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Mitophagy and age-related pathologies: Development of new therapeutics by targeting mitochondrial turnover

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ABSTRACT

Mitochondria are highly dynamic and semi-autonomous organelles, essential for many fundamental cellular processes, including energy production, metabolite synthesis, ion homeostasis, lipid metabolism and initiation of apoptotic cell death. Proper mitochondrial physiology is a prerequisite for health and survival. Generation of new and removal of damaged or unwanted mitochondria are tightly controlled processes that need to be accurately coordinated for the maintenance of mitochondrial and cellular homeostasis. Mitophagy is a conserved, mitochondria-specific autophagic clearance process. An intricate regulatory network balances mitophagy with mitochondrial biogenesis. Proper coordination of these opposing processes is important for stress resistance and longevity. Age-dependent decline of mitophagy both inhibits removal of dysfunctional or superfluous mitochondria and impairs mitochondrial biogenesis resulting in progressive mitochondrial accretion and consequently, deterioration of cell function. Nodal regulatory factors that contribute to mitochondrial homeostasis have been implicated in the pathogenesis of several age-associated pathologies, such as neurodegenerative and cardiovascular disorders and cancer, among others. Thus, mitophagy is emerging as a potential target for therapeutic interventions against diseases associated with ageing. In this review, we survey the molecular mechanisms that govern and interface mitophagy with mitochondrial biogenesis, focusing on key elements that hold promise for the development of pharmacological approaches towards enhancing healthspan and quality of life in the elderly.

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Abbreviations: AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BNIP3, Bcl2/adenovirus E1B 19 kDa-interacting protein 3; BNIP3-like, (BNIP3L)/NIX; DRP1, dynamin related protein 1; ETC, electron transport chain; FUNDC1, FUN14 domain-containing 1; GABARAP, GABA type A receptor-associated protein; HIF1, hypoxia inducible factor 1; IMM, inner mitochondrial membrane; LC3, microtubule-associated protein 1A/1B-light chain 3; LIR, LC3-interacting region; MFN1/2, mitofusins 1/2; MPP, matrix mitochondrial processing peptidase; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; OMM, outer mitochondrial membrane; PGC-1a, proliferator-activated receptor gamma coactivator-1 alpha; PINK1, phosphatase and tensin homolog (PTEN)-induced putative kinase 1; ROS, reactive oxygen species; SIRT1, sirtuin 1; ULK1, Unc-51 Like Autophagy Activating Kinase.

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1. Introduction

Mitochondria are semi-autonomous organelles of prokaryotic origin. During evolution, mitochondria became integral part of the eukaryotic cell, procedure mediated by endosymbiosis billions of years ago. Their number varies in a cell type-specific manner and is spanning from a single up to several thousand mitochondria. Mitochondria contain their own genome composed of only 37 genes in humans, 13 of which encode mitochondrial proteins and the rest tRNAs and rRNAs important for the prokaryotic type of translation taking place inside the organelle matrix. Although mitochondria contain their own genome, their replication and proper function are tightly coupled to the import of nuclear encoded transcripts. Importantly, many of these molecules exhibit selective subcellular localization only in/on mitochondria.

The importance of mitochondria for the eukaryotic cell is highlighted not only by their involvement in vital functions that regulate cellular metabolism, but also by the consequences accompanying mitochondrial dysfunction or damage. More specifically, mitochondria play a key role in adenosine triphosphate (ATP) production, which is the main energy source of the cell. ATP production depends on aerobic respiration and oxidative phosphorylation that is mediated by the electron transport chain (ETC) components located in the inner mitochondrial membrane (IMM). In addition, mitochondria participate in several other functions contributing to calcium homeostasis, lipid metabolism and apoptotic cell death regulation as well as the control of the inflammation response (Kim et al., 2016a; Nicholls, 2005; Picard et al., 2015; Tait & Green, 2010; Zhang et al., 2010). Cell type-specific mitochondrial functions include thermogenesis regulation in brown adipose tissue, ammonia detoxification in liver cells and hormone biogenesis, among others (Lee, Ellis, & Wolfgang, 2015; Soria, Marrone, Calamita, & Marinelli, 2013; Velarde, 2014).

Mitochondrial malfunction is often multifactorial and is manifested by the production of aberrant amounts of ATP and reactive oxygen species (ROS). In most cases, ATP shortage and excessive ROS production due to ETC defects initiate a cascade of cellular events, leading to mitochondrial dysfunction and disruption of cellular homeostasis (Fig. 1A). Indeed, excessive generation of mitochondrial ROS (mtROS) such as superoxide causes mitochondrial DNA (mtDNA) mutations and damage on both mitochondrial and cytoplasmic proteins. Impaired mitochondrial homeostasis has been associated with several human syndromes and age-related diseases such as poor growth and developmental delays, liver and cardiac disease, seizures, infection susceptibility, cancer and various neurological and muscle disorders (Arnoult, Carneiro, Tattoli, & Girardin, 2009; Fillano, Goldenthal, Rhodes, & Marin-Garcia, 2002; Oka et al., 2012; Vyas, Zaganjor, & Haigis, 2016; Zsurka & Kunz, 2015). Mitochondrial-related disorders become more pronounced with advancing age followed by a proportional accumulation of mitochondria. The reason of mitochondrial accrual during ageing was identified as the decline in the efficiency of clearance mechanisms that selectively target mitochondria (Fig. 1A) (Palikaras, Lionaki, & Tavernarakis, 2015b; Rubinsztein, Marino, & Kroemer, 2011). Elucidation of the molecular mechanisms mediating the removal of dysfunctional organelles is the main goal of research in the field of autophagy.

Macroautophagy (hereafter, autophagy) is the most extensively studied type of autophagy (the other two are microautophagy and chaperone-mediated autophagy) and the process is highly conserved among eukaryotes (Glick, Barth, & Macleod, 2010). Such a self-consuming pathway has not been identified yet in prokaryotes but an upcoming evolutionary theory relative to the origin of autophagy, places it in the same conceptual framework with protophagy, a prokaryotic process sharing common features with autophagy (Starokadomskyy & Dmytruk, 2013). Autophagy's prerequisite and discriminative characteristic is the formation of a double-membrane vesicle, the autophagosome, which engulfs superfluous or deleterious cytoplasmic material such as proteins, whole organelles or inflammatory intruders. After its formation is completed, autophagosome fuses with the lysosome and the sequestered cargo is driven for hydrolytic degradation. The resulting degradation products are released back into the cytosol for re-use (Feng, He, Yao, & Klionsky, 2014). Autophagy is divided into two subclasses depending on its cargo: 1. Non-selective, that randomly degrades cytoplasmic material and 2. Selective, that recognizes and degrades specific organelles, including mitochondria (mitophagy), peroxisomes (pexophagy), the nucleus (nucleophagy), among others, or microbes (xenophagy) (Jin, Liu, & Klionsky, 2013; Mochida et al., 2015). Selective autophagy requires specific cargo recognition, which is mediated either by specific receptors that recognize and bind to ubiquitin chains, connecting, in turn, ubiquitinated substrates to autophagosomal proteins LC3 (microtubule-associated protein 1A/1B-light chain 3) and GABARAP (GABA type A receptor-associated protein) or by organelle receptors that lie on the organelle membrane and directly bind to LC3.

In particular, mitophagy (mitochondria-specific autophagy) functions at basal levels under normal conditions to degrade superfluous organelles, thus regulating mitochondrial number depending on the metabolic needs of the cell. Under stress conditions, mitophagy is triggered to target malfunctioning organelles for degradation, promoting cell survival (Palikaras et al., 2015b). Although mitophagy is a very efficient process for mitochondrial damage control, it should be noted that elaborate mechanisms have evolved to repair mitochondria and sustain energy homeostasis (Fig. 1A). These mitochondrial quality control mechanisms are activated prior to mitophagy and include: 1. mitochondrial fusion mechanisms which “dilute” the damage among healthy mitochondria, so malfunction is finally undetectable, 2. activation of the mitochondrial unfolded protein response (mtUPR) system to restore perturbed proteostasis inside mitochondria and 3. formation of mitochondrial derived vesicles, which engulf and isolate specific mitochondrial substrates and translocate them from mitochondria to lysosomes for degradation (Lu, 2009; Pellegrino, Nargund, & Haynes, 2013; Sugiura, McLelland, Fon, & McBride, 2014). Under conditions of extensive and irreversible damage though, these mechanisms are unable to restore homeostasis so mitophagy is induced to eliminate dysfunctional organelles (Tian, Merkwirth, & Dillin, 2016; Twig & Shirihai, 2011).

On the other hand, excessive or persistent mitophagy events and subsequent mitochondria shortage would also lead to impairments in mitochondrial function, contributing to disturbed homeostasis at both the cellular and whole organism level. It is widely accepted that normal cell function requires the presence of a definite functional mitochondrial population. As a result, following mitophagy and as a response to it, a mitochondrial biogenesis program is stimulated not only to balance mitochondrial loss but also to replace the defective organelles by functional ones (Palikaras et al., 2015b). Mitochondrial biogenesis is a complex process that involves the activation of transcription programs in the nucleus and a variety of post-transcriptional events taking place both in the cytoplasm and inside mitochondria (Dominy & Puigserver, 2013; Fox, 2012).

The onset of severe age-related pathologies has been clearly linked with mitochondrial dysfunction. Better understanding of mitochondrial turnover mechanisms is a key requirement for the development of more efficient therapeutic strategies to battle numerous pathological conditions in humans. Here, we summarize important features of these mechanisms both under physiological and disease conditions as well as novel pharmacological agents that have been proposed for the treatment of such mitochondrial-related diseases. Finally, we discuss the future perspectives on the field.

2. Mechanisms of selective mitochondrial autophagy

Mitophagy was first reported in 2005 and since then it has largely attracted the interest of the scientific community (Lemasters, 2005). To date, several mitophagy mechanisms have been identified and additional novel regulators and mechanistic details on the field have started

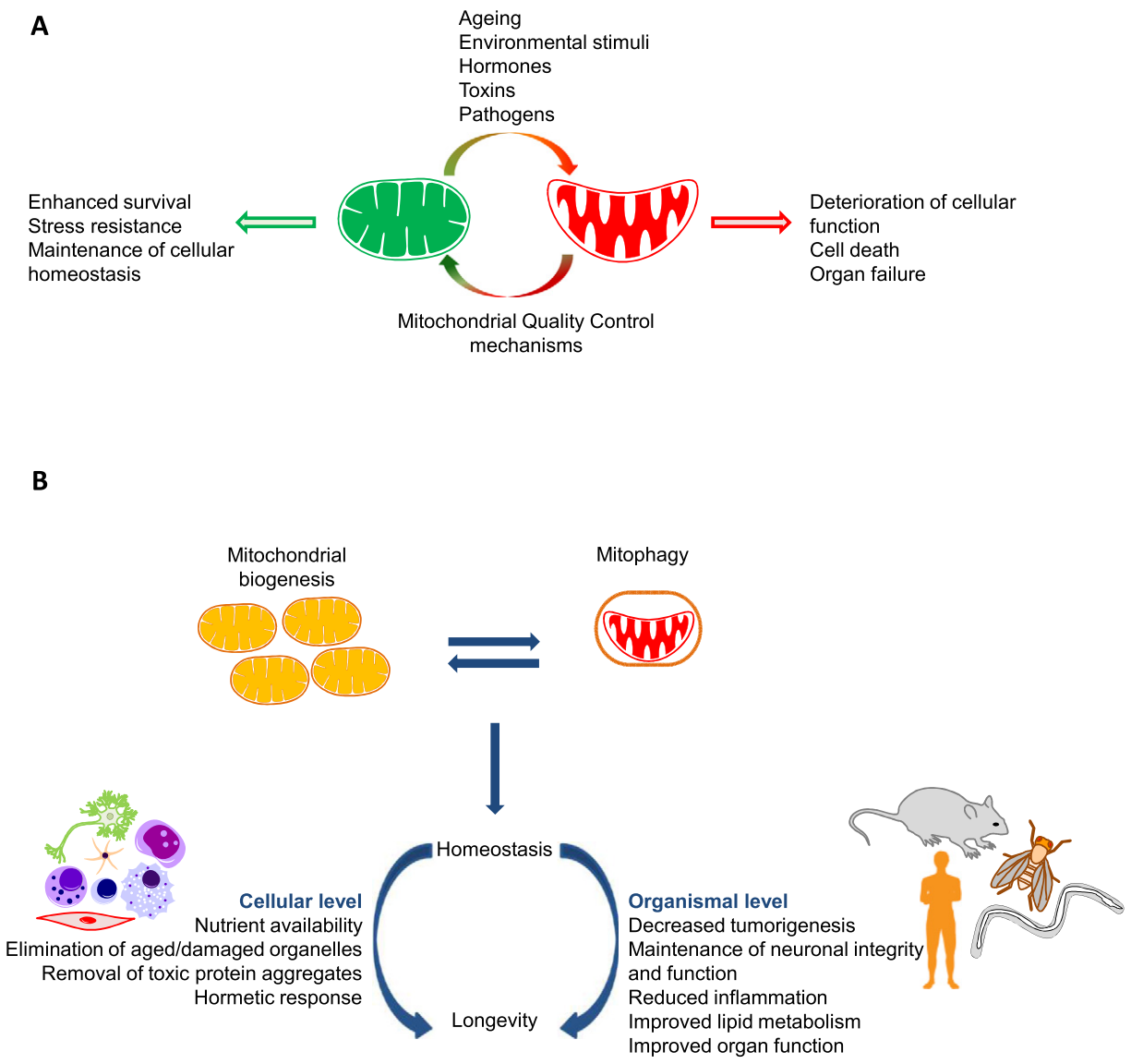


Fig. 1. Proper mitochondrial function and integrity promote cell survival and viability. (A) An intricate crosstalk between mitochondrial quality control mechanisms ensures the fine-tuned mitochondrial activity. Maintenance of mitochondrial homeostasis assures cell survival and stress resistance, whereas excessive mitochondrial dysfunction causes deterioration of cellular function and cell death. (B) The interplay between mitochondrial biogenesis and selective mitochondrial autophagy orchestrates organismal physiology. Coupling of mitochondrial biogenesis and mitophagy promotes energy metabolism homeostasis at the cellular and organismal level resulting in prolonged lifespan and healthspan.

to emerge in several model organisms, highlighting mitophagy conservation (Table 1). In the following paragraphs, we describe the basic molecular mechanisms mediating mitophagy, with emphasis on latest research that shed new light on the process.

2.1. The PINK1/Parkin pathway

One of the best studied mitophagy pathways is the PINK1/Parkin pathway, which is triggered specifically upon mitochondrial

Table 1
The major players of mitochondrial selective autophagy are evolutionarily conserved

Organism					Molecular function
S. cerevisae	*C. elegans*	*D. melanogaster*	*M. musculus*	*H. sapiens*	
–	SQST-1	Ref(2)P	SQST1	p62/SQSTM1	Autophagy adaptor
–	PINK-1	Pink1	PINK1	PINK1	Serine/threonine protein kinase
–	PDR-1	Park	PARK2	PARK2	E3 ubiquitin ligase
ATG8	LGG-1/2	Atg8a	MAP1LC3A/GABARAP	MAP1LC3A/GABARAP	Autophagosomal protein
–	UNC-51	–	ULK1	ULK1	Serine/threonine protein kinase
–	ATG-18	CG11975	WIPI	WIPI	PI(3)P scaffold protein
–	FZO-1	Fzo, Dmfn	MFN2	MFN2	Mitochondrial GTPases
–	DCT-1	–	BNIP3	BNIP3	Mitophagy receptor
–	DCT-1	–	BNIP3L/NIX	BNIP3L/NIX	Mitophagy receptor
DNM1	DRP-1	Drp1	DRP1	DRP1	Mitochondrial GTPases
–	T06D8.7	–	FUNDC1	FUNDC1	Mitophagy receptor

depolarization, although recent studies showed that it plays also a role under basal conditions (Lazarou, 2015). Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1), a serine/threonine kinase, is the most upstream and well-characterized regulator of the pathway up to now. Key to the regulation of PINK1/Parkin activity is the dynamic dual localization of PINK1 either in the inner mitochondrial membrane (IMM) and the cytoplasm or the outer mitochondrial membrane (OMM). In healthy mitochondria, the mitochondrial targeting signal (MTS) of PINK1 mediates its import and anchoring at the IMM through the translocase complexes of the outer (TOM) and inner (TIM) mitochondrial membrane (Okatsu, Kimura, Oka, Tanaka, & Matsuda, 2015). By the time PINK1 enters into the IMM, it is cleaved by the matrix mitochondrial processing peptidase (MPP) and loses a fragment of its N-terminal end. Interestingly, MPP availability is crucial for mitophagy onset due to the tight regulation imposed on PINK1, stretching the need for a strictly controlled system (Greene et al., 2012). In turn, the presenilin associated rhomboid-like protease (PARL), which is also located in the IMM, cleaves PINK1 at its remnant N-terminus. The remaining fragment is then released from the IMM and translocated back to the cytoplasm where it is degraded by the proteasome (Yamano & Youle, 2013). Hence, PINK1 is speculated to retain a dormant state, inhibitory for mitophagy induction even though the fate of this shorter PINK1 fragment remains elusive (Okatsu et al., 2015). Along these lines, a recent study suggests that the short PINK1 fragment is not degraded in the cytoplasm but is driven there to trap Parkin, and thus antagonizes the binding of the second with target substrates on the OMM (Fedorowicz et al., 2014). Raising the mystery of PINK1 fate under mitophagy-silent conditions, it is also proposed that PINK1 is predominantly degraded in the mitochondrial matrix by locally resident Lon proteases, and only upon insufficiency of this system, PINK1 translocates to the cytoplasm for proteolytic cleavage (Fig.2A) (Thomas, Andrews, Burman, Lin, & Pallanck, 2014).

In response to mitochondrial dysfunction, the import of PINK1 into the IMM is blocked and PINK1 is stabilized on the OMM (Okatsu et al., 2015). In turn, PINK1 is self-phosphorylated and dimerized, with its N-terminal end, which contains the kinase domain, facing the cytoplasm (Okatsu et al., 2013; Zhou et al., 2008). This self-activation step of PINK1 is required for mitophagy initiation (Fig. 2B). Accumulation of PINK1 on the mitochondrial surface triggers mitophagy by recruiting Parkin (Riley et al., 2013). Parkin is an E3 ubiquitin ligase remaining latent in the cytoplasm. PINK1 phosphorylates Parkin at residue S65 of its Ub-like (Ubl) domain and promotes Parkin translocation to impaired mitochondria (Kazlauskaite et al., 2015; Wauer et al., 2015a). Moreover, PINK1 mediates ubiquitin phosphorylation, which is also a critical signalling event for Parkin recruitment onto mitochondria (Kazlauskaite et al., 2015; Wauer et al., 2015a). Initially, ubiquitin phosphorylation triggers Parkin binding and partial activation, which is enhanced by a secondary PINK1 phosphorylation event on the Ubl domain of Parkin (Fig. 2B) (Kane et al., 2014). Although, the exact sequence of events that mediate Parkin activation and transport on the OMM are not clear yet, accumulating evidence indicates that Parkin elongates the ubiquitin chains of OMM-proteins triggering local autophagosome formation and enhancing mitophagy rates. Following its translocation, Parkin ubiquitinates several OMM proteins including mitofusins (MFN1 and MFN2), the voltage-dependent anion channel (VDAC) and many components of the mitochondrial translocase complex, among others. However, the relevance of these substrates to mitophagy initiation and progression *per se* remains to be investigated (Palikaras & Tavernarakis, 2012).

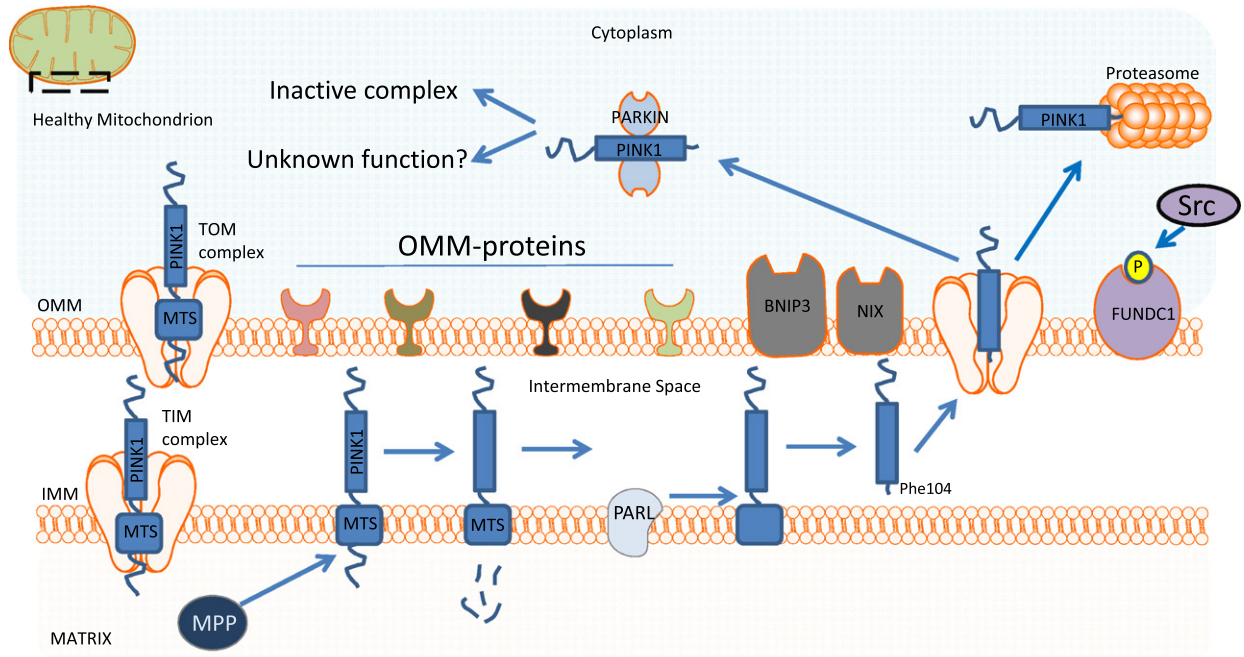
The molecular mechanism that orchestrates autophagosome formation upon polyubiquitination of OMM proteins remains largely unknown. Several studies suggest a role for autophagy adaptor and mediator proteins, which facilitate the autophagosome to lysosome fusion, in this cellular response (Itakura & Mizushima, 2011; Saito & Sadoshima, 2015). Their involvement is proposed due to their localization on the OMM in response to mitophagy-inducing conditions. Despite the fact that these observations have long existed, it was only recently understood how autophagosome formation takes place on the OMM. Towards this direction, studies in HeLa cells showed that the autophagy receptors optineurin and NDP52 first recognize and bind the polyubiquitinated proteins on the OMM. Following receptor recruitment, LC3, ULK1 (Unc-51 Like Autophagy Activating Kinase) and WIPI1 (WD repeat domain phosphoinositide-interacting protein 1) initiate autophagosome formation on the OMM. These events are Parkin–independent in terms of initiation, but need Parkin to be propagated. Interestingly, p62/sequestosome (SQST1) does not participate in autophagosome formation even though data of whether p62 is dispensable or not are controversial (Geisler et al., 2010; Lazarou et al., 2015). A subsequent study revealed the contribution of TBK1 (TANK binding kinase) to mitophagy control. TBK1 regulates the phosphorylation state of autophagy receptors as well as their binding on the ubiquitin chains of OMM-proteins, adding an extra player in the complex regulatory network of mitophagy (Heo, Ordureau, Paulo, Rinehart, & Harper, 2015).

Interestingly, MFN1 and MFN2 are both targeted by Parkin and driven for degradation (Chen & Dorn, 2013; Gegg et al., 2010). As a consequence, mitochondrial fusion is blocked, preventing functional organelles to fuse with their damaged counterparts. Moreover, mitochondrial fission is uninterrupted, facilitating the mitophagy process by supplying smaller organelles that are more likely engulfed by autophagosomes. Fission is required for mitophagy stimulation since depletion of the Dynamin related protein 1 (DRP1), which mediates mitochondrial fission, prevents mitophagy both in nematodes and mammals (Ni, Williams, & Ding, 2015; Palikaras et al., 2015b; Pryde, Smith, Chau, & Schapira, 2016). Interestingly, a recent study has demonstrated that PINK1-mediated phosphorylation of mitofusins acts as a scaffold for Parkin harbouring on the OMM of damaged mitochondria (Chen & Dorn, 2013). In addition, emerging evidence suggests that PINK1 obtains pro-fission activity, which is mediated by AKAP1-PKA (A-kinase anchoring protein 1 - protein kinase A) inhibition, and is independent of Parkin, highlighting PINK1 as the master regulator of mitophagy (Pryde et al., 2016).

Surprisingly, a novel Parkin-independent mitophagy pathway was identified recently in neurons. This pathway depends on PINK1/synphilin-1/seven in absentia homolog (SIAH)-1 protein complex. In particular, synphilin-1 is localized on the OMM and interacts with PINK1 resulting in mitophagy induction. Notably, PINK1 does not phosphorylate synphilin-1 to mediate mitophagy. In turn, synphilin-1 binds and recruits the ubiquitin ligase SIAH-1 facilitating the direct recruitment of LC3 on mitochondria for autophagosome formation (Szargel et al., 2016). Interestingly, synphilin-1 is ubiquitinated by Parkin leading to the formation of pathogenic Lewy-body inclusions in Parkinson's disease patients (Chung et al., 2001). Further investigations are needed to

Fig. 2. The mitophagy process under basal and stress conditions. (A) The fate of mitophagy components under physiological conditions. PINK1 translocates through the TOM and TIM complexes to be finally anchored in the IMM. There, MPP truncates the N- terminal part of PINK1. PINK1 is further cleaved by the IMM protein PARL. The short PINK1 fragment is released back into the cytoplasm, where it is either driven for proteolytic cleavage or targets Parkin. Parkin bound by PINK1 is trapped in the cytoplasm and blocked from binding on OMM proteins. BNIP3 monomer is inactive on the OMM, similar to NIX. FUNDC1 is phorsphorylated and blocked by the kinase Src. (B) In impaired mitochondria with decreased $\Delta\psi$, PINK1 cannot translocate in the IMM through the complex and is anchored in the OMM. There, PINK1 is activated through self-phosphorylation and dimerization. Active PINK1 phosphorylates ubiquitin bound by OMM proteins, triggering Parkin recruitment and its partial activation (1). A second phosphorylation event by PINK1 fully activates Parkin, triggering the elongation of the ubiquitin chains of OMM proteins (2). OMM proteins bound by ubiquitin chains signal for mitochondrial destruction. First, phospho-ubiquitin bound receptors, like optineurin and NDP52, mediate the associations of mitochondria with autophagosome components. Next, autophagy-related factors elongate the autophagosomal membrane to finally engulf damaged organelles (3). In parallel, Parkin polyubiquitinates MFN1/2 leading to their degradation (4). BNIP3 is homodimerized and activated stabilizing PINK1 in the OMM. Active BNIP3 and NIX bind LC3 promoting mitophagy (5). In the absence of Src kinase, FUNDC1 is activated and binds LC3 mediating mitophagy (6). The yellow star on FUNDC1, BNIP3 and NIX is indicative of their activation under mitophagy-inducing conditions.

A


Cytoplasm
Healthy Mitochondrion
Inactive complex
Unknown function?
PARKIN
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OMM-proteins
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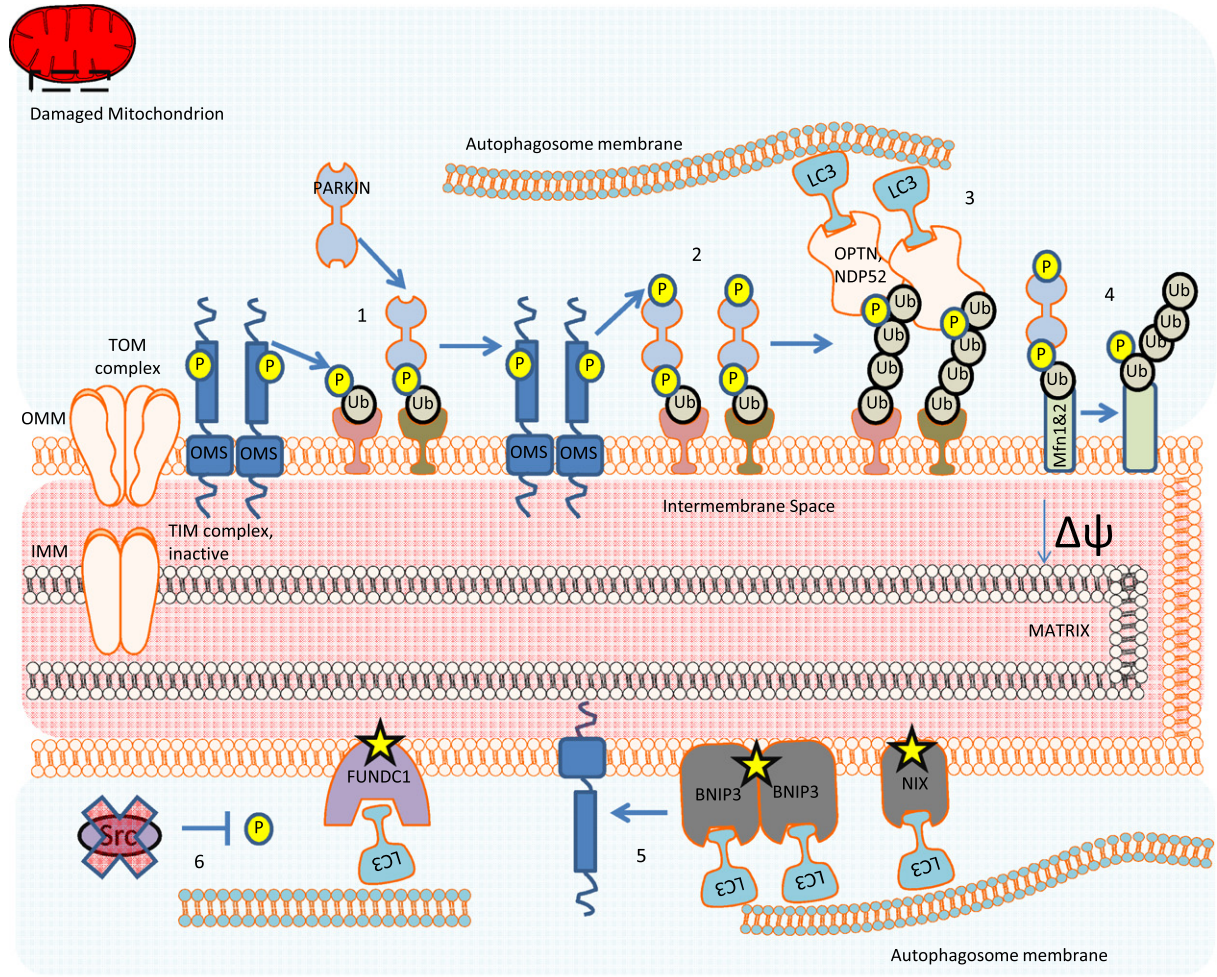
MATRIX

B


Damaged Mitochondrion
Autophagosome membrane
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LC3
LC3
3
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OPTN, NDP52
1
4
TOM complex
OMM
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OMS
OMS
Ub
Mfn1&2
Intermembrane Space
ΔΨ
TIM complex, inactive
IMM
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FUNDC1
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BNIP3
BNIP3
NIX
LC3
LC3
LC3
Autophagosome membrane

elucidate the role of this novel Parkin-independent mitophagy pathway in energy homeostasis, which might provide alternative therapeutic strategies to trigger elimination of defective mitochondria in pathological conditions, such as Parkinson's disease.

Summarizing the latest studies in the field of PINK1/Parkin-mediated mitophagy, several questions have been raised. Several new pathways that involve both or at least one of the PINK1, Parkin proteins have been identified. Urgently, the role of these novel mitophagy pathways need to be investigated under normal and pathological conditions evaluating, in parallel, their tissue specificity, enzymatic function and complementary activity in the maintenance of mitochondrial homeostasis.

2.2. Receptor-mediated mitophagy pathways

Several proteins localized on the OMM serve as autophagy receptors mediating a direct association with autophagosomal proteins leading to encapsulation of defective mitochondria within autophagosomes and their degradation in lysosomes. The common characteristic between receptor-mediated mitophagy pathways is the independency of ubiquitination events from the binding of adaptor proteins, such as p62 and optineurin (Wei, Liu, & Chen, 2015). Bcl2/adenovirus E1B 19kDa-interacting protein 3 (BNIP3), BNIP3-like (BNIP3L)/NIX and FUN14 domain-containing 1 (FUNDC1) are well-characterized protein receptors promoting mitochondrial selective autophagy during development and/or under stress conditions (Hanna et al., 2012; Liu et al., 2012; Novak et al., 2010).

2.2.1. The role of BNIP3 and BNIP3L/NIX in mitochondrial selective autophagy

BNIP3 and BNIP3L/NIX are atypical Bcl2-homology 3 (BH3)-only proteins localized on the OMM. NIX was identified as a mitophagy receptor mediating mitochondrial elimination during erythrocyte development (Novak et al., 2010). NIX-deficient mice display increased mitochondria number in erythrocytes and develop anemia because of the decreased red blood cell survival (Sandoval et al., 2008; Schweers et al., 2007). Both NIX and BNIP3 contain a highly conserved LC3-interacting region (LIR) motif, which mediates mitophagy through the direct binding with LC3 and GABARAP proteins (Novak et al., 2010; Schwarten et al., 2009). Mitochondrial depolarization triggers dimerization of both BNIP3 and NIX enhancing their interaction with LC3 and GABARAP (Fig. 2B) (Novak, 2012). Apart from their role in mitochondrial selective autophagy, BNIP3 and NIX also act as positive regulators of cell death (Zhang & Ney, 2009).

Furthermore, BNIP3 and NIX disrupt the association between BCL-2 and BECLIN1 activating the general autophagic machinery (Bellot et al., 2009). Therefore, BNIP3 and NIX might increase autophagosome formation and enhance mitophagy through BECLIN1 activation. Interestingly, BNIP3 expression levels are upregulated in hepatic cells during starvation. BNIP3 null mice display accumulation of mitochondrial mass, impaired energy metabolism and elevated lipogenesis resulting in increased inflammation and steatohepatitis (Glick et al., 2012). Recently, DCT-1, the *C. elegans* homologue of mammalian BNIP3 and BNIP3L/NIX, has been identified as a key mediator of mitophagy, promoting survival under stress conditions. Similar to mammals, DCT-1 depletion results in increased mitochondrial content, elevated cytoplasmic calcium levels and excessive mitochondrial dysfunction leading to impairment of cellular and organismal homeostasis (Palikaras et al., 2015b).

2.2.2. FUNDC1-meditated mitophagy

Mitochondrial outer membrane protein FUNDC1 acts as a mitophagy receptor promoting mitochondria removal specifically in response to hypoxia (Liu et al., 2012). FUNDC1 associates with LC3 through its typical LIR domain. Src and CK2 kinases phosphorylate the LIR motif of FUNDC1 to prevent mitophagy under normal conditions (Fig. 2A) (Liu, Sakakibara, Chen, & Okamoto, 2014). In contrast, mitochondrial depolarization and hypoxia trigger PGAM5-dependent dephosphorylation of FUNDC1, thereby inducing mitophagy (Chen et al., 2014). Additionally, intracellular ATP levels are reduced during hypoxia and promote autophagy induction via the AMP-activated protein kinase (AMPK)-ULK1 axis. A recent study showed that FUNDC1 is phosphorylated and activated by ULK1 to regulate mitophagy (Wu et al., 2014). Thus, FUNDC1 is activated in response to both general and selective autophagy-inducing signals through ULK1 and PGAM5, respectively (Fig. 2B). Recently, it was suggested that FUNDC1 translocates at the interface between mitochondrial and endoplasmic reticulum (ER) influencing mitochondrial dynamics upon hypoxia (Wu et al., 2016). Notably, FUNDC1 recruits DRP1 to mitochondria, thereby mediating mitochondrial fission, isolating defective mitochondria and subsequently enhancing their elimination under hypoxic conditions (Wu et al., 2016).

There is overlap and redundancy between the mitophagy pathways in response to stress conditions. Both BNIP3 and NIX overexpression triggers the recruitment of Parkin to mitochondria (Ding et al., 2010; Lee, Lee, Hanna, & Gustafsson, 2011). Furthermore, Parkin deficiency prevents BNIP3-mediated mitophagy in cardiomyocytes (Lee et al., 2011). Similar to its mammalian counterpart, the nematode DCT-1 is ubiquitinated upon mitophagy-inducing conditions, indicating the requirement of Parkin and their synergistic function (Palikaras et al., 2015b). Both NIX and BNIP3 are upregulated to promote mitophagy upon hypoxia, like FUNDC1. Congruently, the expression levels of BNIP3 and NIX are upregulated by hypoxia inducible factor 1 (HIF1) (Palikaras, Lionaki, & Tavernarakis, 2016). Although the interplay between FUNDC1, BNIP3 and NIX has not been investigated yet, it is possible that their coordinated action, in parallel with the PINK1/Parkin pathway, assures the efficiency of mitochondrial quality control and energy homeostasis upon stress conditions. Therefore, induction of multiple mitophagy pathways, in response to various stresses, ensures the efficient elimination of damaged organelles.

Accumulating evidence indicates that components of the different mitophagy pathways can either synergistically or in parallel reinforce mitophagic processes under conditions of mitochondrial dysfunction. It is worth noting that the same pathways are active at basal levels under normal conditions and their modulation is triggered by stochastic mitochondrial impairment or (re)programming of mitochondrial mass. The rate of such events is expected to be tissue- or cell cycle- and metabolic state-dependent. In response to different intracellular and/or environmental stimuli, specific mitophagy pathways are activated to maintain mitochondrial and ultimately cellular homeostasis.

Whether the activation of the above-mentioned mitophagy pathways is tissue -specific has lately been under investigation. Recent evidence indicates that certain mitophagy-specific components are not ubiquitously expressed, implying tissue -specific activation of each pathway to support a bioenergetic need or alleviate mitochondrial damage. For instance, BNIP3 is mainly expressed in skeletal muscle, heart and liver and NIX in testes and hematopoietic tissues (Diwan et al., 2007a; Glick et al., 2012; Sandoval et al., 2008; Schweers et al., 2007). Moreover, recent findings suggest that mitophagy rates are different between and within tissues. As shown, organs such as the heart exhibit higher rates of mitophagy, whereas mitophagy is very limited in the thymus. Even within the same tissue, there are areas where the rate of basal mitophagy is higher than others. For example, mitophagy is compartmentalised in the brain in a manner that is more pronounced in the lateral ventricle, the Purkinje cell layer in the cerebellum and the dentate gyrus (Sun et al., 2015)

2.3. Regulation of mitophagy and mitochondrial biogenesis through mTOR and AMPK function

The mammalian target of rapamycin (mTOR) and AMPK are the master regulators of cellular and organismal homeostasis and their functions are linked with the regulation of both mitochondrial biogenesis and mitophagy in eukaryotes. The mTOR pathway is assembled into two different multi-protein molecular complexes, mTOR complex 1 (mTORC1)

and 2 (mTORC2), whose distinct functions are defined by a complex network of co-factors (Kim et al., 2016b). One of the best-characterized functions of mTOR is its ability to regulate autophagy. Indeed, many studies have established the existence of an inverse interplay between mTOR activity and autophagy stimulation (Zoncu, Efeyan, & Sabatini, 2011). Specifically, it has been demonstrated that mTORC1 phosphorylates directly the ULK1 complex preventing autophagy initiation (Ganley et al., 2009; Hosokawa et al., 2009; Jung et al., 2009).

AMPK is one of the master metabolic regulators of cellular and mitochondrial homeostasis. AMPK acts as a cellular energy sensor and once activated by energetic stress, it promotes a complex transcriptional network mediating cellular energy balance (Hardie, 2013). AMPK has a crucial role in autophagy regulation, since its activation could promote autophagy through several signalling pathways. First, AMPK triggers autophagy upon energy depletion through the phosphorylation and inhibition of mTORC1 (Gwinn et al., 2008). Additionally, ULK1 is phosphorylated and activated by AMPK resulting in subsequent induction of mitochondrial selective autophagy under stress conditions, such as starvation (Egan et al., 2011). Notably, ULK1 is not only participating in autophagy initiation, but also phosphorylates and inhibits AMPK enzymatic activity acting as an autophagy negative regulator to terminate the signalling event (Loffler et al., 2011). Therefore, stimulating AMPK could eliminate dysfunctional mitochondria and be beneficial under various stress conditions.

Whether AMPK and mTOR can trigger specific modifications on mitophagy components is under investigation. Towards this direction, it has been shown that the AMPK-mTOR pathway markedly reduces the BNIP3 protein levels during starvation, leading to the hypothesis that BNIP3-mediated mitophagy is not involved in starvation-induced mitochondrial elimination in mammals (Park et al., 2013). On the other hand, evidence that BNIP3 binds and represses Ras homolog enriched in brain (Rheb) and thereof mTOR through a yet unknown mechanism exists (Li et al., 2007). Interestingly, a recent study has shown that after phosphorylation and activation by AMPK, ULK1 translocates to mitochondria and stimulates mitophagy in response to hypoxia (Tian et al., 2015). The mechanisms of ULK1 transport to mitochondria, how it triggers mitophagy or whether this translocation takes place in other stress conditions as well, are still poorly understood. Furthermore, AMPK phosphorylates and activates mitochondrial fission factor (MFF), which subsequently promotes DRP1-mediated mitochondrial fission and mitophagy (Ducommun et al., 2015; Toyama et al., 2016).

In addition to its role in mitophagy, AMPK is a well-described regulator of mitochondrial biogenesis. Interestingly, Sirtuin 1 (SIRT1) phosphorylation by AMPK leads to deacetylation and activation of the proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a), the master regulator of mitochondrial biogenesis (Canto & Auwerx, 2009). PGC-1a acts as a co-activator of multiple transcriptional factors, such as Nuclear respiratory factor 1 (NRF1), myocyte enhancer factor 2 (MEF2) and forkhead O-box (FOXO) transcription factors, triggering the expression of numerous mitochondrial targeted proteins (Ploumi, Daskalaki, & Tavernarakis, 2016). Although the stimuli- and/or tissue-specific role of PGC-1a in mitochondrial biogenesis are well-established, the molecular mechanisms dictating the selection of PGC-1a partner are largely unclear.

3. Mitophagy in pathological conditions

Several molecular pathways stimulate mitophagy to adjust mitochondrial population in response to physiological demands, intracellular and/or environmental signals. Deregulation of these molecular mechanisms alters the tight coordination between mitochondrial biogenesis and elimination leading to energy homeostasis collapse and eventually to cellular dysfunction (Fig. 1B). A variety of human pathological conditions, including tumorigenesis, hepatic and kidney failure, cardiovascular diseases, neurodegeneration and chronic inflammation among others, are associated with mitochondrial dysfunction and aberrant mitochondrial content highlighting the pivotal role of mitophagy in cellular and organismal homeostasis.

3.1. Mitophagy in cancer

Defective mitophagy is causally associated with the onset and progression of carcinogenesis. Recent studies suggest that variations in mitophagy-related genes, such as *PARK2*/*Parkin*, *BNIP3*, *NIX*/*BNIP3L* and *PARK6*/*PINK1* are implicated in numerous pathological conditions including a variety of human tumours (Table 2) (Cesari et al., 2003; Dasgupta et al., 2012; Denison et al., 2003a; Denison et al., 2003b; Hung et al., 2009; Mulholland et al., 2006; Noviello, Courjal, & Theillet, 1996; Orphanos, McGown, Hey, Boyle, & Santibanez-Koref, 1995; Poulogiannis et al., 2010; Pugh et al., 2013; Quinsay et al., 2010; Shah et al., 2012; Thomas & Jacobson, 2012; Veeriah et al., 2010; Viotti et al., 2014). Moreover, the regulation of mitophagy genes by oncogenic (e.g. NF-kB, HIF1, Myc) and tumour suppressive factors (e.g. p53, pRB) factors underlines the essential role of mitophagy in cancer cell biology (Bernardini et al., 2017).

In particular, solid tumours of breast, ovarian, colon and lung cancers harbour deletion or loss of function mutations in the *PARK2*/*Parkin* gene (Picchio et al., 2004; Saito et al., 1996; Xu, Lin, Yin, & Koeffler, 2014). Parkin depletion leads to accumulation of damaged mitochondria and elevated ROS production triggering DNA damage and tumorigenesis (Palikaras et al., 2016). Congruently, Parkin-deficient mice display high incidence of spontaneous liver tumours and increased sensitivity to irradiation-induced lymphomas, underlining the tumour suppressive activity of Parkin (Fujiwara et al., 2008). Interestingly, Myc, a well-known oncogenic protein, has been shown to bind directly to the promoter of the *PARK2*/*Parkin* gene and suppress its expression, explaining the undetectable protein levels of Parkin in several cancer cell lines (West et al., 2004). Myc is highly expressed in tumours and down-regulated in post-mitotic cells, where Parkin is accumulated (Strieder & Lutz, 2002). Thus, there is an inverse correlation between Myc and Parkin protein levels. Deregulation of Parkin expression enhances glioblastoma development uncovering the key role of Parkin depletion in brain tumours (Wang et al., 2001). Beyond its role in mitochondrial quality control, Parkin's tumour suppressor activity is highlighted by its involvement in the regulation of several cell cycle proteins. Both cyclin D and E, which are upregulated in breast and lung cancers, are Parkin substrates (Gong et al., 2014). Interestingly, Parkin overexpression reduces their oncogenic phenotype. In addition to Parkin, impaired BNIP3 and NIX/BNIP3L expression is linked with tumorigenesis (Chourasia et al., 2015). Several studies demonstrate that epigenetic silencing of BNIP3 contributes to cancer aggressiveness, including invasiveness, metastasis and enhanced resistance against chemotherapy, among others (Akada et al., 2005; Calvisi et al., 2007; Erkan et al., 2005; Koop et al., 2009; Murai et al., 2005; Okami, Simeone, & Logsdon, 2004). Thus, Parkin, BNIP3 and NIX share a similar tumour suppressive function.

In addition to its anti-tumorigenic effects, mitophagy may also promote survival of cancer cells, depending on multiple factors such as tumour stage, among others (Bernardini et al., 2017; Chourasia et al., 2015). Several types of tumours adapt to their nutrient and oxygen deprived microenvironments by inducing autophagy (Lin & Baehrecke, 2015). In hypoxic conditions, cancer cells shift their energy production from oxidative phosphorylation to glycolysis resulting in elevated glucose uptake and decreased levels of oxygen consumption. This phenomenon is known as the Warburg effect and is mediated by HIF1 (Yu, Chen, Wang, & Chen, 2016). In solid tumours of breast and colorectal cancer, hypoxic conditions promote mitophagy in a HIF1-dependent manner. In turn, mitophagy reduces mitochondrial mass, rescuing tumour cells from elevated ROS generation and energy consuming mitochondrial activity. Interestingly, HIF1 mediates the transcriptional regulation of BNIP3 and NIX/BNIP3L promoting cancer cell survival during hypoxia (Palikaras et al., 2016; Sowter, Ratcliffe, Watson, Greenberg, & Harris, 2001; Sowter et al., 2003).

Table 2
Genetic variations of mitophagy-related genes in human malignancies

Cancer	Gene	Mutation	Reference
Ovarian	*PARK2*	Copy number variants	(Cesari et al., 2003; Denison et al., 2003b)
Lung	*PARK2*	Missense mutation	(Veeriah et al., 2010)
Glioblastoma	*PARK2*	Missense mutation/Impaired expression	(Mulholland et al., 2006; Veeriah et al., 2010)
Colorectal	*PARK2*	Copy number variants	(Poulogiannis et al., 2010)
Breast	*BNIP3*	Impaired expression	(Koop et al., 2009)
Breast	*PARK2*	Copy number variants	(Orphanos et al., 1995; Shah et al., 2012)
Neuroblastoma	*PARK6/PINK1*	Missense mutation	(Pugh et al., 2013)
Pancreatic cancer	*BNIP3*	Loss of function	(Erkan et al., 2005)
Hepatocellular carcinoma	*BNIP3*	Loss of function	(Calvisi et al., 2007)
Gastric cancer	*BNIP3*	Impaired expression	(Murai et al., 2005)

Recent evidence indicates that mitophagy could promote or suppress oncogenesis in a cell type-dependent manner elucidating its dual role in cancer cells' growth and survival (Cheong, Lu, Lindsten, & Thompson, 2012; Townsend et al., 2012). Therefore, several methods have been suggested to improve therapies against tumorigenesis through mitophagy regulation. Supplementation of mitophagy-inducing compounds in combination with chemotherapy and/or radiotherapy delays and prevents tumour growth and progression (Cheong et al., 2012). On the other hand, inhibition of excessive mitophagy could enhance the efficacy of anti-cancer agents (Townsend et al., 2012; Zhou et al., 2015). Hence, targeting mitophagy-related factors may provide potential benefits leading to the development of novel therapeutic strategies against cancer; however, further delineation of mitophagy function in cancer cells physiology and metabolism is needed.

3.2. Mitophagy in the maintenance of hepatic function

Multiple cellular processes are taking place in hepatocytes reflecting their increased mitochondrial content and high-energy requirements. Mitochondrial selective autophagy was first monitored in hepatocytes upon glucagon stimulation and is associated with proper liver function and homeostasis (De Duve & Wattiaux, 1966). Mitochondria recycling is faster in liver compared to other tissues, including brain, heart and kidney among others, highlighting the intense mitochondrial activity in hepatic cells (Menzies & Gold, 1971).

Mitochondrial biogenesis generates newly synthesized organelles upon elimination of damaged and/or aged mitochondria preserving their healthy population and energy metabolism (Palikaras et al., 2015b). Coordination of mitochondrial biogenesis and mitophagy is a critical cellular process for the maintenance of hepatic function. Impaired mitophagy could disturb hepatic homeostasis leading to several pathological conditions such as steatosis and hepatic tumours (Czaja et al., 2013). Accrual of damaged mitochondria affects lipid metabolism through defective fatty acids beta-oxidation and is associated with progression from steatosis to non-alcoholic steatohepatitis (Lee & Kim, 2014). Consistently, autophagy deficiency results in fatty liver disease due to the inability of the cell to efficiently remove excessive lipids (Singh et al., 2009).

Tissues with high-energy demands display increased sensitivity to ischemia/reperfusion injury (Lee & Kim, 2014). Hepatic cells face hypoxic or anoxic conditions during hepatectomy, liver transplantation and cardiac failure. Pharmacological or genetic stimulation of autophagy could be cytoprotective against ischemia-induced necrotic cell death. Defective autophagy results in general mitochondrial dysfunction and eventually in cell death (Kim et al., 2008; Wang, Behrns, Leeuwenburgh, & Kim, 2012). Antitrypsin disease (ATD) is a relative common liver pathology, which is characterized by proteotoxic stress and impaired mitochondrial function (Kamimoto et al., 2006; Perlmutter, 2009). Autophagy and mitophagy inhibition contributes to ATD disease progression, while hepatic activity is restored upon supplementation of autophagy inducing compounds (Hidvegi et al., 2010; Pastore et al., 2013; Teckman, An, Blomenkamp, Schmidt, & Perlmutter, 2004).

Induction of cytoprotective mechanisms could improve liver function under pathological conditions. In this regard, selective priming of dysfunctional mitochondria could be a novel therapeutic intervention preventing diffusion of mitochondria-derived toxic signals to entire mitochondrial population, and consequently improving cellular energy metabolism and liver function.

3.3. Mitophagy deficiency and kidney failure

Kidney cells contain an increased mitochondrial population due to their high metabolic activity. Therefore, fine-tuned mitochondrial function is a prerequisite for the maintenance of kidney homeostasis. Altered mitochondrial morphology, number and impaired activity are common features in a range of kidney pathologies (Tang, He, Liu, & Dong, 2015).

Enhanced mitochondrial fragmentation and general abnormal mitochondrial morphology is reported upon chronic and acute kidney injury (Brooks, Wei, Cho, & Dong, 2009; Zhan, Brooks, Liu, Sun, & Dong, 2013). Notably, a pronounced mitochondrial dysfunction and a decrease in the number of mitochondria were observed upon cisplatin-induced acute kidney failure indicating an imbalance between mitochondrial biogenesis and mitophagy (Zsengeller et al., 2012). Structural alterations of mitochondrial network in kidney cells are combined with increased ROS production, decreased amount of intracellular ATP, elevated cytoplasmic calcium levels and release of mitochondria-derived pro-apoptotic factors leading to cell death and deterioration of kidney function (Che, Yuan, Huang, & Zhang, 2014; Forbes, Coughlan, & Cooper, 2008; Kruidering et al., 1997; Linkermann et al., 2014; Sanz, Santamaria, Ruiz-Ortega, Egido, & Ortiz, 2008). Furthermore, mitophagy deficiency is associated with the development and progression of several kidney disorders. Recent work suggests that mitophagy preserves renal tube cells homeostasis, since the expression levels of the mitophagy receptor BNIP3 are elevated in a HIF1-dependent manner upon acute kidney injury (Ishihara et al., 2013). Additionally, altered expression of mitochondrial dynamics- and mitophagy-related proteins perturb mitochondrial quality control during renal tubular injury, contributing to the pathogenesis of diabetic kidney disease (Zhan, Usman, Sun, & Kanwar, 2015). Congruently, autophagy deficiency in the nephron is associated with many of the pathogenic features of human focal segmental glomerulosclerosis (FSGS), leading to mitochondrial dysfunction accompanied by excessive ROS production, ultimately ending up to renal failure (Kawakami et al., 2015).

Taken together, mitochondrial selective autophagy serves a cytoprotective function in kidney tissue both in acute and chronic injury. A balanced interplay between mitochondrial biogenesis and mitophagy maintains energy metabolism and could restore renal homeostasis. However, the role of these opposed cellular processes in kidney physiology and pathogenesis needs to be further investigated.

3.4. Mitophagy in cardiac physiology

Heart is one of the most energy consuming tissues in human body and the vast majority of its energy is produced by oxidative phosphorylation in mitochondria. Therefore, maintenance of mitochondrial metabolism is

pivotal for heart function and physiology. Damaged mitochondria generate less ATP and elevated ROS levels triggering cell death pathways (Baines, 2010). Impaired mitochondrial activity is associated with the development and progression of cardiovascular diseases. Moreover, cardiac mitochondria reportedly accumulate mtDNA mutations with age leading to bioenergetic collapse and age-associated cardiomyopathy (Dai et al., 2010).

Several mitochondrial quality control mechanisms preserve mitochondrial integrity and cellular function (Scheibye-Knudsen, Fang, Croteau, Wilson, & Bohr, 2015). Both autophagy and mitophagy contribute to the maintenance of myocardial homeostasis, eliminating toxic protein aggregates and dysfunctional organelles (Dorn, 2016; Galluzzi, Pietrocola, Levine, & Kroemer, 2014; Shires & Gustafsson, 2015). Defective autophagy in myocytes results in altered mitochondrial morphology, accrual of dysfunctional mitochondria contributing to disorganized sarcomeres, contractile impairment and eventually to heart failure (Jaber & Zong, 2013; Nakai et al., 2007; Nishino et al., 2000; Tanaka et al., 2000). Besides general autophagy defects, mitophagy inhibition also contributes to cardiac pathophysiology. In addition to its well-established role in the onset of neurodegenerative disorders, recent work has also implicated the PINK1/Parkin signalling pathway in cardiomyopathies. Marked alterations in mitochondrial network morphology, increased numbers of mitochondria and greater levels of oxidative stress have been observed in cardiomyocytes of PINK1 and Parkin deficient mice, leading to deterioration of cardiac function (Billia et al., 2011; Hoshino et al., 2013; Kubli et al., 2013a; Kubli et al., 2013b; Siddall et al., 2013). Subsequent studies underline the protective role of mitophagy under stress conditions (Palikaras, Lionaki, & Tavernarakis, 2015a). Mitophagy malfunction promotes accumulation of dysfunctional mitochondria, exacerbates heart susceptibility and mortality rates in response to ischemia/reperfusion injury and myocardial stress (Billia et al., 2011; Kubli et al., 2013b). Several studies demonstrate that the mitochondrial receptor proteins NIX and BNIP3 also contribute to the maintenance of heart function. *NIX*$^{-/-}$ mice display abnormal energy metabolism, hypertrophy of cardiac tissue and heart failure (Dorn, 2010). Interestingly, simultaneous ablation of BNIP3 and NIX results in a more pronounced accumulation of damaged mitochondria indicating their possible compensatory activity in mitochondrial elimination.

Although mitophagy deficiency could be detrimental for cellular homeostasis, uncontrolled mitochondrial turnover leads to cardiac dysfunction under stress conditions. Notably, NIX and BNIP3 overexpression triggers apoptotic cell death in cardiomyocytes (Lee et al., 2011; Yussman et al., 2002; Zhang & Ney, 2009). Moreover, tissue-specific depletion of NIX protects against cardiac fibrosis and sustains organ function during pressure overload-induced heart failure (Diwan et al., 2008). Similar to NIX deficiency, BNIP3 genetic ablation rescues from cardiac myocytes apoptosis upon myocardial infarction and ischemia/reperfusion injury (Diwan et al., 2007b; Hamacher-Brady et al., 2007). In addition to excessive mitophagy, mitochondrial biogenesis impairment is a common characteristic in myocardial hypertrophy and ischemic heart failure (Pisano et al., 2016). Therefore, the tight coordination between mitochondrial removal and generation of freshly synthesized mitochondria is indispensable for cardiac homeostasis.

Although major milestones in cardiovascular disease treatment have been achieved, there is an urgent need for novel therapeutic interventions. Age-dependent decline of general and mitochondrial selective autophagy is sufficient to affect heart physiology (Nakai et al., 2007; Nishino et al., 2000). Given the higher incidence of heart failure in aged population, targeting mitophagy could be used as a potential therapeutic modality. Systemic stimulation of general autophagy and mitophagy in heart by overexpression of autophagy-related proteins or supplementation of natural compounds with autophagy-inducing properties could enhance cardioprotection (Eisenberg et al., 2016; Pyo et al., 2013; Rana, Rera, & Walker, 2013). On the other hand, uncontrolled mitochondrial turnover could be detrimental in chronic cardiac disorders. Cardiomyocytes activity requires constantly a healthy mitochondrial content and fine-tuned energy metabolism. Therefore, optimal therapeutic strategies should trigger simultaneously mitophagy and mitochondrial biogenesis to prevent loss of mitochondrial population and cell death.

3.5. Mitophagy in age-associated neurodegenerative diseases

Neurons contain increased number of mitochondria and require constitutively active and fine-tuned energy metabolism to carry out their complex functions and sustain their cellular activity. Post-mitotic neuronal cells are more sensitive to age-related deterioration since they have to survive during the lifetime of the organism. Thus, neuronal function and viability depend on mitochondrial activity and energy homeostasis (Lionaki, Markaki, Palikaras, & Tavernarakis, 2015). Damaged mitochondria not only generate less ATP, but also produce more ROS and display impaired buffering of cytoplasmic calcium. Elevated ROS and cytoplasmic calcium levels could trigger apoptotic and necrotic cell death signalling cascades leading to cellular stress and eventually to neurodegeneration (Rugarli & Langer, 2012). Therefore, surveillance mechanisms monitoring mitochondrial energetics enable the cells either to repair dysfunctional organelles through mitochondrial quality control pathways or to eliminate damaged mitochondria (Scheibye-Knudsen et al., 2015). Defective mitochondrial removal is associated with the onset and progression of several age-related neurodegenerative disorders, including Parkinson's, Alzheimer's and Huntington's disease among others, signifying the pivotal role of mitochondrial homeostasis in the maintenance of neuronal function.

Several studies delineate the role of the PINK1/Parkin pathway in mitochondrial selective autophagy. Depletion of PINK1 and Parkin is sufficient to inhibit elimination of damaged and/or superfluous mitochondria and impair cellular and organismal homeostasis (Palikaras et al., 2015b; Pearlstein, Michel, Save, Ferrari, & Hammond, 2016; Pickrell & Youle, 2015; Solano et al., 2008). Interestingly, mutations in *PARK6*/*PINK1* and *PARK2*/*Parkin* genes have been associated with the hereditary form of parkinsonism. The major hallmark of Parkinson's disease is the loss of dopaminergic neurons in substantia nigra. It is reported that the neurons of Parkinson's disease patients display a higher incidence of mtDNA mutations and/or deletions resulting in pronounced mitochondrial dysfunction (Bender et al., 2006; Kraytsberg et al., 2006). Along similar lines, *Parkin*$^{-/-}$ mice are short-lived, display altered mitochondrial activity and impaired neuroprotection during ageing (Solano et al., 2008).

Post-translational modifications provide a fine-tuned and sophisticated regulation throughout multiple steps of mitophagy (Durcan & Fon, 2015). Indeed, mitophagy is initiated upon PINK1 stabilization in the presence of dysfunctional mitochondria. Then, PINK1 phosphorylates and activates both Parkin and ubiquitin. In turn, Parkin is recruited to mitochondria and ubiquitinates several mitochondrial proteins mediating mitochondrial targeting and removal. Recent studies have shown that depletion of deubiquitinating enzymes, such as USP8, USP15 and USP30, could regulate mitophagy in healthy neurons (Bingol et al., 2014; Cornelissen et al., 2014; Durcan & Fon, 2015). Notably, the mitochondrial deubiquitinase USP30 opposes and reverses Parkin activity on mitochondrial substrates. Thus, USP30 deficiency enhances survival upon oxidative stress, ameliorates defects in dopamine levels and protects against motor disabilities by stimulating mitophagy (Bingol et al., 2014). Interestingly, PINK1-mediated phosphorylation of ubiquitin protects phosphorylated ubiquitins from being cleaved by deubiquitinating enzymes amplifying mitophagy signals and assuring cellular homeostasis (Wauer et al., 2015b). Thus, alterations in post-translational modifications could be detrimental for mitochondrial function and neuronal viability.

It is known that accumulation of protein aggregates, including beta-amyloids, Tau and mutant huntingtin proteins among others, impairs multiple cellular processes triggering neuronal toxicity and death. Emerging evidence implicates impaired mitochondrial function and

mitophagy defects in Alzheimer's disease pathology (Santos, Matijasevich, Domingues, Barros, & Barros, 2010). Altered mitochondrial morphology and metabolism are associated with the presence of tau and beta-amyloids protein aggregates resulting in disease progression (Caldwell, Yao, & Brinton, 2015; Spuch, Ortolano, & Navarro, 2012). Accrual of toxic huntingtin aggregates perturbs energy metabolism and triggers oxidative stress. In congruent, excessive mitochondrial damage is reported in samples of Huntington's disease patients (Bossy-Wetzel, Petrilli, & Knott, 2008; Gu et al., 1996; Panov et al., 2002). Interestingly, mutant huntingtin has been shown to repress PGC-1a, thereby inhibiting mitochondrial biogenesis (Cui et al., 2006). PGC-1a promotes neuronal protection through the activation of transcription factor EB (TFEB) and prevents oxidative damage (Tsunemi et al., 2012; Weydt et al., 2006). TFEB is the master regulator of lysosomal and autophagy-related genes (Cuervo, 2011). Therefore, mitophagy stimulation and clearance of dysfunctional mitochondria might be protective against neurodegeneration in Huntington's disease. Indeed, PINK1 overexpression enhances mitophagy, maintains healthy mitochondrial population and confers neuroprotection against the mutant huntingtin (Khalil et al., 2015). Surprisingly, mutant form of huntingtin affects mitophagy by preventing engulfment and elimination of damage mitochondria by autophagosomes (Khalil et al., 2015). These results are in agreement with a previous study demonstrating that defective cargo recognition is responsible for the decreased degradation of damaged mitochondria in Huntington's disease (Martinez-Vicente et al., 2010).

Environmental stimuli, toxins, mtDNA defects and mitophagy deficiency promote mitochondrial homeostasis collapse and excessive mitochondrial stress triggering cell death pathways and contributing to the pathogenesis of neurodegenerative diseases. Hence, enhancing mitophagy could sustain energy metabolism and protect against neuronal cell death.

3.6. Mitophagy in the immune system

Age-dependent decline of general and mitochondrial selective autophagy results in accumulation of damaged mitochondria during ageing (Palikaras et al., 2015b). Failure to eliminate dysfunctional mitochondria leads to elevated levels of ROS and release of several mitochondrial factors stimulating cell death pathways. Furthermore, mitochondrial-derived signals might be toxic, causing hyperactivation of inflammatory response, ultimately resulting in age-dependent, chronic, low-grade inflammation, known as inflammaging (Franceschi, Garagnani, Vitale, Capri, & Salvioli, 2016).

Innate immunity is the first line of defense against microbial pathogens. Host cells of the innate immune system, such as macrophages, monitor and fight against pathogens invasion (Medzhitov, 2007). Inflammaging is dependent on macrophage activation and is characterized by a complex interplay between pro- and anti-inflammatory responses (Franceschi et al., 2016). Emerging evidence highlights the association between mitochondrial dysfunction and immune system deterioration with age. Aged and/or dysfunctional mitochondria release mtDNA and formyl peptides in the cytoplasm stimulating macrophages, which, in turn, recognize mitochondrial-derived factors through Toll-like receptors and promote a rapid immune response (Sun, Youle, & Finkel, 2016). In addition to macrophage stimulation, mtDNA release also facilitates inflammasome activation leading to the secretion of several cytokines boosting the inflammatory response (Nakahira et al., 2011; Oka et al., 2012; Shimada et al., 2012). General mitochondrial dysfunction is able to promote inflammasome activation through ROS signalling (Zhou, Yazdi, Menu, & Tschopp, 2011). Furthermore, accumulation of damaged mitochondria upon autophagy depletion results in hyperstimulation of inflammasome in response to various signals (Nakahira et al., 2011; Saitoh et al., 2008; Zhou et al., 2011). Therefore, mitophagy induction and antioxidants supplementation could ameliorate the symptoms of inflammatory diseases and preserve the functional integrity of mitochondrial population through fine-tuned inflammasome activity and removal of damaged mitochondria (Dashdorj et al., 2013). However, mitophagy stimulation could also be detrimental for cellular physiology. Alveolar macrophages, one of the most important immune system cells, have essential functions in lung development and homeostasis. A recent study shows that excessive mitophagy reduces mitochondrial content and confers resistance to apoptosis in alveolar macrophages, contributing to the development and progression of idiopathic pulmonary fibrosis (Larson-Casey, Deshane, Ryan, Thannickal, & Carter, 2016).

Given the bacterial origin of mitochondria, eukaryotic cells use the same molecular mechanisms to regulate both bacterial autophagy, a process termed xenophagy, and mitophagy. Similar to dysfunctional mitochondria, bacteria are detected and targeted for degradation by the autophagic machinery. Several autophagy adaptor proteins, including p62 and optineurin among others, recognize ubiquitinated bacteria and mediate their autophagosomal engulfment (Boyle & Randow, 2013; Johansen & Lamark, 2011; Wild et al., 2011). A recent report suggests that Parkin promotes elimination of *Mycobacterium tuberculosis* via xenophagy (Manzanillo et al., 2013). Notably, Parkin deficient mice, flies and nematodes are more vulnerable to bacterial infections (Kirienko, Ausubel, & Ruvkun, 2015; Manzanillo et al., 2013). Congruently, genetic polymorphisms in *PARK2*/*Parkin* gene have been associated with increased susceptibility to bacterial pathogens in humans (Ali et al., 2006; Mira et al., 2004). Thus, mitophagy serves as a cytoprotective mechanism against bacterial infection and is crucial for supporting immune system thereby promoting organismal homeostasis.

The current understanding of how mitochondrial metabolism influences immune cells' function is expanding. Mitochondrial quality control pathways and mitophagy sustain energy homeostasis and orchestrate several aspects of immunity. Recent observations, which associate autoimmune diseases and increased incidence of infection with primary mitochondrial disorders, further highlight the pivotal role of mitochondria in the proper immune system function.

4. Mitophagy modulators: new therapeutics of mitochondrial-related diseases

Impaired mitochondrial activity is a shared hallmark of diverse age-associated pathologies. Numerous quality control mechanisms are implicated in the maintenance of mitochondrial network integrity and function, including mitochondrial biogenesis and mitophagy, among others. General and selective mitochondrial autophagy could be a potential target for therapeutic interventions against age-associated disorders, which are characterized by impaired mitochondrial homeostasis. Several autophagy-inducing drugs, such as rapamycin and metformin, have been already approved for the treatment of various diseases. Therefore, modulation of autophagy and mitophagy has emerged as a novel therapeutic strategy to counteract many pathological conditions via repairing energy homeostasis.

4.1. Modulation of mTOR and AMPK activity to restore mitochondrial homeostasis

Adaptation to extreme environmental conditions, such as non-continuous energy supply, resulted in the evolution of several conserved signalling pathways that regulate cellular metabolism. mTOR and AMPK are the core energy sensors and master regulators of cellular and organismal homeostasis. Moreover, the regulation of both mitochondrial biogenesis and mitophagy is orchestrated in part though modulations of mTOR and AMPK activity.

Rapamycin, which is a well-known inhibitor of mTOR signalling pathway, exhibits strong immunosuppressive and anti-proliferative effects in mammalian cells (Fig. 3A) (Benjamin, Colombi, Moroni, & Hall, 2011). Furthermore, rapamycin is an autophagy-inducing compound and its activities against cancer and neurodegenerative disorders, including Huntington's and Parkinson's disease, among others, have been extensively tested (Bove, Martinez-Vicente, & Vila, 2011; Mita, Mita, &

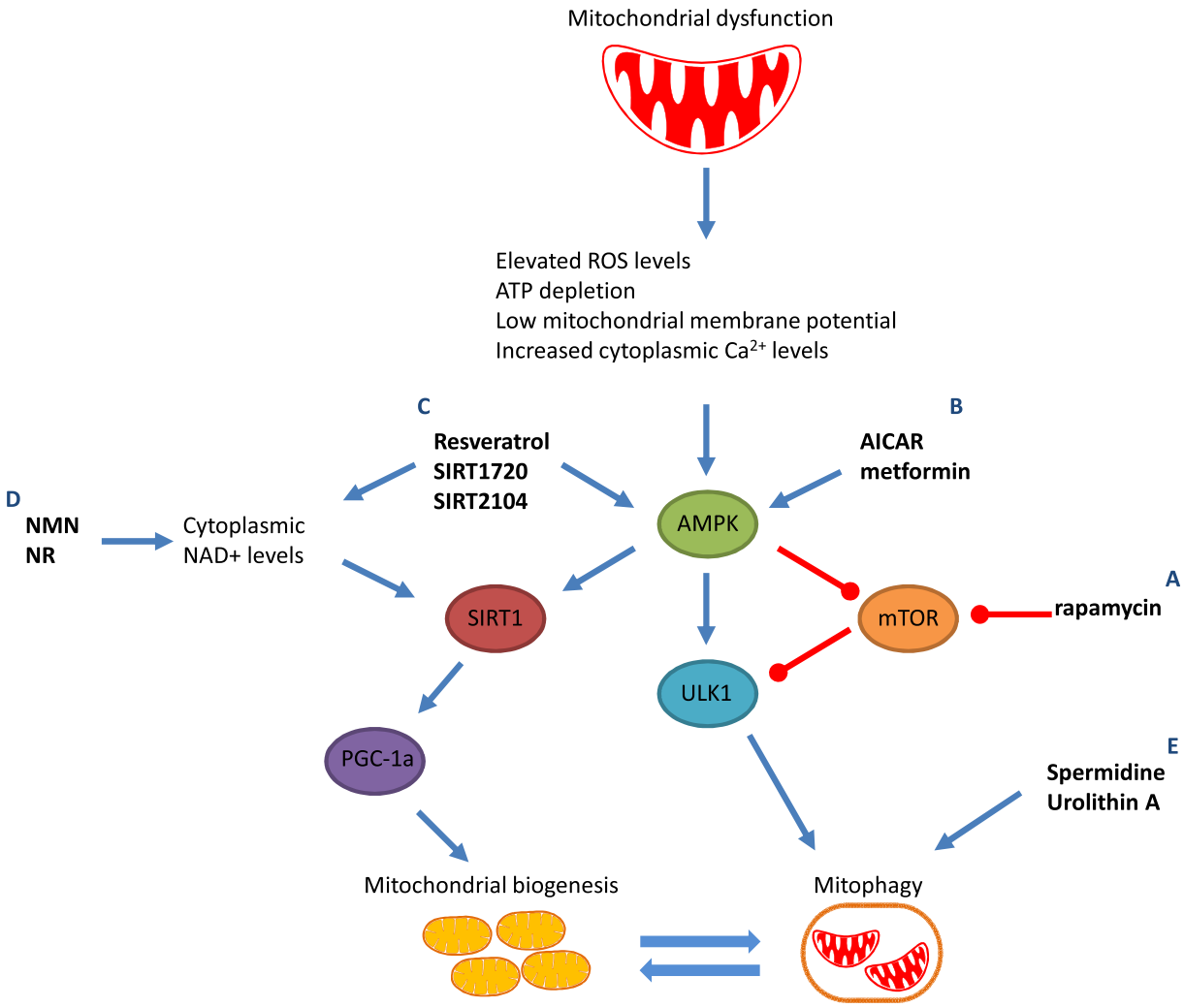

Fig. 3. Pharmacological induction of mitophagy and mitochondrial biogenesis to sustain energy metabolism. Several mitophagy pathways are stimulated to maintain cellular homeostasis in response to mitochondrial dysfunction. (A) Rapamycin inhibits mTOR signalling stimulating mitophagy through AMPK and ULK1 activation. (B) Supplementation of AICAR and metformin triggers AMPK enzymatic activity leading to phosphorylation and activation of ULK1. In turn, ULK1 promotes autophagy initiation and elimination of defective mitochondria. Furthermore, PGC-1a is activated by AMPK mediating mitochondrial biogenesis. (C, D) Resveratrol, synthetic drugs, such as SIRT1720 and SIRT2104, and NAD^+ suppliers enhance indirectly SIRT1 activity through AMPK activation and subsequent elevation of cytoplasmic NAD^+ levels. Then, SIRT1 induces autophagy and triggers PGC-1a activation. (E) Spermidine and urolithin A are natural compounds with mitophagy-inducing properties preserving energy metabolism and organismal homeostasis.

Rowinsky, 2003; Sarkar et al., 2008). A recent study has suggested that the beneficial effects of rapamycin in mitochondrial-related pathologies are due to mitophagy induction (Li et al., 2014). Consistent with this possibility, rapamycin-induced mitophagy promotes cell survival and stress resistance upon mitochondrial dysfunction in human chondrocytes and neurons (Lopez de Figueroa, Lotz, Blanco, & Carames, 2015; Pan et al., 2009). Furthermore, rapamycin administration promotes survival and motor function, as well as alleviates neuronal inflammation and disease progression in a mouse model of Leigh disease (Johnson et al., 2013).

AMPK can also be activated by the supplementation of several Food and Drug Administration (FDA)-approved natural and chemical compounds, such as analog 5-aminoimidazole-4-carboxamide-1-β-ribofuranoside (AICAR) and metformin (Hardie, 2013). AICAR is transported into the cell by adenosine transporter and mimics the function of AMP on AMPK activation (Corton, Gillespie, Hawley, & Hardie, 1995). AICAR supplementation in human fibroblasts with deficient mitochondrial function reportedly promotes cell growth, elevates ATP levels and decreases ROS generation (Golubitzky et al., 2011). Furthermore, mitochondrial content is amplified upon AICAR treatment indicating stimulation of mitochondrial biogenesis (Fig. 3B). In this context, PGC-1a might be activated, since AMPK is triggered in the presence of AICAR (Irrcher, Ljubicic, Kirwan, & Hood, 2008). PGC-1a is phosphorylated directly by AMPK and mediates mitochondrial biogenesis through the transcriptional regulation of several mitochondrial-related genes (Jager, Handschin, St-Pierre, & Spiegelman, 2007; Ventura-Clapier, Garnier, & Veksler, 2008). Activation of PGC-1a enhances mitochondrial bioenergetics and suppresses mitochondrial myopathy phenotypes (Wenz, Diaz, Spiegelman, & Moraes, 2008). Although, AICAR alleviates metabolic defects and symptoms associated with mitochondrial deficiency and its beneficial effects on mitochondrial activity have been documented in several diseases models, its activity on mitophagy *per se* should be evaluated (Ayasolla, Singh, & Singh, 2005; Dulovic et al., 2014; Jose et al., 2011; Kuznetsov et al., 1998; Pauly et al., 2012).

The most widely prescribed anti-diabetic drug, which is orally administrated as a treatment of metabolic syndrome and type 2 diabetes, is metformin. Metformin acts as anti-hyperglycemic agent reducing circulating lipids without influencing insulin secretion (Parkinson Study Group et al., 2014; Yoritaka et al., 2015). Furthermore, metformin's beneficial effect is underlined by its neuroprotective, cardioprotective, tumour suppressive and anti-ageing functions (Anisimov et al., 2011; Dowling, Goodwin, & Stambolic, 2011; Gillis, 1994; Johnson, Simpson, Toth, & Majumdar, 2005; Kooncumchoo, Sharma, Porter, Govitrapong, & Ebadi, 2006; Onken & Driscoll, 2010). It is reported that metformin

recapitulates caloric restriction affecting cell metabolism at multiple levels and alleviating most of the energy-consuming cellular processes to maintain cellular and organismal homeostasis (Mair & Dillin, 2008). Supplementation of metformin is shown to trigger AMPK activity and subsequently induce autophagy by downregulating mTOR and insulin/IGF-1 signalling pathways (Fig. 3B) (Bolster, Crozier, Kimball, & Jefferson, 2002; Pierotti et al., 2013). Interestingly, metformin treatment facilitates Parkin-mediated mitophagy by reducing cytosolic p53 and enhancing mitofusins degradation (Song et al., 2016).

Taken together, modulation of the mTOR pathway and AMPK activity might be a potential therapeutic strategy against mitochondria-related pathologies combining the simultaneous induction of mitophagy to eliminate dysfunctional organelles and mitochondrial biogenesis to generate a healthy mitochondrial population.

4.2. Targeting sirtuins to sustain mitochondrial function in pathological conditions

Sirtuins are nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases and their enzymatic activity is involved in various cellular processes. Additionally, the activity of several transcription factors and co-factors, including p53, FOXO and PGC-1a among others, known to orchestrate mitochondrial biogenesis, is also regulated by sirtuins. In mammals, the sirtuin family is composed of seven proteins (SIRT1-7), which differ in tissue specificity, subcellular localization, enzymatic activity and substrates preference (Houtkooper, Pirinen, & Auwerx, 2012). SIRT1 is the most well-studied member of the sirtuin protein family and its activity influences cellular metabolism (Sebastian, Satterstrom, Haigis, & Mostoslavsky, 2012).

Restriction of calorie intake, but not malnutrition, promotes longevity in many species (Pitt & Kaeberlein, 2015). In mammals, nutrient deprivation results in the delay of various detrimental aspects of ageing. Although caloric restriction effect on primate lifespan remains ambiguous, its beneficial impact on preventing a wide range of age-related pathologies is generally accepted (Colman et al., 2009; Masoro, 2005). Sirtuins' activity is reportedly required for caloric restriction effects on organismal physiology (Lin, Defossez, & Guarente, 2000). Given the difficulty to apply and maintain caloric restriction in higher organisms, the investigation for the identification of compounds with caloric restriction mimetic properties has been intensified in nowadays, and particular emphasis is placed on sirtuin activating compounds (Houtkooper et al., 2012; Madeo, Pietrocola, Eisenberg, & Kroemer, 2014).

Resveratrol is a polyphenolic compound, mainly found in red grapes skin, with beneficial properties for organismal homeostasis (Howitz et al., 2003). Resveratrol stimulates indirectly SIRT1 through the activation of AMPK and subsequent elevation of cytoplasmic NAD^+ levels, which in turn trigger SIRT1 activity (Fig. 3C) (Beher et al., 2009; Canto & Auwerx, 2009; Pacholec et al., 2010). In the context of mitochondrial physiology, resveratrol supplementation promotes mitochondrial biogenesis and energy metabolism via PGC-1a activation, which improves muscular function and healthspan in obese mice (Baur et al., 2006; Lagouge et al., 2006). Interestingly, autophagy is induced in a SIRT1-dependent manner upon resveratrol treatment (Morselli et al., 2010; Morselli et al., 2011). SIRT1-deficient mice display accumulation of p62 autophagic substrate and damaged mitochondria in several tissues (Lee et al., 2008). Moreover, genetic ablation of SIRT1 leads to increased mitochondrial dysfunction in hepatocytes, probably as a consequence of the primary mitophagy defects (Boily et al., 2008). In addition to natural compounds, several synthetic drugs have been demonstrated to activate SIRT1, such as SRT1720 and SRT2104 (Fig. 3C). Although the precise mechanism of their action is not delineated, SIRT1 activity is triggered upon SRT1720 and SRT2104 supplementation leading to lifespan extension and fine-tuned mitochondrial function, protecting against diet-induced obesity, similar to resveratrol (Feige et al., 2008; Milne et al., 2007). Considering the dependence of sirtuins on NAD^+, their enzymatic activity could be manipulated by increasing the cytoplasmic levels of the NAD^+ co-factor. Indeed, supplementation of nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR) elevates intracellular NAD^+ levels resulting in enhanced mitochondrial function, improved exercise endurance and decreased insulin sensitivity in a SIRT1-dependent manner (Fig. 3D) (Canto et al., 2012; Yoshino, Mills, Yoon, & Imai, 2011). Therefore, the modulation of sirtuins activity might be a potential therapeutic strategy coordinating removal of defective mitochondria and induction of mitochondrial biogenesis to maintain energy homeostasis and delay disease onset and progression.

4.3. Spermidine and Urolithin A: natural compounds with mitophagy-inducing properties

4.3.1. Spermidine-induced mitophagy in maintenance of energy metabolism

The polyamines, putrescine, spermidine and spermine, are ubiquitous small organic molecules influencing organismal physiology by interfacing multiple cellular processes, including cell growth, proliferation and survival, among others. Several studies demonstrated and correlated the significant decline in the cellular content of polyamines during ageing and disease development (Minois, Carmona-Gutierrez, & Madeo, 2011). Food intake, activation of cellular biosynthetic pathways and intestinal microbial synthesis are the main source of polyamines in organisms.

Spermidine is synthesized from putrescine and could serve as a precursor molecule of spermine generation (Minois et al., 2011). Spermidine concentration is decreased in several tissues, including thymus, heart, kidney and liver among others, with age in mammals (Nishimura, Shiina, Kashiwagi, & Igarashi, 2006). Thus, maintaining the cellular levels of spermidine stable might be proved beneficial during ageing. Indeed, dietary supplementation of spermidine prolongs lifespan of several organisms, including yeast, nematodes, flies and mice, significantly alleviating age-related symptoms (Eisenberg et al., 2009). Interestingly, spermidine promotes longevity by upregulating autophagy. Conversely, inhibition of autophagy abolishes the lifespan-extending properties of spermidine underlining the essential role of autophagy in spermidine-mediated cytoprotection (Eisenberg et al., 2009). Spermidine acts as acetylase inhibitor independently of SIRT1, indicating that resveratrol and spermidine activate the autophagic degradation pathway through distinct mechanisms. However, both autophagy-inducing agents influence cellular acetylproteome in a similar fashion (Morselli et al., 2011).

A new study has demonstrated that dietary spermidine supplementation in mice ameliorates cardiovascular pathologies, such as hypertension and cardiac defects, which are associated with heart failure and death (Eisenberg et al., 2016). Spermidine administration prevents cardiac hypertrophy and age-related changes in cardiomyocytes, enhances diastolic function and eventually promotes longevity. These data are congruent with a previous study showing spermidine ability to alleviate arterial stiffness and sustain arterial homeostasis in old animals (LaRocca, Gioscia-Ryan, Hearon, & Seals, 2013). Interestingly, spermidine supplementation promotes basal autophagic flux and stimulates mitophagy repairing mitochondrial activity in aged cardiomyocytes. Thereby, genetic inhibition of autophagy abolishes the cardioprotective effects of spermidine (Eisenberg et al., 2016). Importantly, ataxia telangiectasia mutated (ATM) protein plays a crucial role in the cellular response to mitochondrial damage by triggering mitophagy (Fang et al., 2016; Qi, Qiu, Gu, Tian, & Zhang, 2016). Ataxia telangiectasia is a rare autosomal recessive genetic disorder, which is causally associated with ATM deficiency leading to progressive neurodegeneration and cerebellar ataxia (Nissenkorn & Ben-Zeev, 2015). ATM is a master regulator of DNA damage response and a known modulator of mitochondrial function contributing to the maintenance of cellular homeostasis (Fang et al., 2016). Specifically, ATM induces the initiation of the PINK1/Parkin pathway to eliminate defective mitochondria upon spermidine treatment (Qi et al., 2016). The incidence of cardiovascular pathologies is increased with age and frequently is associated with other pathological conditions, such as obesity, neurodegeneration and cognitive impairment, hepatic and kidney failure. Therefore, dietary supplementation of spermidine

results in enhancement of autophagy and mitophagy preserving mitochondrial and cellular homeostasis and might subsequently improve and/or prolong healthspan in aged individuals (Fig. 3E). Notably, epidemiological studies corroborate the beneficial impact of autophagy-inducing compounds, since spermidine-rich diets protect against age-related diseases in humans (Eisenberg et al., 2016).

4.3.2. Urolithin A: first-in-class mitophagy-inducing agent

Ellagitannins belong to a wide family of bioactive polyphenols, found in fruits and nuts, exerting antioxidant, anti-inflammatory and tumour suppressive properties (Amakura, Okada, Tsuji, & Tonogai, 2000; Castonguay et al., 1997; Losso, Bansode, Trappey, Bawadi, & Truax, 2004). Pomegranate juice contains the most abundant concentration of ellagitannins representing their most prominent source in nature (Johanningsmeier & Harris, 2011). Upon their consumption, ellagitannins are metabolized from gut microbiota into urolithins, which are absorbed and distributed to the entire human body through blood stream (Espin, Larrosa, Garcia-Conesa, & Tomas-Barberan, 2013). Although the precise molecular mechanism of urolithins function was not well understood, several studies underlined their beneficial effects on tumorigenesis, inflammation and lipid metabolism (Kang, Kim, Tomas-Barberan, Espin, & Chung, 2016; Lansky, Harrison, Froom, & Jiang, 2005; Piwowarski, Kiss, Granica, & Moeslinger, 2015; Seeram et al., 2007).

A recent report provided critical insights into the biological impact of urolithins on organismal homeostasis during ageing. This study revealed that supplementation of urolithin A, which is the most prevalent ellagitannins-derived metabolite in humans, promotes mitophagy in nematodes and mammals (Fig. 3E) (Ryu et al., 2016). Mitochondrial selective autophagy degrades aged and/or defective mitochondria and its deficiency results in progressive mitochondrial dysfunction and gradual proteostasis collapse, which are shared hallmarks of ageing (Lopez-Otin, Blasco, Partridge, Serrano, & Kroemer, 2013). Therefore, mitophagy might be a potential therapeutic target for preventing specific age-associated phenotypes. Indeed, urolithin A-induced mitophagy leads to a general improvement of cellular and organismal homeostasis with age (Ryu et al., 2016). Interestingly, the activity of urolithin A might coordinate mitochondrial biogenesis and mitophagy to maintain energy metabolism, since short-term administration of urolithin A reduces mitochondrial population while sustaining maximum respiratory capacity and its long-term exposure promotes mitochondrial biogenesis increasing mitochondrial number later in life (Palikaras et al., 2015b; Ryu et al., 2016). Furthermore, rodents treated with urolithin A display elevated mitophagy in muscle cells, which contributes to improved muscle cells quality and enhances exercise endurance without influencing muscular mass. Notably, the beneficial effects of urolitin A on muscle physiology are independent of dietary conditions and age (Ryu et al., 2016). Thus, nutritional supplementation with urolithin A could be used as an alternative intervention to preserve mitochondrial metabolism enhancing muscles function and preventing motor disabilities, which are frequently observed in the elderly (Fried et al., 2001).

5. Conclusions and future perspectives

Altered mitochondrial homeostasis characterized by low ATP levels, elevated cytoplasmic calcium and excessive ROS generation are the main key features of several pathological conditions and ageing. Additionally, accumulation of defective mitochondria is supposed to be the first-in class cause of the age-associated disorders, including neurodegenerative diseases, cardiomyopathies and cancer. Therefore, efficient mitochondrial quality control is pivotal for cellular and organismal homeostasis.

Despite the extensive studies focusing on the molecular mechanisms that govern mitophagy, numerous controversial questions remain to be addressed about mitophagy tissue-specificity and its dependency on pathological conditions. Congruently, mitophagy stimulation might be both beneficial and detrimental for tissue homeostasis depending on cellular bioenergetics under certain pathophysiological conditions. Alongside, recent evidence highlights the significance of mitochondrial biogenesis for cellular physiology suggesting that it should not be investigated independently of mitophagy, since both processes are concomitant and interconnected (Palikaras et al., 2015b).

Thus, new therapeutic interventions to be effective should coordinate mitochondrial biogenesis and the clearance of damaged mitochondria through mitophagy to maintain a healthy mitochondrial population and proper organ function. In the upcoming years, an increase in awareness of mitochondrial homeostasis will be observed that will allow the therapeutic application of natural compounds such as spermidine, resveratrol and urolithin A, and certain already FDA-approved drugs, including rapamycin and metformin among others. Indeed, the results obtained from studies in animal models are encouraging given the beneficial effects of mitophagy modulators on cellular energy metabolism and organismal healthspan. A major question, however, that remains is how these compounds impact on human physiology and what is their potential in clinical settings. Therefore, interventional studies are required to test the therapeutic efficiency of mitophagy- and mitochondrial biogenesis-regulators against mitochondrial related diseases.

However, not only the use of food supplements and/or drugs, which promote general quality control mechanisms, but also life-style interventions, such as physical exercise, represent promising candidates to counteract deterioration of mitochondrial metabolism and prevent neurodegeneration, inflammation, organ failure and general homeostasis collapse during ageing.

Conflict of interest

The authors declare no conflict of interest.

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