inflammation and thus cancer while promoting healthy aging.[93-96]

Therefore, mitochondria may be pivotal for autophagy in cancer, with changes in mitochondrial function regulating the autophagic process, resulting in promotion of tumor formation and/or preservation.

Mitochondria as Regulators of Autophagic Flux

Mitochondria are powerful metabolic organelles, producing precursors for lipid and amino acid synthesis, energy and signaling molecules, like reactive oxygen species (ROS). The central autophagy-regulating pathways, AMPK and mTOR, are controlled by energy levels.[97-106] Loss of mitochondrial ATP production can thus induce autophagy in an mTOR/AMPK-dependent manner.[100,107-109] Interestingly, mTOR and AMPK not only respond to mitochondrial output but also regulate mitochondrial function and biogenesis.[110-112] For example, the pharmacological inhibition of mTOR rapidly affects mitochondrial metabolism and decreases oxidative phosphorylation.[111] This clearly demonstrates the tight bidirectional connection between autophagy and mitochondria through signaling networks, which could play a central role for lifespan extension and age-related disorders.[95]

An additional mitochondrial product that influences autophagy is ROS. During nutrient starvation, an increase in H_2O_2 levels is essential for autophagy induction.[113] The autophagy protein ATG4 was identified as the basis for the redox sensitivity of autophagy. Throughout the formation of an autophagosome, the mammalian homologs of ATG8, LC3A or LC3B, are covalently attached to the nascent autophagosome, driving its expansion. The cysteine protease ATG4 can counteract the autophagosomal expansion through the removal of the ATG8 homologs from the autophagosomal membrane. ATG4 can be regulated by oxidation of a cysteine residue near its catalytic domain, which inhibits ATG4's cleavage activity and allows ATG8-mediated autophagosome expansion to proceed. Thus far, ATG4 is the only autophagy protein known to be regulated by ROS signaling, but other proteins might further contribute to the redox regulation of the autophagic process, including the autophagy master regulator mTOR itself.[92,95,114,115]

A recent study in yeast further expands the regulatory potential of mitochondria on the autophagic pathway. During specific starvation conditions, it was shown that mitochondrial integrity influences autophagic initiaion and/or autophagosomal degradation on the other side.[7] The authors identified the mitochondrial membrane potential, but not ATP production, as regulator of autophagic flux. Interestingly, mitochondrial depolarization and loss of oxygen consumption have also been linked to reduced turnover of autophagosomes in mammalian cells (Rambold AS and Lippincott-Schwartz JL, unpublished results).[9] Whereas mitochondrial dysfunction seemed to inhibit the recruitment of autophagy-initiation kinase ATG1/13 to the phagosomal initiation site in yeast, mitochondrial dysfunction has been linked with reduced lysosomal acidification in mammalian cells.[7,9] The exact mechanism by which mitochondrial dysfunction influences autophagic flux still remains to be established in both systems.

Clearly, several mitochondrial outputs can regulate autophagy, either through targeting the autophagy machinery itself or autophagy regulating signaling pathways. Mitochondrial control of mTOR (through ATP and ROS)[100,107-109,115] is of particular interest, as mTOR regulates a range of essential cellular functions, including protein translation and autophagy, and has been linked to aging in lower eukaryotes.[116] Accumulating evidence suggests that mTOR also influences aging in mammals, and that the triad between mitochondria, mTOR and autophagy (all being able to regulate one another) might present an integral regulatory node during aging and thus age-related diseases.[92,95,96,115,117]

Mitochondria in the Autophagy: Apoptosis Crosstalk

Mitochondria play an essential role during apoptosis. Extensive cellular stress can lead to MMP, release of pro-apoptotic molecules, activation of caspases and, finally, apoptotic cell death. However, if MMP is limited to only a subset of mitochondria, this will result in the selective autophagosomal elimination of the depolarized mitochondria. This suggests efficient autophagic recognition of dysfunctional mitochondria could set a higher threshold for MMP to set an irreparable or deadly event in motion.

It is interesting to note the induction of autophagy and apoptosis are partially regulated by the same proteins. The anti-apoptotic protein Bcl-2 regulates autophagy and apoptosis through binding of the pro-autophagic protein Beclin1 and the pro-apoptotic protein Bax (and others).[79,118] Cellular stress can lead to the release of both proteins. Nutrient depletion first leads to the release of Beclin1, causing the activation of PI3K and induction of autophagy.[79,119,120] Upon extended nutrient deprivation the pro-apoptotic protein Bax is also released from Bcl-2,[120] allowing it to induce apoptosis. The molecular coupling of both events, autophagy and apoptosis, could suggest that the cellular response to stress is determined by the severity and longevity of the insult. In an alternative to the stress-severity model, the different subcellular localizations of Bcl-2 (ER and mitochondria) might be integral to the fate switch between autophagy and apoptosis. While the Beclin1 sequestration seems to be mainly controlled through ER-localized Bcl-2,[79] apoptosis could be regulated through Bcl-2 on mitochondria. Independent of the exact mechanism, it is clear that the health of mitochondria might determine the cellular outcome: autophagy or apoptosis. Thus, mitochondrial damage could overwhelm to pro-survival autophagy pathway and direct

the cell toward release of pro-apoptotic Bax from Bcl-2 to induce cell death.

There are a number of additional mechanisms that couple autophagic demise to apoptotic onset involving mitochondria. The autophagy-regulating proteins Beclin1, the class III PI3K and ATG4D can all be cleaved by caspases upon which they translocate to mitochondria, where they acquire new functions and can amplify mitochondria-mediated apoptosis.[121,122] In addition to this, caspase-dependent cleavage destroys the pro-autophagic function of Beclin1 and PI3K. Another protein that links apoptosis and autophagy is ATG5.[123] Upon autophagy induction, ATG5 enables the extension of the autophagosome at its site of biogenesis. However, in response to high cellular stress levels, ATG5 can be cleaved by calpains. The ATG5-cleavage product translocates to mitochondria, where it binds Bcl-X_L. In contrast to cleaved Beclin1, class III PI3K or ATG4D, calpain-processed ATG5 is able to induce apoptosis without the need for additional pro-apoptotic stimuli. These data exemplify the importance of mitochondrial integrity and their localized protein networks throughout the regulation of autophagy.

Conclusion

Mitochondria have been primarily connected to cellular ATP production and metabolism but have recently begun to take center stage in many other cellular processes. Mitochondria's connection to the autophagosomal system in particular has garnered much interest in recent years. To date, several lines of evidence support the notion that mitochondria are autophagic substrates and can also shape the autophagic response in several ways. The localization of many autophagic regulators on mitochondria, the integration of mitochondria in several signaling networks and their potential to modulate these pathways all suggest a powerful mitochondrial influence on autophagy. That said, we are still at the beginning of understanding the impact mitochondria have on autophagy. Delineating the multiple factors that underlie disorders that depend on autophagy, including neurodegenerative (like Parkinson disease) inflammatory diseases or cancer, and in particular, clarifying the tight link between cancer-associated changes in mitochondrial metabolism and dependence on autophagy during different steps of tumor formation and preservation will be invaluable for devising new ways to treat and prevent these diseases.

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