Biochimica et Biophysica Acta 1837 (2014) 451–460

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Review

Mitochondrial dismissal in mammals, from protein degradation to mitophagy ☆

Silvia Campello [a,*], Flavie Strappazzon [a,b], Francesco Cecconi [a,b,c,**]

[a] IRCCS Fondazione Santa Lucia, 00143 Rome, Italy
[b] Department of Biology, University of Rome Tor Vergata, 00133 Rome, Italy
[c] Unit of Cell Stress and Survival, Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark

ARTICLE INFO

Article history:
Received 29 August 2013
Received in revised form 6 November 2013
Accepted 15 November 2013
Available online 22 November 2013

Keywords:
Mitochondrion
Mitochondria fusion/fission
Autophagy
Ubiquitylation
Neurodegeneration
Mitochondria Quality Control

ABSTRACT

Mitochondria are double-membraned highly dynamic organelles; the shape, location and function of which are determined by a constant balance between opposing fusion and fission events. A fine modulation of mitochondrial structure is crucial for their correct functionality and for many physiological cell processes, the status of these organelles, being thus a key aspect in a cell's fate. Indeed, the homeostasis of mitochondria needs to be highly regulated for the above mentioned reasons, and since a) they are the major source of energy; b) they participate in various signaling pathways; albeit at the same time c) they are also the major source of reactive oxygen species (ROS, the main damaging detrimental players for all cell components). Elaborate mechanisms of mitochondrial quality control have evolved for maintaining a functional mitochondrial network and avoiding cell damage. The first mechanism is the removal of damaged mitochondrial proteins within the organelle via chaperones and protease; the second is the cytosolic ubiquitin–proteasome system (UPS), able to eliminate proteins embedded in the outer mitochondrial membrane; the third is the removal of the entire mitochondria through mitophagy, in the case of extensive organelle damage and dysfunction. In this review, we provide an overview of these mitochondria stability and quality control mechanisms, highlighting mitophagy, and emphasizing the central role of mitochondrial dynamics in this context. This article is part of a Special Issue entitled: Dynamic and ultrastructure of bioenergetic membranes and their components.

1. Introduction

Mitochondria are subcellular organelles crucial for the life of the cell. They are the main energy converters, and are essential components of various signaling pathways. They are sensors of metabolic homeostasis, and regulate the levels of intracellular signaling molecules, such as Ca^{2+}. Ca^{2+} is buffered in micro-domains at the ER proximity in order to modulate cytoplasmic signaling, and to support efficient oxidative phosphorylation and ATP production in the mitochondrial matrix [1]. On the other hand, mitochondria can be detrimental for the cell, being the major source of reactive oxygen species (ROS), which may oxidize and damage proteins, lipids and DNA [2], all of these becoming totally dysfunctional and dangerous for the cell life.

For all these reasons, mitochondria homeostasis needs to be highly regulated. Elaborate mechanisms of mitochondrial quality control have evolved to maintain a functional mitochondrial network and avoid cell damage. The crucial role of these defense pathways for cellular homeostasis and survival is supported by the fact that mitochondrial dysfunction is related to aging, cancer and a wide range of neurological pathologies [3–5]. The cell protects itself by removing or isolating what is damaged, from mitochondria-located proteins to the same organelles [6,7]. To this purpose, the cell accomplishes two main strategies. The first one is used to remove misfolded, denatured or oxidized proteins. This strategy is based both on the activity of mitochondrial proteases that remove proteins resident in the mitochondrial milieu [8,9], and on the activity of the cytosolic ubiquitin–proteasome system (UPS), which in turn recognizes and removes mistargeted or misfolded mitochondrial proteins before they reach the organelle, and mediates the degradation of proteins embedded in the outer mitochondrial membrane (OMM) [10,11].

The second strategy is based on the intrinsic characteristic of mitochondria being highly dynamic organelles, continually fusing and fragmenting in a strictly regulated manner [12,13], and in response to different physiological needs of the cell [14]. In this second defensive strategy, entire parts of the same organelles are removed. Thus,

☆ This article is part of a Special Issue entitled: Dynamic and ultrastructure of bioenergetic membranes and their components.

* Correspondence to: S. Campello, IRCCS, Fondazione Santa Lucia, via del fosso di fiorano 64, 00143 Rome, Italy. Tel.: +39 06501703218.
** Correspondence to: F. Cecconi, Department of Biology, Università di Roma Tor Vergata, via della Ricerca Scientifica, 00133 Rome, Italy. Tel.: +39 0672594230.
E-mail addresses: s.campello@hsantalucia.it (S. Campello), francesco.cecconi@uniroma2.it, cecconi@cancer.dk (F. Cecconi).

0005-2728
http://dx.doi.org/10.1016/j.bbabio.2013.11.010

based on steric principles, damaged mitochondria are tilted toward a fragmented phenotype, so as to be more disposed to segregation and removal [15,16], while healthy or highly active mitochondria tend to fuse among themselves in order to favor the replacement of essential components, as well as maintaining the mitochondrial genome in the network [17–19]. The main mechanism used by the cell to remove damaged organelles and proteins is autophagy. The term autophagy encloses any processes regarding cytosolic component degradation via lysosomes. As we will see in more detail later, the process termed macroautophagy is generally responsible for the engulfment and removal of cytosolic components. However, a more specific autophagy pathway comes into play in conditions of severe mitochondrial dysfunction, this to selectively remove damaged mitochondria, hence the term 'mitophagy'.

Albeit beyond the scope of this review, we should also mention a third level of quality control, which occurs at a cellular level. It takes place when extensive mitochondrial damage promotes release of pro-apoptotic factors, so resulting in the cell's suicide through apoptosis [20].

In this review, we provide an overview of the mentioned mechanisms of mitochondria stability and quality control, focusing on the relationships existing between these processes (UPS and autophagy) and mitochondria dynamics, and on mitophagy, the latter being the principal process controlling mitochondria homeostasis. Considering the complexity of the subjects and the impressive amount of data present in the literature, we will give particular emphasis to recent findings in the field, focusing on mammals.

2. Outlines on mitochondrial dynamics

As mentioned, mitochondria are highly dynamic organelles, their shape, location and function being defined by a constant balance and equilibrium between opposing fusion and fission events. These dynamic processes are crucial in many physiological and pathophysiological cellular conditions, the modulation of the same, being pivotal for determining cell life and death [14]. Thus, mitochondria morphology needs to be strictly regulated by a set of 'mitochondria-shaping' proteins, the number of which is constantly increasing. The machineries involved in mitochondrial fusion and fission are highly complex; we will only summarize them briefly here: For further extensive reading see other reviews (i.e. [12,21,22]). In mammals, mitofusin 1 (Mfn1) and 2 (Mfn2) together with OPA1 are required for the fusion of the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), respectively. Mfns are integrated in the OMM and form homo- and hetero-oligomers, which promote tethering and fusion of the OMMs from two different mitochondria [23,24]. The pleiotropic protein OPA1 localizes in complexes at the IMM, facing the inter membrane space (IMS), and drives fusion on the IMM. OPA1 complexes are composed of post-translational proteolytically cleaved short and long forms, deriving from the several splicing variants existing [25]. Fusion, along with the anti-apoptotic role that OPA1 exerts on the mitochondrial cristae structures [26], requires both the short and long forms of OPA1 [27].

Mitochondrial fission depends on the GTPase cytosolic dynamin-related protein 1 (Drp1), which is located in the cytosol and needs to be activated and to translocate to mitochondria in order to constrict and cut the organelles [28]. Post-translational modifications, such as phosphorylation, SUMOylation and ubiquitylation modulate Drp1 activity so as to ensure adaptation to the various cellular needs [21,29,30]. Furthermore, the OMM protein hFis1 has been proposed as a Drp1 receptor, being so necessary for mitochondrial fission. hFis1 mechanism of action is still highly controversial [31,32]; on the other hand, new possible Drp1 receptors have been recently identified: Mff (the OMM-anchored mitochondrial fission factor, [32]), and human MIEF1/MiD51 (the OMM-bound mitochondrial elongation factor1/mitochondrial dynamics 51) with its variant MiD49 [33,34]. The latter were reported to directly and specifically recruit Drp1 in a Fis1-independent manner, but with opposite effects on the mitochondrial morphology, depending on the protein levels [33–35].

Changes in mitochondria morphology influence crucial physiological functions in the cells, such as Ca^{2+} signaling, generation of reactive oxygen species, neuronal plasticity and lymphocyte migration [14]. Moreover, the ultrastructure and shape of the organelles have also been linked to pathophysiological aspects, from muscle atrophy to lifespan determination, and to apoptosis [14], and are affected in several human genetic diseases [22] (see Table 1).

The remarkable structural dynamism of mitochondria has a particular bearing upon the mitochondrial quality control system. The strict interconnection between mitochondria dynamics and mitochondrial quality control, detectable at different levels, will be discussed in the following paragraphs.

3. Mitochondrial proteostasis: the degradation of mitochondrial proteins

3.1. Mitochondrial proteases and removal of proteins within the organelle

The mechanisms developed by mitochondria to maintain their homeostasis are numerous (see Fig. 1). The first line of defense is located in the organelles and acts at a molecular level in conditions of *mild* mitochondrial damage. It consists of several proteases and chaperones operating within the mitochondrion [36].

The majority of the mitochondrial proteins are synthesized in the cytosol and subsequently imported into the organelle [37]. The unwanted but probable interaction and aggregation among proteins entering the organelle in a relatively unfolded state are prevented by a group of chaperones, members of the heat shock family [38].

A highly conserved group of proteases is responsible for the removal of unfolded or damaged proteins within the mitochondria. For example, in concert with chaperones, the AAA^{+} (*A*TPase *a*ssociated with a wide variety of cellular *a*ctivities) soluble hLon protease family removes denatured or oxidatively mildly damaged proteins [39,40]. A second soluble protease group belongs to the bacterial Clp protein family (*c*aseinolytic *p*rotease [41]), mitochondrially represented by mtClpXP (chaperone-protease complex), the activity of which is still undefined. The inner mitochondrial membrane (IMM) is highly enriched in proteins, which are more susceptible to oxidative damage due to their proximity

Table 1
List of the main physiological and/or patho-physiological processes, in which mitochondria dynamics play a crucial role. The main organelle phenotype is shown, together with a selected number of correlated references.

Patho-/physiological process	Mitochondrial phenotype	References
Ca^{2+} signaling	Variable depending on the pathophysiological condition	Szabadkai et al. [155]
Generation of reactive oxygen species (ROS)	Fragmentation	Yu et al. [156]
Maintenance of dendritic spines and neuronal plasticity	Fragmentation	Li et al. [157]
Lymphocyte migration	Fragmentation and relocalization	Campello et al. [158]
Metastatic cell migration	Fragmentation and relocalization	Zhao et al. [159]
Muscle atrophy	Fragmentation	Romanello et al. [160]
Lifespan	Fragmentation (in aging)	Scheckhuber et al. [161]
Apoptosis	Fragmentation and cristae-remodeling	Scorrano [162]
Neurodegenerative diseases (AD, PD, HD, ADOA…)	Mostly fragmentation, in some cases: cristae disruption, impaired trafficking, reduction in number	Corrado et al. [22]; Cho et al. [5]
Cancer	Fragmentation	Grandemange et al. [163]; Qian et al. [164]; Corrado et al. [22]
Cardiovascular disease	Mainly fragmentation	Ong et al. [165]; Piquereau et al. [166]

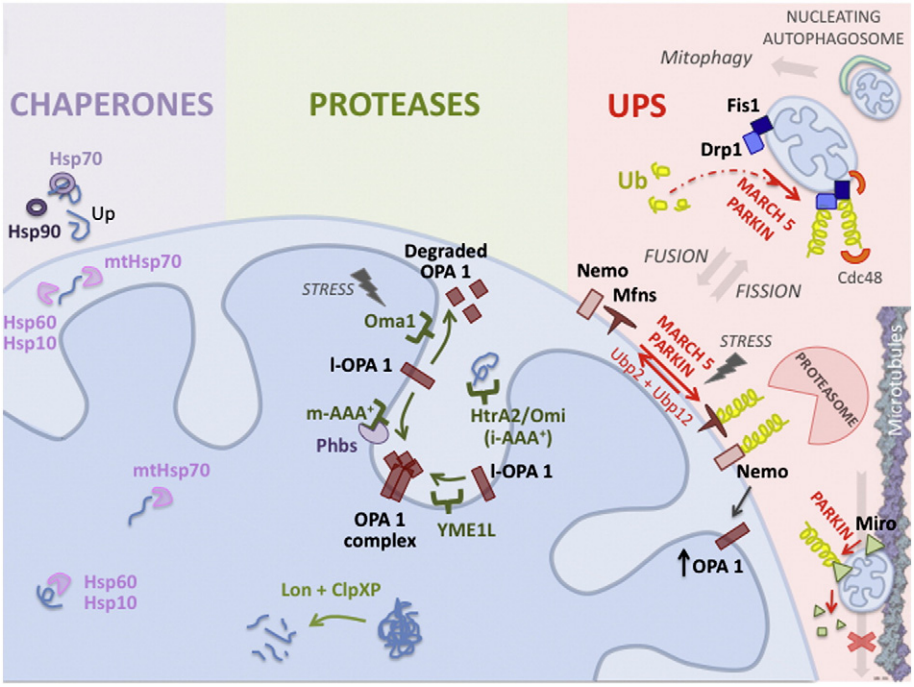

Fig. 1. Schematic representation of the mitochondrial degradation main mechanisms. *On the left*, the *chaperone system* with some of the main players indicated. Hsp70, Hsp90 families' members (in violet) help nuclear encoded proteins to enter the mitochondria in an unfolded state (Up, unfolded protein). Moreover, mtHsp70 and, in some conditions, Hsp60/Hsp10 members facilitate protein folding within the mitochondria. *Centered* in the depiction, the mitochondria *protease system* is represented, with the main protease classes shown. Lon and Clp protein families are dedicated to degradation of damaged or unfolded proteins in the matrix. Unassembled or damaged inner membrane proteins are degraded by the membrane embedded AAA^+ proteases, the m-AAA^+ and the i-AAA^+, facing the matrix or the inter-membrane space, respectively. Some members of both protease classes are shown (in green). i-AAA^+ YME1L and m-AAA^+ (the latter in complex with Prohibitins (Phbs)) are responsible for OPA1 processing and complex formation, composed by short and long forms. On the contrary, the m-AAA^+ Oma1 degrades the long OPA1 form, under stress conditions. Also the i-AAA^+ HtrA2/Omi participate to the turnover of misfolded inter-membrane space proteins. *On the right*, some players of the *ubiquitin–proteasome system (UPS)*, important in the regulation of mitochondria homeostasis and shape, are represented. Outer membrane proteins are ubiquitylated (Ub, and yellow spring in depiction) by a cascade of E-ligases to be removed then through the ubiquitin–proteasome degradation system. Some examples: Mfns, Nemo, Drp1, Fis1, Miro are alternatively ubiquitylated by March5, Parkin in order to modulate mitochondrial dynamics, by respectively impinging in the fusion (Mfns and Nemo), fission (Drp1 and Fis1) or transport (Miro) of mitochondria. These machineries are activated under stress/damage conditions (promoting fission) or in response to physiological conditions requiring high efficiency in ATP production or component mixing (promoting fusion in this case). Mfn2 is also independently deubiquitylated by Ubp2 and Ubp12. Cdc48 helps in extracting the outer mitochondrial membrane embedded protein (here it is shown acting on Fis1, as an example). In case of excessive mitochondria damage, the same organelles are removed through mitophagy.

to produced ROS. Thus, the quality control in this subcompartment is crucial; two membrane-integrated AAA^+ metalloprotease complexes, belonging to the FtsH (*f*ilament-forming *t*emperature-sensitive) protease family, ensure this function [41,42]. The m-AAA protease is directed and works in the matrix, while the i-AAA works facing the intermembrane space (IMS) [43]. An example of i-AAA protease is the human Omi/HtrA2, whose levels increase in response to various stresses, and for which a role has been proposed in autophagy [44] and in apoptosis [45,46].

Interestingly, these proteases form a hexamer in solution, creating a sort of ring-like structure with a proteolytic cavity, where substrates enter to be cleaved [47]. Of note, in mammals, the proteases m-AAA, YME1L (an i-AAA protease) and the metallopeptidase OMA1 (overlapping activity with m-AAA protease 1) are, in various ways, responsible for the cleavage of one key protein controlling mitochondria fusion, OPA1 (see above; [27,48–50]). In this way, they modulate mitochondria morphology. Another intriguing regulation of mitochondria shape and stability comes from a class of IMM proteins, the prohibitins [51,52]. These molecules apparently function as scaffold proteins, forming a complex together with m-AAA [53,54] and orchestrating OPA1 processing as well. Lack of prohibitins increases the proteolitic activity of m-AAA, consequently destabilizing the long form of OPA1 and leading to fusion inhibition [51,52].

3.2. The UPS and ubiquitylation system: removing proteins from the outer mitochondrial membrane

Mitochondrial protein quality control is also influenced by the ubiquitin–proteasome system (UPS, see Fig. 1) [10,55,56]. UPS is the major nonlysosomal system for degrading proteins in the cell. It is involved in regulating a plethora of biological functions. In eukaryotes, the UPS is a conserved proteolytic process, composed of the E1 (ubiquitin activating), E2 (ubiquitin conjugating), and E3 (ubiquitin ligating) enzymes. Together these cooperate in mediating attachment of ubiquitin (monomers or chains) to a multitude of target proteins, then recognized and degraded by the proteasome. The proteasome is constituted of the 19S regulatory unit and the 20S core unit, responsible, respectively, for the recognition and proteolysis of the ubiquitylated substrates [57]. Several mitochondrial E3 ligases have been recently identified [10] as being regulators of the mitochondria fusion/fission balance by directly targeting the 'mitochondria-shaping' proteins. Nevertheless, the physiological role of these ligases is still controversial and unclear, and further studies are needed to clarify their action mechanism.

MARCH5/MITOL is an important E3 ligase showing opposite effects on mitochondria morphology. It has been shown, in works that seem to contradict each other, that 1) it mainly binds Drp1 and Fis1 and thus blocks fission [58,59]; 2) it activates Mfn2 and fusion [58]; and 3) it binds and degrades Mfn1 by promoting fission [60], especially in the cell's G2/M phase [61]. Recent works have also reported a role for MARCH5 in the mitochondrial quality control in nitrosative stress responses [62,63].

The MULAN/MAPL E3 ligase causes mitochondrial fragmentation by directly mediating Mfn2 ubiquitylation and degradation [64], thus facilitating mitochondria removal via mitophagy (see below). Interestingly, Mfn2 activity is not only regulated by ubiquitylation, but also by the deubiquitylases Ubp2 and Ubp12, through independent pathways [65]. MULAN/MAPL is the first mitochondrial-anchored SUMO E3 ligase characterized [66]. It regulates the structure of mitochondria not only through Mfn2 ubiquitylation, but also by directly controlling the

fission machinery. Indeed, it directly orchestrates Drp1 SUMOylation, thus stimulating mitochondrial fission. These findings define for the SUMOylation process an important role in regulating mitochondrial quality control. SUMOylation is another crucial mechanism controlling the stability and the ubiquitin-dependent degradation of mitochondrial proteins. At variance with what has been assumed for a long time, i.e. that SUMO was acting as a ubiquitin antagonist, it is now known that SUMO conjugation can mediate ubiquitin-dependent degradation by the proteasome, the two processes functioning in a tightly integrated and cooperative manner [67].

A few cytosolic E3 ligases, such as Parkin, Huwe1/Mule/HectH9 and the yeast Mdm30 of the CRL E3 complex, regulate the mitochondria morphology mainly through Mfn2 (or the yeast homolog Fzo1) degradation, conferring on the UPS a key role on the regulation of mitochondrial shape [68–70]. As described later, upon CCCP treatment, Parkin mediates ubiquitylation and removal of Mfns, so inducing mitophagy. Interestingly, Drp1 also is a substrate of Parkin in unstressed conditions [71], indicating again that E3 ligases may change their role depending on the physiological cell conditions. It should be noted that, under cellular stress, a very recent paper has shown that Parkin increases linear ubiquitylation of NF-κB essential modulator (NEMO), resulting in OPA1 transcriptional upregulation, this maintaining mitochondria integrity and protecting the cell from stress-induced cell death [72].

Finally, UPS has also recently been found to modulate the mitochondria motility, through Parkin-dependent degradation of Miro (an OMM protein involved in mitochondrial transport along microtubules) [71]. Again, the arrest of mitochondria movement (together with a small size) may also facilitate mitophagy.

The question now arises as to how exactly the cytosolic proteasome is able to degrade integral mitochondrial membrane proteins. A key role for the AAA^{+} ATPase VCP/p97 (Cdc48, in yeast) in this process has recently been demonstrated, even though other mechanisms of mitochondrial protein retro-translocation may exist, since the loss of p97 function does not completely abrogate protein degradation through the proteasome [73]. This chaperone would facilitate the extraction of substrates embedded in the OMM [74]. In the case of Mfn1 and Mcl1, for example, the two proteins are retro-translocated from mitochondria to the cytosol, prior to, or concurrent with, proteasomal degradation, in a p97 ATPase domain-dependent manner [75]. Of note, indeed, it has been demonstrated that also p97 associates with mitochondria in mammalian cells [76]. These results suggest a conserved role for AAA-ATPase protein family members in the regulation of mitochondrial proteostasis. Moreover, the fact that p97 mediates degradation of pro-fusion mitochondrial proteins leading to increased mitochondria fragmentation, in concert with the interesting observation that proteasomal inhibitors such as lactacystin and MG132 also inhibit mitochondria degradation [77], create a link between p97 activity and mitophagy.

Importantly, the UPS-dependent mitochondria control is regulated at different levels: the E3 ligases transcripts are tissue specific [78]; various proteins regulate the E3 ligase functions [79]; E3 ligase activity, as well as the substrate selectivity, is under the control of post-translational modifications, such as phosphorylations [71] or S-nitrosylations [80]; E3 ligases also autoubiquitinate and degrade themselves [59].

In higher eukaryotes, a mitochondria-specific unfolded protein response (UPR) is also present, to attenuate as well the increase of misfolded proteins in mitochondria [81,82].

4. Mitochondria stability and consequent changes in their shape: opposite responses to autophagy

4.1. Outlines on autophagy

Autophagy (from Greek, meaning *self-eating*) is a catabolic process occurring in all eukaryotic cells, by which cytoplasmic material (e.g., proteins, lipids and organelles) is degraded through the lysosome machinery. This process involves de novo formation of double-membraned vesicles, termed autophagosomes, which sequester the cytoplasm-derived materials and transport them to the lysosomes for degradation. There are three classes of autophagy: microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy [83]. Macroautophagy is well conserved from yeast to mammals and is the predominant pathway of autophagy. The non-selective autophagy (bulk autophagy) is induced by starvation while selective autophagy is induced when organelles (such as mitochondria, and in this case the process is called mitophagy) are damaged or unwanted in the cell.

Autophagy is regulated in five steps 1) initiation of the isolation membrane 2) elongation of it, 3) closure of the isolation membrane and autophagosome nucleation, 4) autophagosome–lysosome fusion and 5) lysosomal degradation [84]. These five mechanisms are also similar during the selective removal of mitochondria [85]. Thanks to genetic screens in yeast *Saccharomyces cerevisiae*, 35 genes regulating autophagy (ATGs) have been identified [86]. ATGs are well conserved in mammalian cells and, except for ATG13, the core machinery involved in non-selective autophagy is also involved in selective autophagy, such as mitophagy [87].

4.2. Different types of autophagy and different cell needs induce different mitochondrial shaping pathways

When the mitochondria damage becomes *too extreme* for the cell and is accompanied by dissipation of the mitochondrial membrane potential, the fusion process is blocked; mitochondria are selectively removed by autophagy, precisely through mitophagy [68,88], with a characteristic phenotype of fragmented organelles. Interfering with mitochondrial fission inhibits the autophagic degradation of damaged mitochondria [74,89], this illustrating the intimate relationship between mitochondrial dynamics and quality control. The fact that mitochondria are fragmented during this process, is probably attributable to sterical constrains. Indeed, large or elongated mitochondria would be sterically problematic for autophagosomes engulfment, while small fragmented organelles would easily fit within those structures. For this reason, it has been suggested that mitochondrial fragmentation precedes mitophagy [17,18,89,90]. In fact, this was proven in yeast by Nowikovsky and colleagues [91], even though a more recent work has shown that rapamycin induces mitophagy in the same organisms, independently of mitochondria fission, raising doubts about fission's role during this selective autophagy [92]. From what is known to date, we can conclude that mitochondria fission is not able to trigger mitophagy per se; the dysfunction of the organelles, or other unknown signals, are otherwise required. An elegant recent work showed the existence of a selection process that distinguishes 'good' from 'bad' mitochondria, targeting only the former to autophagosomes engulfment [18].

Macroautophagy is an energy-consuming process which, to protect the cell from damage, needs high amounts of ATP i.e., namely, highly functional mitochondria. In this context, mitochondria unbalance the morphological equilibrium toward fusion. Indeed, elongated organelles have more cristae, with increased ATP synthase activity and, consequently, more ATP production. Furthermore, an entire mitochondrial network is sterically far from being engulfed by autophagosomes during autophagy. Thus, mitochondria protect themselves from autophagic removal by blocking the fission machinery and promoting fusion. This is exactly what Scorrano and colleagues [19] also nicely showed in vivo (as confirmed in parallel by another independent study [15]), when macroautophagy was induced by starvation or mTOR inhibition. The mechanism regulating this process is based on the increase of cAMP levels induced by starvation. cAMP activates PKA which phosphorylates Drp1 Ser637, thus blocking its activation and its capability to induce fragmentation. In summary, we can conclude that mitochondria morphology determines the cellular fate by opposing different phenotypes in response to different types of autophagy.

5. Mitochondria removal through mitophagy

As already said above, when mitochondria are defective, the cell removes them through the mitophagic process (Fig. 2). Mitophagy is also a mechanism which regulates the number of mitochondria in response to developmental signals. Indeed, two types of mechanism can be described on this regard: 1) 'programmed' mitophagy, in the case of reticulocyte differentiation [93] and during elimination of parental mitochondria in the fertilized oocyte [94,95]; and 2) 'reactionary' mitophagy when mitochondria are defective. According to these two programs of mitophagy, three well-known effectors emerge: First is Nix/BNIP3L, a protein resident on mitochondria [96–98] and the main player of mitophagy during reticulocyte differentiation; second and third are PINK1 [99] and Parkin [100], two genes linked to autosomal-recessive juvenile Parkinsonism in humans and involved in mitophagy when mitochondria are damaged. PINK1 is a mitochondrially targeted serine/threonine kinase, whereas Parkin is an E3 ubiquitin ligase, as we said above.

5.1. Classical effectors of mitophagy

Selective mitophagy is necessary during development of red blood cells (RBCs). In fact, these cells need to lose their mitochondria in order to transport and not consume oxygen [93]. Mitophagy in RBCs involves Nix, a Bcl-2 related OMM protein, with an atypical BH3 domain. Nix participates in the incorporation of mitochondria into autophagosomes by using its LC3-binding motif [101]. Consequently, in this context, Nix functions as a receptor targeting mitochondria for degradation. Another type of programmed mitophagy occurs during elimination of parental mitochondria in the fertilized oocyte [94]. However in this situation, no clear actor has been yet defined, even though it seems clear that the autophagic machinery is required [102–104]. Interestingly, in fertilized oocytes, mitochondria ubiquitylation is a controversial issue: the organelles have been shown to be not ubiquitylated prior to degradation (103–105), whereas others studies indicate that ubiquitylation of parental mitochondrial proteins occurs, indeed, prior to degradation [77,95,105].

In addition, it is not clear if mitochondria are depolarized or not before engulfment by autophagosomes (Fig. 3). Further investigations are required to better characterize this pathway.

To date, a body of evidence places the PINK1/Parkin couple as the major pathway of mitophagy in immortalized cells. Even if many questions remain, this pathway is the best described for the mitophagic degradation of dysfunctional, depolarized-mitochondria. A strong decrease in mitochondrial potential induced by the uncoupler CCCP, leads to PINK1's recruitment to the OMM, through the TOM20 complex [106–109]. In this manner, PINK1 works as a sensor of mitochondrial potential. In a second step, PINK1 recruits Parkin from the cytosol, phosphorylates it and promotes Parkin's E3 ubiquitin ligase activity [110–114]. Then, ubiquitylated mitochondria recruit ubiquitin-binding adaptor proteins, such as p62/SQSTM1 [110,115,116]. Nevertheless, some studies exclude p62 from this pattern [96,110,115]. The binding of mitochondria to p62 is followed by clustering of mitochondria around the nucleus [110,115,116]. LC3 is needed as a scaffold protein recruiting the autophagic machinery [68]. A direct link with the classical autophagy machinery does, indeed, exist. In fact, PINK1 and Parkin can interact with the Beclin 1–PI3K complex [117,118]. AMBRA1, an activator of the Beclin 1 complex, is recruited by Parkin to mitochondria in order to activate the Beclin 1 complex [117].

5.2. PINK1/PARKIN independent pathways

The mitophagic PINK1/Parkin pathway has been demonstrated as being relevant in cases of mitochondrial damage. Indeed, in most related studies, the mitochondrial uncoupler CCCP is the best agent to induce mitophagy. However, it is not known yet what happens in cells upon a physiological induction of mitophagy. Are PINK1/Parkin acting under physiological conditions? The fact that 1) patients with mutations in the PINK1/Parkin pathway do not show an increased mitochondrial mass, and 2) the most prominent pathology of adult Parkin null flies is in the flight musculature, which is plagued by muscle degeneration and pronounced mitochondrial lesions [119], leads to the conclusion that other pathways independent of PINK1/Parkin do, indeed,

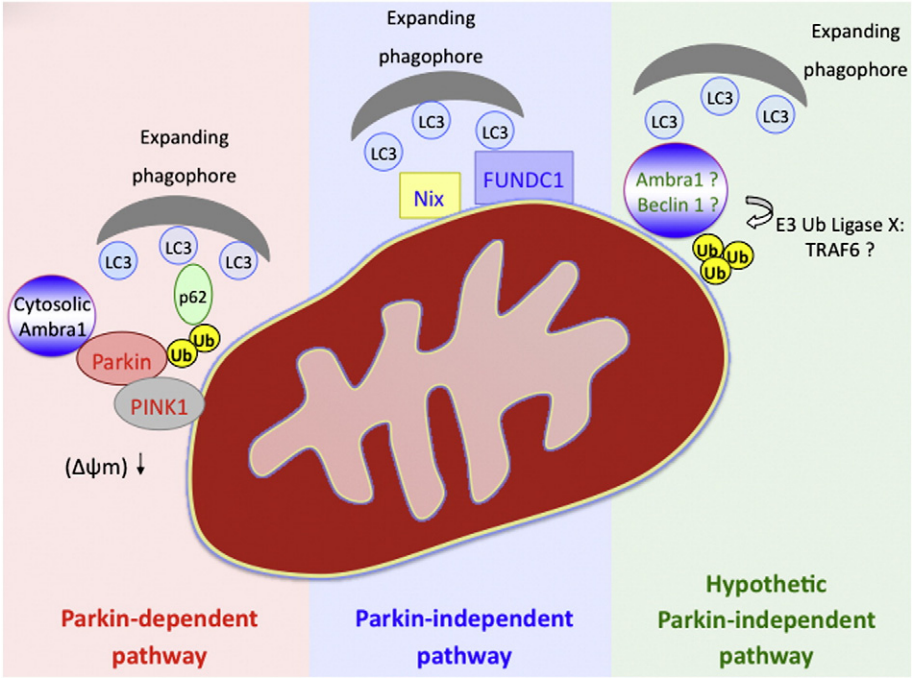

Fig. 2. Mitophagy models in mammalian cells. The mitophagic mechanism in the presence of Parkin, is represented *on the left* of the drawn mitochondrion. When Parkin is absent, Nix and FUNDC1 are the main effectors of mitophagy and are represented *on the central part* of the drawn mitochondrion. Finally, *on the right part* of the mitochondrion, proteins of the autophagic machinery, such as Ambra1, Beclin 1, namely resident on mitochondria, could also play a role in selective mitophagy by serving as scaffold proteins to directly recruit the phagophore expanding to mitochondria.

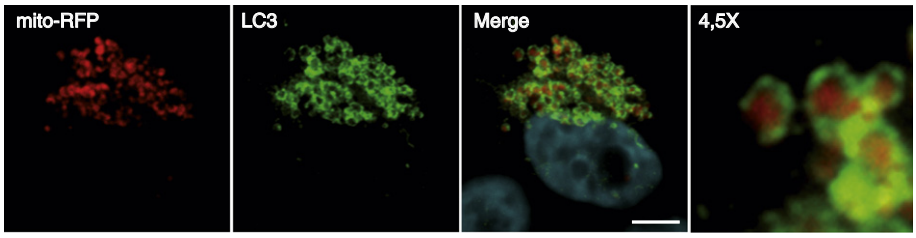

Fig. 3. Mitochondrial engulfment by autophagosomes. HEK293 cells were transfected with vectors encoding mito-RFP (red) and a Parkin-overexpressing construct. Twenty-four hours after transfection, cells were treated with CCCP in order to induce mitophagy, fixed and stained with an anti-LC3 antibody (green). The merge of the fluorescence signals is shown in the right panel, together with a higher magnification image (4.5×). Of note, in these conditions, mitochondria-containing autophagosomes are visible in a sort of large aggregate, termed mito-aggresome. Scale bar, 6 μm.

exist in the cell in order to remove damaged mitochondria. This conclusion is strengthened by the fact that PINK1 or Parkin knock-out mice do not present strong phenotypes as expected in cases where the damaged mitochondria removal is totally abrogated [120]. Additional studies illustrate the fact that the PINK1/Parkin pathway is not the universal mitophagic pathway in cell lines. First, it has been shown that Nix function is not restricted to erythrocyte differentiation: In HeLa cells, a cell line free of Parkin, the binding of Nix and LC3 increases following CCCP treatment [97,121]. This work suggests a parallel function of Nix in mitophagy upon mitochondrial damage. Second, it has been shown that Nix is involved in mitophagy also following hypoxia in human fibroblasts [101]. During this process, necessary to remove ROS production, Nix expression increases and disrupts the Bcl-2–Beclin 1 binding, thus increasing ATG5-dependent autophagy [122]. Moreover, in the context of hypoxia, a novel player of mitophagy has been found: FUNDC1 [123]. Indeed, FUNDC1 binds LC3 protein through its LIR motif and helps the mitochondria engulfment by autophagosomes.

In conclusion, Nix can participate in different mitophagy pathways. In particular, it appears to be able to substitute PINK1/Parkin when they are absent. Moreover, the characterization of a new actor on mitophagy, FUNDC1, underlines the fact that other mitophagic ways exist and maybe are activated differentially according to the stimulus and/or the cell type.

Interestingly, the PINK1/Parkin pathway of mitophagy has been characterized in non-neuronal cell lines. For what concerns neurons, different behaviors of Parkin have been published. In one case, it has been observed that after depolarization of neuronal mitochondria, Parkin is not recruited to the organelles and their clearance does not occur [124]. On the other hand, various studies indicate that Parkin is recruited to damaged mitochondria [125,126]. The physiological relevance of PINK1/Parkin pathway cannot be addressed for all cell lines; other studies are required to a better understanding of mitophagy in neurons. Certainly, new players in neuronal mitophagy will emerge and contribute to the discovery of novel therapeutic targets for neurodegenerative diseases.

Since all the pathways described hitherto converge on the core apparatus of autophagy, some core autophagy apparatus proteins likely control the mitophagic process directly. Recently, it has been demonstrated that conjugated LC3 proteins can act as scaffolds to recruit various proteins to the phagophore. The interactions with ATG8 homologues occur thanks to a LIR (LC3-interacting region) motif. This motif was found in p62 for the first time [127,128] but subsequently has been found in several other proteins as well [129]. Despite their specific binding to ATG8 family proteins, these molecules with a LIR motif are not always autophagy substrates, underlining the fact that LIR-mediated interactions with ATG8 are also used to scaffold proteins on the surface of autophagosomes. It should be pertinent to examine among the proteins of the autophagy core apparatus, which one can localize to mitochondria or which other can be recruited to mitochondria, and, this being the case, which possesses such a LIR motif. Indeed, among these proteins, a very good candidate has emerged in recent years to act as a catalyzer of mitophagy.

An endogenous pool of AMBRA1 (a component of the autophagy initiation complex, see above) has been shown to be localized at the mitochondria [130]. Moreover, a tandem affinity purification and mass spectrometry allowed identifying AMBRA1 as an interactor of Parkin. Interaction found to increase strongly during prolonged mitochondrial depolarization, even though no Parkin-dependent ubiquitylation of AMBRA1 has yet been identified. Ambra1 is important for the mitochondrial clearance and not for Parkin translocation to mitochondria [117]. It would be of interest to investigate the role of mitochondrial AMBRA1 in mitophagy. AMBRA1 can be found associated in complex with ATG4 [131]; thus, it could recruit, through a potential interaction with LC3, the autophagic machinery to mitochondria in order to remove them. Interestingly, AMBRA1 can bind the E3 Ubiquitin ligase TRAF6 [132]. It would be interesting to investigate whether the binding between mitochondrial AMBRA1 and TRAF6 is an important event on mitochondria ubiquitylation. However, other candidates could also help AMBRA1 to ubiquitylate mitochondria. In fact, Ambra1 has been found to be associated with CUL4-DDB1 (a E3 ubiquitin-protein ligase complex comprising the large subunit of the damaged DNA-binding protein complex (the DDB complex), required for DNA repair) [131,133].

Another autophagy core apparatus protein, found localized at the mitochondria is Beclin 1. Mitochondrial Beclin 1 could play an additional role to recruit the autophagic machinery to help mitochondria engulfment. In fact, a recent work indicates that Beclin1 possesses a LIR motif in its sequence [134]. Thus, we can speculate that Beclin 1 could have this crucial recruiter role on some mitophagic contexts. Further studies are required to clarify Beclin 1's function at the mitochondria.

6. Pathological implications in neurodegenerative diseases

We have reported in this review how imperative it is, in the presence of misfolded or damaged proteins, that these 'bad' molecules be removed from the cell to prevent the formation of toxic folding intermediates, as well as the accumulation of lethal protein aggregates. Incorrect functionality of the protection machineries is often linked to severe diseases and to aging. Several neurodegenerative diseases share a common pathogenic mechanism, in which aggregates of a particular protein form and accumulate in the cytosol, the nucleus, or in the mitochondria. Examples are: accumulation of the amyloid-b peptide in Alzheimer's disease [135,136], accumulation of a-synuclein in Parkinson's disease [137], and aggregation of a mutant form of the huntingtin protein in Huntington's disease [138]. Although the exact mechanism of pathogenesis for these diseases remains unknown, mitochondrial dysfunction is implicated in their progression. This fact causes loss of neurological cell populations, since they are particularly sensitive to the quality of mitochondria [139]. Many diseases are related to the different steps of mitochondrial quality control. At the IMM level of protein degradation, for example, the importance of a proper quality control is highlighted by the finding that mutations in paraplegin and Afg3l2 proteins (the two subunits constituting the protease m-AAA in humans) lead to the neurological diseases hereditary spastic paraplegia (HSP) and spinocerebellar ataxia type 28 (SCA28), respectively [140,141].

Interestingly, neuron-specific ablation of prohibitin2 in the mouse forebrain causes tau hyperphosphorylation and filament formation in the hippocampus, with consequent behavioral impairments. The mechanism underlying these observations is impairment of OPA1 stability, affecting mitochondria ultrastructure and inducing accumulation of aberrant mitochondria [142].

Also an aberrant UPS function has been reported in many neuropathologies such as Parkinson's diseases [143], ischemia [144] and age-related Alzheimer's disease [145].

Alterations in mitophagy pathway can be found in several neurodegenerative diseases [146]. Parkinson's-disease (PD)-associated genes, such as PINK1 and Parkin are involved in mitophagy, as previously said. It is thus expected that in PD brain, removal of mitochondria is disturbed and that the dopaminergic neurons are dying. However, the role of these proteins in physiological conditions remains to be elucidated. In Alzheimer's disease (AD), Parkin is able to reduce intraneuronal amyloid-β levels in lentiviral models [147]. In addition, Parkin is able to ubiquitylate intracellular amyloid-β in vivo and can stimulate autophagy and clearance of defective mitochondria [147]. Mitochondrial dysfunction has also been associated with Huntington's disease due to deregulation of PGC1-α, a transcription factor important for mitochondrial biogenesis [148]. The mechanisms and role of mitophagy in these neurodegenerative diseases need further investigation.

Finally, other alterations in mitochondria function not strictly related to their quality control but rather to their transport or shape are linked to neurodegenerative diseases. In some sporadic cases of Alzheimer's disease (AD), trafficking alteration has been observed, for example, due to mutation in *Kinesin1* [149]. Works using a mouse model for Huntington's disease (HD), produced similar results. Mutated *Htt* (the gene of huntingtin protein) is able to block mitochondrial movement [150], by causing a redistribution of kinesin and dynein in primary cortical neurons [151]. On the other hand, mutations in mitochondria-shaping proteins are also directly related to neurodegenerative diseases, such as autosomal dominant optic atrophy (ADOA) and Charcot–Marie–Tooth disease type 2A, deriving from mutations in OPA1 and Mfn2, respectively [152–154].

7. Comments and conclusions

Although mitochondria are essential for determining the cell fate, supporting its energy balance and regulating its dismissal through a direct control of apoptosis, we only recently acquired sufficiently detailed molecular insights about the destiny of the mitochondria within the cells. Whilst several proteins have been shown to participate in the degradation of individual mitochondrial proteins, either for recycling the entire protein set of the organelle or for regulating the half-life of specific targets, surprisingly few factors seem to be involved in mitophagy. However well established their role in neurodegeneration, the relevance of Parkin and Pink1, to date the main two actors in this scenario, still remains in doubt under physiological conditions. Other new molecules, related to autophagy regulation, may play important roles in this context.

Besides its crucial role in the nervous system, mitochondria homeostasis is certainly involved in cancer ontogenesis and progression. Although discussion of this issue is beyond this paper's scope, we can share here the knowledge that damaged mitochondria may impact the oxidative balance of the cells and stimulate DNA damage and chromosomal instability. Mitophagy (and the proteasomal degradation of mitochondrial factor) can thus also be considered as a forefront target pathway both in cancer and, more generally, in human metabolic disorders.

Acknowledgements

The authors wish to thank Juliane Becher for helpful discussions, and Cristina Valacca and Valentina Cianfanelli for technical support.

SC is presently funded by the Italian Ministry of Health (GR-2009-1606827) and the AIRC Program MyFAG (MFAG-12120). FC lab is supported by grants from AIRC (IG2010 and IG2012 to FC), FISM (2009), the Italian Ministry of University and Research (PRIN 2009 and FIRB Accordi di Programma 2011) and the Italian Ministry of Health (Ricerca Finalizzata and Ricerca Corrente to FC).

References

[1] W.F. Graier, M. Frieden, R. Malli, Mitochondria and Ca(2+) signaling: old guests, new functions, Pflugers Arch. 455 (2007) 375–396.
[2] R. Scherz-Shouval, Z. Elazar, Regulation of autophagy by ROS: physiology and pathology, Trends Biochem. Sci. 36 (2011) 30–38.
[3] J. Nunnari, A. Suomalainen, Mitochondria: in sickness and in health, Cell 148 (2012) 1145–1159.
[4] W.J. Koopman, P.H. Willems, J.A. Smeitink, Monogenic mitochondrial disorders, N. Engl. J. Med. 366 (2012) 1132–1141.
[5] D.H. Cho, T. Nakamura, S.A. Lipton, Mitochondrial dynamics in cell death and neurodegeneration, Cell. Mol. Life Sci. 67 (2010) 3435–3447.
[6] M.J. Baker, T. Tatsuta, T. Langer, Quality control of mitochondrial proteostasis, Cold Spring Harb. Perspect. Biol. 3 (2011).
[7] R. Anand, T. Langer, M.J. Baker, Proteolytic control of mitochondrial function and morphogenesis, Biochim. Biophys. Acta 1833 (2013) 195–204.
[8] F. Gerdes, T. Tatsuta, T. Langer, Mitochondrial AAA proteases—towards a molecular understanding of membrane-bound proteolytic machines, Biochim. Biophys. Acta 1823 (2012) 49–55.
[9] O. Khalimonchuk, M.Y. Jeong, T. Watts, E. Ferris, D.R. Winge, Selective Oma1 protease-mediated proteolysis of Cox1 subunit of cytochrome oxidase in assembly mutants, J. Biol. Chem. 287 (2012) 7289–7300.
[10] N. Livnat-Levanon, M.H. Glickman, Ubiquitin–proteasome system and mitochondria—reciprocity, Biochim. Biophys. Acta 1809 (2011) 80–87.
[11] M. Karbowski, R.J. Youle, Regulating mitochondrial outer membrane proteins by ubiquitination and proteasomal degradation, Curr. Opin. Cell Biol. 23 (2011) 476–482.
[12] B. Westermann, Mitochondrial fusion and fission in cell life and death, Nat. Rev. Mol. Cell Biol. 11 (2010) 872–884.
[13] C.S. Palmer, L.D. Osellame, D. Stojanovski, M.T. Ryan, The regulation of mitochondrial morphology: intricate mechanisms and dynamic machinery, Cell. Signal. 23 (2011) 1534–1545.
[14] S. Campello, L. Scorrano, Mitochondrial shape changes: orchestrating cell pathophysiology, EMBO Rep. 11 (2010) 678–684.
[15] A.S. Rambold, B. Kostelecky, N. Elia, J. Lippincott-Schwartz, Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 10190–10195.
[16] L. Ernster, G. Schatz, Mitochondria: a historical review, J. Cell Biol. 91 (1981) 227s–255s.
[17] P.A. Parone, S. Da Cruz, D. Tondera, Y. Mattenberger, D.I. James, P. Maechler, F. Barja, J.C. Martinou, Preventing mitochondrial fission impairs mitochondrial function and leads to loss of mitochondrial DNA, PLoS One 3 (2008) e3257.
[18] G. Twig, B. Hyde, O.S. Shirihai, Mitochondrial fusion, fission and autophagy as a quality control axis: the bioenergetic view, Biochim. Biophys. Acta 1777 (2008) 1092–1097.
[19] L.C. Gomes, G. Di Benedetto, L. Scorrano, During autophagy mitochondria elongate, are spared from degradation and sustain cell viability, Nat. Cell Biol. 13 (2011) 589–598.
[20] M. Wasilewski, L. Scorrano, The changing shape of mitochondrial apoptosis, Trends Endocrinol. Metab. 20 (2009) 287–294.
[21] H. Otera, K. Mihara, Molecular mechanisms and physiologic functions of mitochondrial dynamics, J. Biochem. 149 (2011) 241–251.
[22] M. Corrado, L. Scorrano, S. Campello, Mitochondrial dynamics in cancer and neurodegenerative and neuroinflammatory diseases, Int. J. Cell Biol. 2012 (2012) 729290.
[23] N. Ishihara, Y. Eura, K. Mihara, Mitofusin 1 and 2 play distinct roles in mitochondrial fusion reactions via GTPase activity, J. Cell Sci. 117 (2004) 6535–6546.
[24] M. Neuspiel, R. Zunino, S. Gangaraju, P. Rippstein, H. McBride, Activated mitofusin 2 signals mitochondrial fusion, interferes with Bax activation, and reduces susceptibility to radical induced depolarization, J. Biol. Chem. 280 (2005) 25060–25070.
[25] N. Ishihara, Y. Fujita, T. Oka, K. Mihara, Regulation of mitochondrial morphology through proteolytic cleavage of OPA1, EMBO J. 25 (2006) 2966–2977.
[26] C. Frezza, S. Cipolat, O. Martins de Brito, M. Micaroni, G.V. Beznoussenko, T. Rudka, D. Bartoli, R.S. Polishuck, N.N. Danial, B. De Strooper, L. Scorrano, OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion, Cell 126 (2006) 177–189.
[27] Z. Song, H. Chen, M. Fiket, C. Alexander, D.C. Chan, OPA1 processing controls mitochondrial fusion and is regulated by mRNA splicing, membrane potential, and Yme1L, J. Cell Biol. 178 (2007) 749–755.
[28] E. Smirnova, L. Griparic, D.L. Shurland, A.M. van der Bliek, Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells, Mol. Biol. Cell 12 (2001) 2245–2256.
[29] J.T. Cribbs, S. Strack, Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death, EMBO Rep. 8 (2007) 939–944.
[30] G.M. Cereghetti, A. Stangherlin, O. Martins de Brito, C.R. Chang, C. Blackstone, P. Bernardi, L. Scorrano, Dephosphorylation by calcineurin regulates translocation of Drp1 to mitochondria, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 15803–15808.

[31] Y. Yoon, E.W. Krueger, B.J. Oswald, M.A. McNiven, The mitochondrial protein hFis1 regulates mitochondrial fission in mammalian cells through an interaction with the dynamin-like protein DLP1, Mol. Cell. Biol. 23 (2003) 5409–5420.
[32] H. Otera, C. Wang, M.M. Cleland, K. Setoguchi, S. Yokota, R.J. Youle, K. Mihara, Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells, J. Cell Biol. 191 (2010) 1141–1158.
[33] C.S. Palmer, L.D. Osellame, D. Laine, O.S. Koutsopoulos, A.E. Frazier, M.T. Ryan, MiD49 and MiD51, new components of the mitochondrial fission machinery, EMBO Rep. 12 (2011) 565–573.
[34] J. Zhao, T. Liu, S. Jin, X. Wang, M. Qu, P. Uhlen, N. Tomilin, O. Shupliakov, U. Lendahl, M. Nister, Human MIEF1 recruits Drp1 to mitochondrial outer membranes and promotes mitochondrial fusion rather than fission, EMBO J. 30 (2011) 2762–2778.
[35] C.S. Palmer, K.D. Elgass, R.G. Parton, L.D. Osellame, D. Stojanovski, M.T. Ryan, MiD49 and MiD51 can act independently of Mff and Fis1 in Drp1 recruitment and are specific for mitochondrial fission, J. Biol. Chem. 288 (2013) 27584–27593.
[36] W. Voos, Chaperone-protease networks in mitochondrial protein homeostasis, Biochim. Biophys. Acta 1833 (2013) 388–399.
[37] W. Neupert, J.M. Herrmann, Translocation of proteins into mitochondria, Annu. Rev. Biochem. 76 (2007) 723–749.
[38] L. Zeng, J. Tan, W. Lu, T. Lu, Z. Hu, The potential role of small heat shock proteins in mitochondria, Cell. Signal. 25 (2013) 2312–2319.
[39] C.K. Suzuki, K. Suda, N. Wang, G. Schatz, Requirement for the yeast gene LON in intramitochondrial proteolysis and maintenance of respiration, Science 264 (1994) 891.
[40] D.A. Bota, K.J. Davies, Lon protease preferentially degrades oxidized mitochondrial aconitase by an ATP-stimulated mechanism, Nat. Cell Biol. 4 (2002) 674–680.
[41] R.T. Sauer, T.A. Baker, AAA+ proteases: ATP-fueled machines of protein destruction, Annu. Rev. Biochem. 80 (2011) 587–612.
[42] M. Koppen, T. Langer, Protein degradation within mitochondria: versatile activities of AAA proteases and other peptidases, Crit. Rev. Biochem. Mol. Biol. 42 (2007) 221–242.
[43] K. Leonhard, B. Guiard, G. Pellecchia, A. Tzagoloff, W. Neupert, T. Langer, Membrane protein degradation by AAA proteases in mitochondria: extraction of substrates from either membrane surface, Mol. Cell 5 (2000) 629–638.
[44] B. Li, Q. Hu, H. Wang, N. Man, H. Ren, L. Wen, N. Nukina, E. Fei, G. Wang, Omi/HtrA2 is a positive regulator of autophagy that facilitates the degradation of mutant proteins involved in neurodegenerative diseases, Cell Death Differ. 17 (2010) 1773–1784.
[45] L.M. Martins, I. Iaccarino, T. Tenev, S. Gschmeissner, N.F. Totty, N.R. Lemoine, J. Savopoulos, C.W. Gray, C.L. Creasy, C. Dingwall, J. Downward, The serine protease Omi/HtrA2 regulates apoptosis by binding XIAP through a reaper-like motif, J. Biol. Chem. 277 (2002) 439–444.
[46] Y. Suzuki, K. Takahashi-Niki, T. Akagi, T. Hashikawa, R. Takahashi, Mitochondrial protease Omi/HtrA2 enhances caspase activation through multiple pathways, Cell Death Differ. 11 (2004) 208–216.
[47] S. Lee, S. Augustin, T. Tatsuta, F. Gerdes, T. Langer, F.T. Tsai, Electron cryomicroscopy structure of a membrane-anchored mitochondrial AAA protease, J. Biol. Chem. 286 (2011) 4404–4411.
[48] L. Griparic, T. Kanazawa, A.M. van der Bliek, Regulation of the mitochondrial dynamin-like protein Opa1 by proteolytic cleavage, J. Cell Biol. 178 (2007) 757–764.
[49] S. Ehses, I. Raschke, G. Mancuso, A. Bernacchia, S. Geimer, D. Tondera, J.C. Martinou, B. Westermann, E.I. Rugarli, T. Langer, Regulation of OPA1 processing and mitochondrial fusion by m-AAA protease isoenzymes and OMA1, J. Cell Biol. 187 (2009) 1023–1036.
[50] B. Head, L. Griparic, M. Amiri, S. Gandre-Babbe, A.M. van der Bliek, Inducible proteolytic inactivation of OPA1 mediated by the OMA1 protease in mammalian cells, J. Cell Biol. 187 (2009) 959–966.
[51] C. Merkwirth, S. Dargazanli, T. Tatsuta, S. Geimer, B. Lower, F.T. Wunderlich, J.C. von Kleist-Retzow, A. Waisman, B. Westermann, T. Langer, Prohibitins control cell proliferation and apoptosis by regulating OPA1-dependent cristae morphogenesis in mitochondria, Genes Dev. 22 (2008) 476–488.
[52] S. Sato, A. Murata, T. Orihara, T. Shirakawa, K. Suenaga, H. Kigoshi, M. Uesugi, Marine natural product aurilide activates the OPA1-mediated apoptosis by binding to prohibitin, Chem. Biol. 18 (2011) 131–139.
[53] G. Steglich, W. Neupert, T. Langer, Prohibitins regulate membrane protein degradation by the m-AAA protease in mitochondria, Mol. Cell. Biol. 19 (1999) 3435–3442.
[54] J. Piechota, M. Kolodziejczak, I. Juszczak, W. Sakamoto, H. Janska, Identification and characterization of high molecular weight complexes formed by matrix AAA proteases and prohibitins in mitochondria of *Arabidopsis thaliana*, J. Biol. Chem. 285 (2010) 12512–12521.
[55] C.M. Haynes, D. Ron, The mitochondrial UPR—protecting organelle protein homeostasis, J. Cell Sci. 123 (2010) 3849–3855.
[56] Q. Ling, P. Jarvis, Dynamic regulation of endosymbiotic organelles by ubiquitination, Trends Cell Biol. 23 (2013) 399–408.
[57] D. Finley, Recognition and processing of ubiquitin–protein conjugates by the proteasome, Annu. Rev. Biochem. 78 (2009) 477–513.
[58] N. Nakamura, Y. Kimura, M. Tokuda, S. Honda, S. Hirose, MARCH-V is a novel mitofusin 2- and Drp1-binding protein able to change mitochondrial morphology, EMBO Rep. 7 (2006) 1019–1022.
[59] R. Yonashiro, S. Ishido, S. Kyo, T. Fukuda, E. Goto, Y. Matsuki, M. Ohmura-Hoshino, K. Sada, H. Hotta, H. Yamamura, R. Inatome, S. Yanagi, A novel mitochondrial ubiquitin ligase plays a critical role in mitochondrial dynamics, EMBO J. 25 (2006) 3618–3626.
[60] Y.Y. Park, S. Lee, M. Karbowski, A. Neutzner, R.J. Youle, H. Cho, Loss of MARCH5 mitochondrial E3 ubiquitin ligase induces cellular senescence through dynamin-related protein 1 and mitofusin 1, J. Cell Sci. 123 (2010) 619–626.
[61] Y.Y. Park, H. Cho, Mitofusin 1 is degraded at G2/M phase through ubiquitylation by MARCH5, Cell Div. 7 (2012) 25.
[62] R. Yonashiro, A. Sugiura, M. Miyachi, T. Fukuda, N. Matsushita, R. Inatome, Y. Ogata, T. Suzuki, N. Dohmae, S. Yanagi, Mitochondrial ubiquitin ligase MITOL ubiquitinates mutant SOD1 and attenuates mutant SOD1-induced reactive oxygen species generation, Mol. Biol. Cell 20 (2009) 4524–4530.
[63] R. Yonashiro, Y. Kimijima, T. Shimura, K. Kawaguchi, T. Fukuda, R. Inatome, S. Yanagi, Mitochondrial ubiquitin ligase MITOL blocks S-nitrosylated MAP1B-light chain 1-mediated mitochondrial dysfunction and neuronal cell death, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 2382–2387.
[64] S. Lokireddy, I.W. Wijesoma, S. Teng, S. Bonala, P.D. Gluckman, C. McFarlane, M. Sharma, R. Kambadur, The ubiquitin ligase Mul1 induces mitophagy in skeletal muscle in response to muscle-wasting stimuli, Cell Metab. 16 (2012) 613–624.
[65] F. Anton, G. Dittmar, T. Langer, M. Escobar-Henriques, Two deubiquitylases act on mitofusin and regulate mitochondrial fusion along independent pathways, Mol. Cell 49 (2013) 487–498.
[66] E. Braschi, R. Zunino, H.M. McBride, MAPL is a new mitochondrial SUMO E3 ligase that regulates mitochondrial fission, EMBO Rep. 10 (2009) 748–754.
[67] J. Schimmel, K.M. Larsen, I. Matic, M. van Hagen, J. Cox, M. Mann, J.S. Andersen, A.C. Vertegaal, The ubiquitin–proteasome system is a key component of the SUMO-2/3 cycle, Mol. Cell. Proteomics 7 (2008) 2107–2122.
[68] R.J. Youle, D.P. Narendra, Mechanisms of mitophagy, Nat. Rev. Mol. Cell Biol. 12 (2011) 9–14.
[69] M.M. Cohen, G.P. Leboucher, N. Livnat-Levanon, M.H. Glickman, A.M. Weissman, Ubiquitin–proteasome-dependent degradation of a mitofusin, a critical regulator of mitochondrial fusion, Mol. Biol. Cell 19 (2008) 2457–2464.
[70] G.P. Leboucher, Y.C. Tsai, M. Yang, K.C. Shaw, M. Zhou, T.D. Veenstra, M.H. Glickman, A.M. Weissman, Stress-induced phosphorylation and proteasomal degradation of mitofusin 2 facilitates mitochondrial fragmentation and apoptosis, Mol. Cell 47 (2012) 547–557.
[71] H. Wang, P. Song, L. Du, W. Tian, W. Yue, M. Liu, D. Li, B. Wang, Y. Zhu, C. Cao, J. Zhou, Q. Chen, Parkin ubiquitinates Drp1 for proteasome-dependent degradation: implication of dysregulated mitochondrial dynamics in Parkinson disease, J. Biol. Chem. 286 (2011) 11649–11658.
[72] A.K. Muller-Rischart, A. Pilsl, P. Beaudette, M. Patra, K. Hadian, M. Funke, R. Peis, A. Deinlein, C. Schweimer, P.H. Kuhn, S.F. Lichtenthaler, E. Motori, S. Hrelia, W. Wurst, D. Trumbach, T. Langer, D. Krappmann, G. Dittmar, J. Tatzelt, K.F. Winklhofer, The E3 ligase parkin maintains mitochondrial integrity by increasing linear ubiquitination of NEMO, Mol. Cell 49 (2013) 908–921.
[73] M. Esaki, T. Ogura, Cdc48p/p97-mediated regulation of mitochondrial morphology is Vms1p-independent, J. Struct. Biol. 179 (2012) 112–120.
[74] A. Tanaka, M.M. Cleland, S. Xu, D.P. Narendra, D.F. Suen, M. Karbowski, R.J. Youle, Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin, J. Cell Biol. 191 (2010) 1367–1380.
[75] S. Xu, G. Peng, Y. Wang, S. Fang, M. Karbowski, The AAA-ATPase p97 is essential for outer mitochondrial membrane protein turnover, Mol. Biol. Cell 22 (2011) 291–300.
[76] S.W. Taylor, E. Fahy, B. Zhang, G.M. Glenn, D.E. Warnock, S. Wiley, A.N. Murphy, S.P. Gaucher, R.A. Capaldi, B.W. Gibson, S.S. Ghosh, Characterization of the human heart mitochondrial proteome, Nat. Biotechnol. 21 (2003) 281–286.
[77] P. Sutovsky, T.C. McCauley, M. Sutovsky, B.N. Day, Early degradation of paternal mitochondria in domestic pig (*Sus scrofa*) is prevented by selective proteasomal inhibitors lactacystin and MG132, Biol. Reprod. 68 (2003) 1793–1800.
[78] L. Bouman, A. Schlierf, A.K. Lutz, J. Shan, A. Deinlein, J. Kast, Z. Galehdar, V. Palmisano, N. Patenge, D. Berg, T. Gasser, R. Augustin, D. Trumbach, I. Irrcher, D.S. Park, W. Wurst, M.S. Kilberg, J. Tatzelt, K.F. Winklhofer, Parkin is transcriptionally regulated by ATF4: evidence for an interconnection between mitochondrial stress and ER stress, Cell Death Differ. 18 (2011) 769–782.
[79] A. Pilsl, K.F. Winklhofer, Parkin, PINK1 and mitochondrial integrity: emerging concepts of mitochondrial dysfunction in Parkinson's disease, Acta Neuropathol. 123 (2012) 173–188.
[80] V. Calabrese, C. Mancuso, M. Calvani, E. Rizzarelli, D.A. Butterfield, A.M. Stella, Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity, Nat. Rev. Neurosci. 8 (2007) 766–775.
[81] C.M. Haynes, C.J. Fiorese, Y.F. Lin, Evaluating and responding to mitochondrial dysfunction: the mitochondrial unfolded-protein response and beyond, Trends Cell Biol. 23 (2013) 311–318.
[82] M.W. Pellegrino, A.M. Nargund, C.M. Haynes, Signaling the mitochondrial unfolded protein response, Biochim. Biophys. Acta 1833 (2013) 410–416.
[83] N. Mizushima, M. Komatsu, Autophagy: renovation of cells and tissues, Cell 147 (2011) 728–741.
[84] I. Tanida, Autophagy basics, Microbiol. Immunol. 55 (2011) 1–11.
[85] T. Kanki, D.J. Klionsky, K. Okamoto, Mitochondria autophagy in yeast, Antioxid. Redox Signal. 14 (2011) 1989–2001.
[86] D.J. Klionsky, J.M. Cregg, W.A. Dunn Jr., S.D. Emr, Y. Sakai, I.V. Sandoval, A. Sibirny, S. Subramani, M. Thumm, M. Veenhuis, Y. Ohsumi, A unified nomenclature for yeast autophagy-related genes, Dev. Cell 5 (2003) 539–545.
[87] T. Kanki, K. Wang, D.J. Klionsky, A genomic screen for yeast mutants defective in mitophagy, Autophagy 6 (2010) 278–280.
[88] K. Wang, D.J. Klionsky, Mitochondria removal by autophagy, Autophagy 7 (2011) 297–300.
[89] D. Arnoult, N. Rismanchi, A. Grodet, R.G. Roberts, D.P. Seeburg, J. Estaquier, M. Sheng, C. Blackstone, Bax/Bak-dependent release of DDP/TIMM8a promotes Drp1-mediated mitochondrial fission and mitoptosis during programmed cell death, Curr. Biol. 15 (2005) 2112–2118.
[90] L.C. Gomes, L. Scorrano, High levels of Fis1, a pro-fission mitochondrial protein, trigger autophagy, Biochim. Biophys. Acta 1777 (2008) 860–866.

[91] K. Nowikovsky, S. Reipert, R.J. Devenish, R.J. Schweyen, Mdm38 protein depletion causes loss of mitochondrial K+/H+ exchange activity, osmotic swelling and mitophagy, Cell Death Differ. 14 (2007) 1647–1656.
[92] N. Mendl, A. Occhipinti, M. Muller, P. Wild, I. Dikic, A.S. Reichert, Mitophagy in yeast is independent of mitochondrial fission and requires the stress response gene WHI2, J. Cell Sci. 124 (2011) 1339–1350.
[93] P.A. Ney, Normal and disordered reticulocyte maturation, Curr. Opin. Hematol. 18 (2011) 152–157.
[94] R. Dumollard, M. Duchen, J. Carroll, The role of mitochondrial function in the oocyte and embryo, Curr. Top. Dev. Biol. 77 (2007) 21–49.
[95] P. Sutovsky, R.D. Moreno, J. Ramalho-Santos, T. Dominko, C. Simerly, G. Schatten, Ubiquitin tag for sperm mitochondria, Nature 402 (1999) 371–372.
[96] W.X. Ding, H.M. Ni, M. Li, Y. Liao, X. Chen, D.B. Stolz, G.W. Dorn II, X.M. Yin, Nix is critical to two distinct phases of mitophagy, reactive oxygen species-mediated autophagy induction and Parkin-ubiquitin-p62-mediated mitochondrial priming, J. Biol. Chem. 285 (2010) 27879–27890.
[97] I. Novak, V. Kirkin, D.G. McEwan, J. Zhang, P. Wild, A. Rozenknop, V. Rogov, F. Lohr, D. Popovic, A. Occhipinti, A.S. Reichert, J. Terzic, V. Dotsch, P.A. Ney, I. Dikic, Nix is a selective autophagy receptor for mitochondrial clearance, EMBO Rep. 11 (2010) 45–51.
[98] J. Zhang, M.S. Randall, M.R. Loyd, F.C. Dorsey, M. Kundu, J.L. Cleveland, P.A. Ney, Mitochondrial clearance is regulated by Atg7-dependent and -independent mechanisms during reticulocyte maturation, Blood 114 (2009) 157–164.
[99] E.M. Valente, P.M. Abou-Sleiman, V. Caputo, M.M. Muqit, K. Harvey, S. Gispert, Z. Ali, D. Del Turco, A.R. Bentivoglio, D.G. Healy, A. Albanese, R. Nussbaum, R. Gonzalez-Maldonado, T. Deller, S. Salvi, P. Cortelli, W.P. Gilks, D.S. Latchman, R.J. Harvey, B. Dallapiccola, G. Auburger, N.W. Wood, Hereditary early-onset Parkinson's disease caused by mutations in PINK1, Science 304 (2004) 1158–1160.
[100] T. Kitada, S. Asakawa, N. Hattori, H. Matsumine, Y. Yamamura, S. Minoshima, M. Yokochi, Y. Mizuno, N. Shimizu, Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism, Nature 392 (1998) 605–608.
[101] I. Novak, I. Dikic, Autophagy receptors in developmental clearance of mitochondria, Autophagy 7 (2011) 301–303.
[102] S. Al Rawi, S. Louvet-Vallee, A. Djeddi, M. Sachse, E. Culetto, C. Hajjar, L. Boyd, R. Legouis, V. Galy, Postfertilization autophagy of sperm organelles prevents paternal mitochondrial DNA transmission, Science 334 (2011) 1144–1147.
[103] J.M. Cummins, Fertilization and elimination of the paternal mitochondrial genome, Hum. Reprod. 15 (Suppl. 2) (2000) 92–101.
[104] M. Sato, K. Sato, Degradation of paternal mitochondria by fertilization-triggered autophagy in *C. elegans* embryos, Science 334 (2011) 1141–1144.
[105] P. Sutovsky, R.D. Moreno, J. Ramalho-Santos, T. Dominko, C. Simerly, G. Schatten, Ubiquitinated sperm mitochondria, selective proteolysis, and the regulation of mitochondrial inheritance in mammalian embryos, Biol. Reprod. 63 (2000) 582–590.
[106] A.W. Greene, K. Grenier, M.A. Aguileta, S. Muise, R. Farazifard, M.E. Haque, H.M. McBride, D.S. Park, E.A. Fon, Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment, EMBO Rep. 13 (2012) 378–385.
[107] S.M. Jin, M. Lazarou, C. Wang, L.A. Kane, D.P. Narendra, R.J. Youle, Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL, J. Cell Biol. 191 (2010) 933–942.
[108] M. Lazarou, S.M. Jin, L.A. Kane, R.J. Youle, Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase Parkin, Dev. Cell 22 (2012) 320–333.
[109] D.P. Narendra, S.M. Jin, A. Tanaka, D.F. Suen, C.A. Gautier, J. Shen, M.R. Cookson, R.J. Youle, PINK1 is selectively stabilized on impaired mitochondria to activate Parkin, PLoS Biol. 8 (2010) e1000298.
[110] S. Geisler, K.M. Holmstrom, D. Skujat, F.C. Fiesel, O.C. Rothfuss, P.J. Kahle, W. Springer, PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1, Nat. Cell Biol. 12 (2010) 119–131.
[111] M. Lazarou, D.P. Narendra, S.M. Jin, E. Tekle, S. Banerjee, R.J. Youle, PINK1 drives Parkin self-association and HECT-like E3 activity upstream of mitochondrial binding, J. Cell Biol. 200 (2013) 163–172.
[112] N. Matsuda, S. Sato, K. Shiba, K. Okatsu, K. Saisho, C.A. Gautier, Y.S. Sou, S. Saiki, S. Kawajiri, F. Sato, M. Kimura, M. Komatsu, N. Hattori, K. Tanaka, PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy, J. Cell Biol. 189 (2010) 211–221.
[113] K. Shiba-Fukushima, Y. Imai, S. Yoshida, Y. Ishihama, T. Kanao, S. Sato, N. Hattori, PINK1-mediated phosphorylation of the Parkin ubiquitin-like domain primes mitochondrial translocation of Parkin and regulates mitophagy, Sci. Rep. 2 (2012) 1002.
[114] C. Vives-Bauza, C. Zhou, Y. Huang, M. Cui, R.L. de Vries, J. Kim, J. May, M.A. Tocilescu, W. Liu, H.S. Ko, J. Magrane, D.J. Moore, V.L. Dawson, R. Grailhe, T.M. Dawson, C. Li, K. Tieu, S. Przedborski, PINK1-dependent recruitment of Parkin to mitochondria in mitophagy, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 378–383.
[115] D. Narendra, L.A. Kane, D.N. Hauser, I.M. Fearnley, R.J. Youle, p62/SQSTM1 is required for Parkin-induced mitochondrial clustering but not mitophagy; VDAC1 is dispensable for both, Autophagy 6 (2010) 1090–1106.
[116] K. Okatsu, K. Saisho, M. Shimanuki, K. Nakada, H. Shitara, Y.S. Sou, M. Kimura, S. Sato, N. Hattori, M. Komatsu, K. Tanaka, N. Matsuda, p62/SQSTM1 cooperates with Parkin for perinuclear clustering of depolarized mitochondria, Genes Cells 15 (2010) 887–900.
[117] C. Van Humbeeck, T. Cornelissen, H. Hofkens, W. Mandemakers, K. Gevaert, B. De Strooper, W. Vandenberghe, Parkin interacts with Ambra1 to induce mitophagy, J. Neurosci. 31 (2011) 10249–10261.
[118] S. Michiorri, V. Gelmetti, E. Giarda, F. Lombardi, F. Romano, R. Marongiu, S. Nerini-Molteni, P. Sale, R. Vago, G. Arena, L. Torosantucci, L. Cassina, M.A. Russo, B. Dallapiccola, E.M. Valente, G. Casari, The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy, Cell Death Differ. 17 (2010) 962–974.
[119] J.C. Greene, A.J. Whitworth, I. Kuo, L.A. Andrews, M.B. Feany, L.J. Pallanck, Mitochondrial pathology and apoptotic muscle degeneration in *Drosophila* parkin mutants, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 4078–4083.
[120] H.L. Melrose, S.J. Lincoln, G.M. Tyndall, M.J. Farrer, Parkinson's disease: a rethink of rodent models, Exp. Brain Res. 173 (2006) 196–204.
[121] M. Schwarten, J. Mohrluder, P. Ma, M. Stoldt, Y. Thielmann, T. Stangler, N. Hersch, B. Hoffmann, R. Merkel, D. Willbold, Nix directly binds to GABARAP: a possible crosstalk between apoptosis and autophagy, Autophagy 5 (2009) 690–698.
[122] H. Zhang, M. Bosch-Marce, L.A. Shimoda, Y.S. Tan, J.H. Baek, J.B. Wesley, F.J. Gonzalez, G.L. Semenza, Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia, J. Biol. Chem. 283 (2008) 10892–10903.
[123] L. Liu, D. Feng, G. Chen, M. Chen, Q. Zheng, P. Song, Q. Ma, C. Zhu, R. Wang, W. Qi, L. Huang, P. Xue, B. Li, X. Wang, H. Jin, J. Wang, F. Yang, P. Liu, Y. Zhu, S. Sui, Q. Chen, Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells, Nat. Cell Biol. 14 (2012) 177–185.
[124] V.S. Van Laar, B. Arnold, S.J. Cassady, C.T. Chu, E.A. Burton, S.B. Berman, Bioenergetics of neurons inhibit the translocation response of Parkin following rapid mitochondrial depolarization, Hum. Mol. Genet. 20 (2011) 927–940.
[125] X. Wang, D. Winter, G. Ashrafi, J. Schlehe, Y.L. Wong, D. Selkoe, S. Rice, J. Steen, M.J. LaVoie, T.L. Schwarz, PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility, Cell 147 (2011) 893–906.
[126] Q. Cai, H.M. Zakaria, A. Simone, Z.H. Sheng, Spatial parkin translocation and degradation of damaged mitochondria via mitophagy in live cortical neurons, Curr. Biol. 22 (2012) 545–552.
[127] Y. Ichimura, T. Kumanomidou, Y.S. Sou, T. Mizushima, J. Ezaki, T. Ueno, E. Kominami, T. Yamane, K. Tanaka, M. Komatsu, Structural basis for sorting mechanism of p62 in selective autophagy, J. Biol. Chem. 283 (2008) 22847–22857.
[128] S. Pankiv, T.H. Clausen, T. Lamark, A. Brech, J.A. Bruun, H. Outzen, A. Overvatn, G. Bjorkoy, T. Johansen, p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy, J. Biol. Chem. 282 (2007) 24131–24145.
[129] N.N. Noda, Y. Ohsumi, F. Inagaki, Atg8-family interacting motif crucial for selective autophagy, FEBS Lett. 584 (2010) 1379–1385.
[130] F. Strappazzon, M. Vietri-Rudan, S. Campello, F. Nazio, F. Florenzano, G.M. Fimia, M. Piacentini, B. Levine, F. Cecconi, Mitochondrial BCL-2 inhibits AMBRA1-induced autophagy, EMBO J. 30 (2011) 1195–1208.
[131] C. Behrends, M.E. Sowa, S.P. Gygi, J.W. Harper, Network organization of the human autophagy system, Nature 466 (2010) 68–76.
[132] F. Nazio, F. Strappazzon, M. Antonioli, P. Bielli, V. Cianfanelli, M. Bordi, C. Gretzmeier, J. Dengjel, M. Piacentini, G.M. Fimia, F. Cecconi, mTOR inhibits autophagy by controlling ULK1 ubiquitylation, self-association and function through AMBRA1 and TRAF6, Nat. Cell Biol. 15 (2013) 406–416.
[133] J. Jin, E.E. Arias, J. Chen, J.W. Harper, J.C. Walter, A family of diverse Cul4-Ddb1-interacting proteins includes Cdt2, which is required for S phase destruction of the replication factor Cdt1, Mol. Cell 23 (2006) 709–721.
[134] A.B. Birgisdottir, T. Lamark, T. Johansen, The LIR motif—crucial for selective autophagy, J. Cell Sci. 126 (2013) 3237–3247.
[135] R. Kayed, E. Head, J.L. Thompson, T.M. McIntire, S.C. Milton, C.W. Cotman, C.G. Glabe, Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis, Science 300 (2003) 486–489.
[136] R.E. Tanzi, L. Bertram, Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective, Cell 120 (2005) 545–555.
[137] M.G. Spillantini, M.L. Schmidt, V.M. Lee, J.Q. Trojanowski, R. Jakes, M. Goedert, Alpha-synuclein in Lewy bodies, Nature 388 (1997) 839–840.
[138] M. DiFiglia, E. Sapp, K.O. Chase, S.W. Davies, G.P. Bates, J.P. Vonsattel, N. Aronin, Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain, Science 277 (1997) 1990–1993.
[139] C. Rodolfo, F. Ciccosanti, G.D. Giacomo, M. Piacentini, G.M. Fimia, Proteomic analysis of mitochondrial dysfunction in neurodegenerative diseases, Expert Rev. Proteomics 7 (2010) 519–542.
[140] P. Martinelli, E.I. Rugarli, Emerging roles of mitochondrial proteases in neurodegeneration, Biochim. Biophys. Acta 1797 (2010) 1–10.
[141] D. Di Bella, F. Lazzaro, A. Brusco, M. Plumari, G. Battaglia, A. Pastore, A. Finardi, C. Cagnoli, F. Tempia, M. Frontali, L. Veneziano, T. Sacco, E. Boda, A. Brussino, F. Bonn, B. Castellotti, S. Baratta, C. Mariotti, C. Gellera, V. Fracasso, S. Magri, T. Langer, P. Plevani, S. Di Donato, M. Muzi-Falconi, F. Taroni, Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28, Nat. Genet. 42 (2010) 313–321.
[142] C. Merkwirth, P. Martinelli, A. Korwitz, M. Morbin, H.S. Bronneke, S.D. Jordan, E.I. Rugarli, T. Langer, Loss of prohibitin membrane scaffolds impairs mitochondrial architecture and leads to tau hyperphosphorylation and neurodegeneration, PLoS Genet. 8 (2012) e1003021.
[143] W. Le, S.H. Appel, Mutant genes responsible for Parkinson's disease, Curr. Opin. Pharmacol. 4 (2004) 79–84.
[144] C. Liu, S. Chen, F. Kamme, B.R. Hu, Ischemic preconditioning prevents protein aggregation after transient cerebral ischemia, Neuroscience 134 (2005) 69–80.
[145] B.M. Riederer, G. Leuba, Z. Elhajj, Oxidation and ubiquitination in neurodegeneration, Exp. Biol. Med. (Maywood) 238 (2013) 519–524.
[146] V.S. Van Laar, S.B. Berman, The interplay of neuronal mitochondrial dynamics and bioenergetics: implications for Parkinson's disease, Neurobiol. Dis. 51 (2013) 43–55.
[147] P.J. Khandelwal, A.M. Herman, H.S. Hoe, G.W. Rebeck, C.E. Moussa, Parkin mediates beclin-dependent autophagic clearance of defective mitochondria and ubiquitinated Abeta in AD models, Hum. Mol. Genet. 20 (2011) 2091–2102.
[148] L. Cui, H. Jeong, F. Borovecki, C.N. Parkhurst, N. Tanese, D. Krainc, Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration, Cell 127 (2006) 59–69.

[149] G.B. Stokin, C. Lillo, T.L. Falzone, R.G. Brusch, E. Rockenstein, S.L. Mount, R. Raman, P. Davies, E. Masliah, D.S. Williams, L.S. Goldstein, Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease, Science 307 (2005) 1282–1288.
[150] D.T. Chang, G.L. Rintoul, S. Pandipati, I.J. Reynolds, Mutant huntingtin aggregates impair mitochondrial movement and trafficking in cortical neurons, Neurobiol. Dis. 22 (2006) 388–400.
[151] E. Trushina, R.B. Dyer, J.D. Badger II, D. Ure, L. Eide, D.D. Tran, B.T. Vrieze, V. Legendre-Guillemin, P.S. McPherson, B.S. Mandavilli, B. Van Houten, S. Zeitlin, M. McNiven, R. Aebersold, M. Hayden, J.E. Parisi, E. Seeberg, I. Dragatsis, K. Doyle, A. Bender, C. Chacko, C.T. McMurray, Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro, Mol. Cell. Biol. 24 (2004) 8195–8209.
[152] C. Alexander, M. Votruba, U.E. Pesch, D.L. Thiselton, S. Mayer, A. Moore, M. Rodriguez, U. Kellner, B. Leo-Kottler, G. Auburger, S.S. Bhattacharya, B. Wissinger, OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28, Nat. Genet. 26 (2000) 211–215.
[153] C. Delettre, G. Lenaers, J.M. Griffoin, N. Gigarel, C. Lorenzo, P. Belenguer, L. Pelloquin, J. Grosgeorge, C. Turc-Carel, E. Perret, C. Astarie-Dequeker, L. Lasquellec, B. Arnaud, B. Ducommun, J. Kaplan, C.P. Hamel, Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy, Nat. Genet. 26 (2000) 207–210.
[154] S. Zuchner, I.V. Mersiyanova, M. Muglia, N. Bissar-Tadmouri, J. Rochelle, E.L. Dadali, M. Zappia, E. Nelis, A. Patitucci, J. Senderek, Y. Parman, O. Evgrafov, P.D. Jonghe, Y. Takahashi, S. Tsuji, M.A. Pericak-Vance, A. Quattrone, E. Battaloglu, A.V. Polyakov, V. Timmerman, J.M. Schroder, J.M. Vance, Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot–Marie–Tooth neuropathy type 2A, Nat. Genet. 36 (2004) 449–451.
[155] G. Szabadkai, A.M. Simoni, M. Chami, M.R. Wieckowski, R.J. Youle, R. Rizzuto, Drp-1-dependent division of the mitochondrial network blocks intraorganellar Ca^{2+} waves and protects against Ca^{2+}-mediated apoptosis, Mol. Cell 16 (2004) 59–68.
[156] T. Yu, J.L. Robotham, Y. Yoon, Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 2653–2658.
[157] Z. Li, K. Okamoto, Y. Hayashi, M. Sheng, The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses, Cell 119 (2004) 873–887.
[158] S. Campello, R.A. Lacalle, M. Bettella, S. Manes, L. Scorrano, A. Viola, Orchestration of lymphocyte chemotaxis by mitochondrial dynamics, J. Exp. Med. 203 (2006) 2879–2886.
[159] J. Zhao, J. Zhang, M. Yu, Y. Xie, Y. Huang, D.W. Wolff, P.W. Abel, Y. Tu, Mitochondrial dynamics regulates migration and invasion of breast cancer cells, Oncogene 32 (2013) 4814–4824.
[160] V. Romanello, E. Guadagnin, L. Gomes, I. Roder, C. Sandri, Y. Petersen, G. Milan, E. Masiero, P. Del Piccolo, M. Foretz, L. Scorrano, R. Rudolf, M. Sandri, Mitochondrial fission and remodelling contributes to muscle atrophy, EMBO J. 29 (2010) 1774–1785.
[161] C.Q. Scheckhuber, N. Erjavec, A. Tinazli, A. Hamann, T. Nystrom, H.D. Osiewacz, Reducing mitochondrial fission results in increased life span and fitness of two fungal ageing models, Nat. Cell Biol. 9 (2007) 99–105.
[162] L. Scorrano, Opening the doors to cytochrome c: changes in mitochondrial shape and apoptosis, Int. J. Biochem. Cell Biol. 41 (2009) 1875–1883.
[163] S. Grandemange, S. Herzig, J.C. Martinou, Mitochondrial dynamics and cancer, Semin. Cancer Biol. 19 (2009) 50–56.
[164] W. Qian, J. Wang, B. Van Houten, The role of dynamin-related protein 1 in cancer growth: a promising therapeutic target? Expert Opin. Ther. Targets 17 (2013) 997–1001.
[165] S.B. Ong, A.R. Hall, D.J. Hausenloy, Mitochondrial dynamics in cardiovascular health and disease, Antioxid. Redox Signal. 19 (2013) 400–414.
[166] J. Piquereau, F. Caffin, M. Novotova, C. Lemaire, V. Veksler, A. Garnier, R. Ventura-Clapier, F. Joubert, Mitochondrial dynamics in the adult cardiomyocytes: which roles for a highly specialized cell? Front. Physiol. 4 (2013) 102.