Cell Death &
Differentiation

REVIEW ARTICLE

Functions of outer mitochondrial membrane proteins: mediating the crosstalk between mitochondrial dynamics and mitophagy

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Abstract

Most cellular stress responses converge on the mitochondria. Consequently, the mitochondria must rapidly respond to maintain cellular homeostasis and physiological demands by fine-tuning a plethora of mitochondria-associated processes. The outer mitochondrial membrane (OMM) proteins are central to mediating mitochondrial dynamics, coupled with continuous fission and fusion. These OMM proteins also have vital roles in controlling mitochondrial quality and serving as mitophagic receptors for autophagosome enclosure during mitophagy. Mitochondrial fission segregates impaired mitochondria in smaller sizes from the mother mitochondria and may favor mitophagy for eliminating damaged mitochondria. Conversely, mitochondrial fusion mixes dysfunctional mitochondria with healthy ones to repair the damage by diluting the impaired components and consequently prevents mitochondrial clearance via mitophagy. Despite extensive research efforts into deciphering the interplay between fission–fusion and mitophagy, it is still not clear whether mitochondrial fission essentially precedes mitophagy. In this review, we summarize recent breakthroughs concerning OMM research, and dissect the functions of these proteins in mitophagy from their traditional roles in fission–fusion dynamics, in response to distinct context, at the intersection of the OMM platform. These insights into the OMM proteins in mechanistic researches would lead to new aspects of mitochondrial quality control and better understanding of mitochondrial homeostasis intimately tied to pathological impacts.

Facts

- Mitochondria undergo continuous fission and fusion events, referred as mitochondrial dynamics.
- Mitochondrial quality control is precisely governed by autophagic degradation, termed as "mitophagy".

- Whether the interplay of mitochondrial dynamics and mitochondrial quality control simply bases on mitochondrial morphology or size remains to be answered.
- Fused mitochondria might be permissible to mitochondrial elimination, mostly relying on the orchestration of OMM proteins.
- The crosstalk between mitochondrial dynamics and mitophagy should be an emerging area to be addressed.

Open questions

- How does specific OMM proteins engage in regulating mitochondrial homeostasis by coordinating mitochondrial dynamics and mitochondrial quality control?
- How are tubular mitochondria segregated and directly pinched off to be engulfed by the autophagy isolation membrane?
- Given the interplay of distinct molecular pathways of mitophagy, what signal in physiological contexts would stimulate specific route of mitochondrial elimination?

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- Is mitochondrial fission a prerequisite for mitochondrial clearance?
- In tight coordination with damaged mitochondrial degradation, how would mitochondrial biogenesis be involved to maintain proper organelle homeostasis, coupled with mitochondrial dynamics?
- In light of the actions of mitophagic modulators, what therapeutic strategy would be administrated to target mitochondria-related diseases?

Introduction

Mitochondria are double-membrane-bound subcellular organelles found within the cells of all multicellular eukaryotes. This organelle is considered a "powerhouse" at the heart of cell metabolism, catalyzing the production of adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS) [1, 2]. The outer and inner membranes of the mitochondria are composed of a mosaic of proteins and phospholipids, with a distinct intermembrane space between them. The inner membrane invaginates and curves inward into the mitochondrial matrix to form the cristae [3, 4]. A number of assembled complexes involved in OXPHOS and ATP synthesis are located on the cristae [5, 6].

Mitochondria undergo continuous cycles of fusion, during which segregated mitochondria join; and fission, during which the mitochondria divide. Collectively, this process is referred to as "mitochondrial dynamics" [7–13]. The mitochondrial fission and fusion adapt well to maintain the mitochondrial size, morphology, and position [14, 15]. Adapting to distal metabolic demand, mitochondrial fission facilitates mitochondrial traffic and is crucial to maintain organelle distribution [16, 17]. In contrast, mitochondrial fusion serves in the communication of mitochondrial content, including mitochondrial DNA (mtDNA) and mitochondrial proteins involved in OXPHOS [18, 19], as well as buffering acute damages within mitochondria [20, 21]. Unrestricted fission in response to cellular stress leads to small and fragmented mitochondria, during which calcium signaling and cell death pathways are activated [22]. Conversely, excessive fusion not only leads to a hyper-fused mitochondrial network, that is proposed to counteract environmental insults and maintain cellular integrity, but also confers an abnormal copy number of mtDNA [18, 21].

The mitochondrion has acquired a myriad of functions over its evolution, such as regulating calcium homeostasis, redox signaling, and heme synthesis [23–25]. In addition, mitochondria are essential hubs for several inflammatory processes, including NLRP3 inflammasome activation [26–28] and cGAS-STING pathways [29]. Moreover, increasing evidence supports that mitochondria can sense cellular stress challenges and collaborate with various cellular processes, including apoptosis, autophagy and mitophagy, to maintain cellular homeostasis [1, 30–34]. Notably, mitochondrial turnover, achieved by selective autophagy (mitophagy), is one such terminal response to extreme stress. Mitophagy is a highly hierarchical process that is composed of isolation membrane enclosure of mitochondria, formation of mitophagosome and digestion of mitochondria within lysosome [35–39].

Up till now, most studies have considered mitophagy to go in-hand with mitochondrial dynamics: short mitochondria generated by mitochondrial fragmentation are easily targeted by mitophagy, as these small and isolated mitochondria are readily engulfed by the autophagy machinery and permissible for elimination [40–43]. Yet, our understanding on their interplay remains limited. Of note, many proteins accounting for mitochondrial dynamics are also involved in mitophagic progression [42, 44, 45]. Specifically, the outer mitochondrial membrane (OMM) proteins have been intensively studied for their roles in mitochondrial morphology and mitochondrial elimination [42, 43, 46]. However, whether OMM proteins mediate mitochondrial division, while simultaneously coordinating mitophagy as a coherent mechanism remains unclear. In this review, we aim to summarize the recent breakthroughs on the functions of OMM proteins in mediating the crosstalk of mitochondrial dynamics and mitochondrial quality control. We then convey our insights into how mitochondrial dynamics and mitophagy are coordinated and provide our perspectives on the future research to advance this field.

Mitochondrial dynamics

Mitochondria are dynamic and mobile organelles [22], which are transported by various motor proteins along the cytoskeleton [47]. Fundamentally, the process of mitochondrial fusion allows for the mixing of numerous mitochondrial contents between neighboring mitochondria. The complementation process of fusion between damaged mitochondrion and healthy mitochondrion helps buffer transient stresses or defects within a mitochondrion by diluting toxins [18, 48, 49]. Moreover, any imbalance to fission or fusion during cell division can impair mtDNA segregation. Consequently, the dysregulation of the mitochondrial fission–fusion leads to defects in a recalibration of cellular responses and transmission of diffusible signals within mitochondria, which subsequently cause mitochondria-associated diseases at the organismal level [50–54].

Mitochondrial fission machinery

Mitochondrial division is primarily mediated by dynamin-related guanosine triphosphatases (GTPase) protein,

dynamin 1 (Dnm1) in yeast [15] and dynamin-related protein 1 (Drp1) in mammals [55]. Drp1 predominantly localizes to the cytoplasm and is recruited onto the OMM by accessory receptors [51, 56]. This oligomeric ring-like Drp1 structure forces the OMM to furrow; as a result, its GTPase activity at the scission sites causes the mitochondria to divide [57]. Despite the importance of Drp1 for the OMM constriction, Drp1 lacks a transmembrane domain to target the OMM directly. Several other OMM proteins must help recruit Dnm1/Drp1: in yeast, the mitochondrial outer membrane-anchored mitochondrial fission 1 protein (Fis1) [7], mitochondrial division protein 1 (Mdv1) [58] and CCR4-associated factor 4 (Caf4) [59] are responsible for Dnm1 accumulation on the mitochondria. However, to date, no Mdv1 and Caf4 orthologs have been identified in mammals. Rather, it seems that mammals employ different OMM proteins to achieve Drp1-mediated fission (Fig. 1A), including the mitochondrial fission factor (Mff) [10, 60], mitochondrial dynamics proteins 49 and 51 (MiD49 and MiD51) [11, 12, 61]. Although these proteins are all crucial for mitochondrial fission, they differentially modulate the activity of Drp1.

For example, overexpression of high Mff levels leads to mitochondrial fragmentation, whereas cells depleted of Mff by siRNA or Mff-null cells, have highly-fused mitochondria and dysregulated Drp1 assembly [10, 11]. While Mff exists in all metazoans, MiD49 and MiD51 are chordate-specific to orchestrate mitochondrial dynamics [12]. Cellular overexpression of MiD49 or MiD51 causes excessive inactive Drp1 by inhibiting its GTPase activity, causing them to be sequestered from the OMM [11, 12, 61, 62]. Conversely, cells loosing MiD49 or MiD51, or MiDs-depleted cells show abolished oligomerization of Drp1 on the OMM, resulting in mitochondrial elongation or collapse [11].

The nucleotidyl transferase domain of MiD51 has a high affinity for adenosine diphosphate (ADP): in the presence of ADP as an MiD51 cofactor, Drp1 assembles to form spirals with a high GTPase activity that warps around the mitochondrial tubules to sever the OMM [63, 64]. Thus, ADP binding is structurally indispensable for Drp1-mediated mitochondrial fission. However, MiD49 shows only partial conservation as with the MiD51 ADP-binding sequence and ADP is not considered as a MiD49 cofactor for stimulating mitochondrial fission [64]. In addition to the distinct structures of MiD49 and MiD51, little is known about whether MiD49 and MiD51 differentially regulate mitochondrial homeostasis. Until very recently, we revealed that MiD51, but not MiD49, possesses a specific regulation on cell death and mitophagy, independent of its fission–fusion function [65].

In another mitochondrial fission regulatory protein, the functions of the 16-kDa OMM protein Fis1 on mitochondria dynamics has been of great interest. Fis1 contains a single
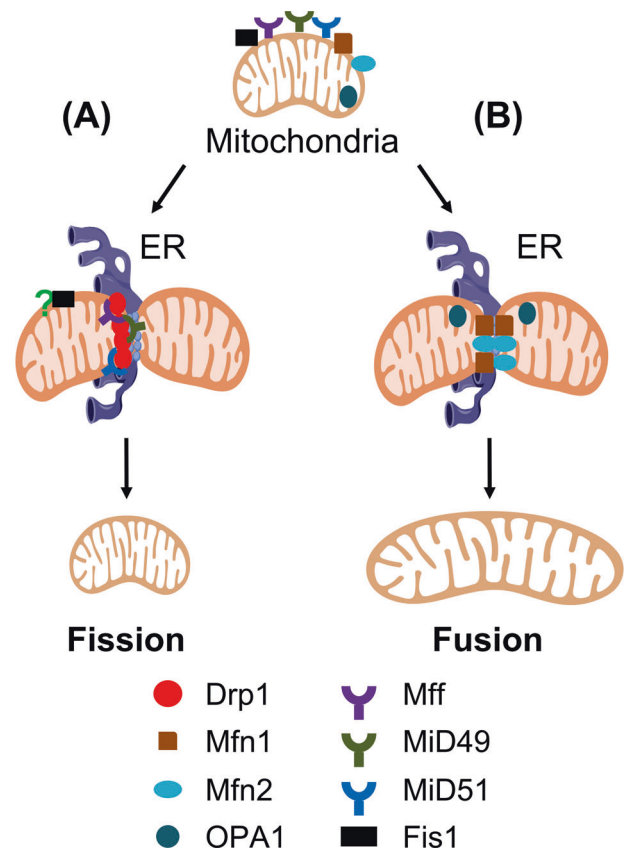

Fig. 1 Molecular mechanisms of mammalian mitochondrial dynamics. A During mitochondrial division, the endoplasmic reticulum (ER) converges with mitochondria. At the constriction sites spatially marked by mitochondria-associated membranes (MAM), Drp1 is recruited by Mff, MiD49 or MiD51 onto the cytosolic surface of mitochondria and acts as a GTPase to complete the scission of outer mitochondrial membrane (OMM). Although Fis1 was originally identified as an essential Drp1 adapter for fission in yeast, it is dispensable for mitochondrial dynamics in mammals. **B** In contrast to fission, OMM proteins Mfn1 and Mfn2 form mitofusin complexes by homo-dimerization or hetero-dimerization to tether the adjacent outer membranes. Driven by mitofusin proteins GTPase activity, OMM first fuses, followed by the subsequent inner mitochondrial membrane (IMM) fusion, due to the GTPase activity of OPA1.

transmembrane domain that integrates with the OMM [8] and was originally identified in budding yeast *Saccharomyces cerevisiae*. Fis1 physically interacts with Dnm1 and mediates Dnm1 assembly on the OMM [7]. Although the loss of Fis1 in yeast induces defects in mitochondrial Dnm1 recruitment and contributes to failed fission [66], its role in mammalian cells is debated in recent years [10, 60, 67]. For example, while high levels of Fis1 in HeLa and COS7 cells induce fission [67], conditional knockout of Fis1 in colon carcinoma cells causes Drp1 assembly and mitochondrial fragmentation [10]. Overall, it seems that Mff, MiD49, and MiD51 have a more predominant role than Fis1 in regulating Drp1 recruitment onto mitochondria-associated membranes (MAM) in mammals [10–12, 68].

Mitochondrial fusion machinery

OMM fusion is mediated by the GTPase proteins mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) (Fzo1 in yeast) [69]. Subsequent fusion of the inner membrane is achieved by OPA1 (Mgm1 in yeast) [70] (Fig. 1B). Prior to fusion, Mfn1 and Mfn2 assemble as homotypic and heterotypic dimers to tether to the adjacent OMM. They then undergo a conformational change driven by the GTP hydrolysis that facilitates the fusion process [71]. Interestingly, loss of Mfn1 alone displays short mitochondrial tubules or spheres in uniform sizes; whereas, Mfn2-depleted cells exhibit mitochondrial spheres of widely varying sizes [50]. However, depletion of both Mfn1 and Mfn2 together induces a greater impact of mitochondrial fragmentation with almost uniformed characteristic mitochondrial fragmentation, either with very short mitochondrial tubules or very small spheres. Pathologically, missense mutations of Mfn2 in human can lead to Charcot–Marie–Tooth neuropathy type 2A (CMT2A), an axonal peripheral sensorimotor neuropathy, and autosomal dominant peripheral neuropathy [72]. Additionally, mice lacking mitofusin proteins die during mid-gestation [50], implying that mitochondrial fusion is critical to embryonic development.

OPA1 is the best-studied inner mitochondrial membrane (IMM) fusion protein: it localizes to the inner membrane, where it binds negative charged phospholipids and controls cristae structure [51]. Although intrinsic OPA1 GTPase activity is low, self-oligomerization induced by association with phospholipids, such as cardiolipin, promotes GTP hydrolysis and results in deformation and tubulation of the inner membrane [52]. There are eight OPA1 isoforms that are produced by RNA splicing. These isoforms include the inner membrane-anchored long isoform L-OPA1 and the intermembrane space-localized short isoform S-OPA1 [73]. The IMM peptidase OMA1 mediates OPA1 cleavage, responding to mitochondrial membrane potential dissipation, as a balance between L-OPA1 and S-OPA1 is essential in maintaining mitochondrial morphology [73, 74].

Mitochondrial fusion is presumably to compensate defects by diluting stress inside of mitochondria. However, when the damage reaches to a certain threshold that fusion is uncapable to fix, a terminal response as destined mitochondrial removal may serve to maintain cellular homeostasis. Clearly, how interconnected mitochondria undergo clearance would usher more in-depth understanding of crosstalk among mitochondrial dynamics.

Mitochondria-associated diseases linked to mitochondrial dynamics

Inherited defects in genes serving for the machinery of mitochondrial dynamics contribute to mitochondrial disorders. Charcot–Marie–Tooth neuropathy type 2A (CMT2A) is a well-known genetically inherited neuronal disease, implicated in peripheral nervous system, caused by Mfn2 gene mutations [75–77]. Most of these mutations locate within or close to its GTPase domain and mitochondrial targeting region, which are responsible for mitochondrial fusion competency [76, 78]. OPA1 dysregulation confers susceptibility to dominant optic atrophy, a hereditary optic neuropathy, coupled with unopposed fragmented mitochondria [79, 80]. Imbalance of mitochondrial fission–fusion also causes neurodegenerative diseases. In the case of Parkinsonism, caused by autosomal recessive mutations of PINK1 or Parkin gene, possesses small mitochondria and abnormal accumulation of Drp1 [21, 81, 82]. In fibroblasts derived from patients with Huntington's disease, dysfunctional huntingtin interacts with Drp1 and facilitates its GTPase activity, resulting in unrestricted mitochondrial division [83]. In addition to cardiomyopathies arising from hyper-fission, the skeletal muscle from obese and type 2 diabetic patients displays small and rounded mitochondria [78, 84–86]. Although significant progresses have been achieved, readout of fission–fusion dysregulation may not be sufficiently precise to understand a variety of pathologic symptoms in mitochondria-associated diseases. Clearly, continued efforts to understand mitochondrial behaviors, linking mitochondrial dynamics together with other actions, such as its quality control pathway, are required. This would essentially contribute to a more comprehensive perspective in therapeutic interventions about mitochondrial diseases.

Mitochondrial quality control

Mitochondrial unfolded protein response

Mitochondria employ different signaling pathways to maintain organelle quality in response to cellular stress. One such pathway is the mitochondrial unfolded protein response (UPR^{mt}), which ensures mitochondrial proteostasis. This response is activated upon the aggregation of unfolded proteins within the mitochondria, or an imbalance of nuclear-encoded and mitochondria-encoded proteins, which confers proteotoxic stress [87–90]. UPR^{mt} is well-characterized in *C. elegans*, which requires the matrix peptide exporter HAF1 and the bZIP transcription factor ATFS-1 [91]. In cells with healthy mitochondria, ATFS-1 localizes to the mitochondrial matrix, whereby it is constitutively degraded by AAA+-protease LON [92]. However, mitochondrial depolarization impairs ATFS-1 import into the mitochondria, mediated by the transporter protein HAF1 and triggers UPR^{mt}. A large body of evidence suggests that UPR^{mt} activation recovers mitochondria from

damage and prolongs life span of organisms and is physiologically implicated in longevity and aging [90, 93, 94]. It remains unknow whether the regulation of UPR^mt in *C. elegans* is developmentally conserved among different species. Therefore, how this process is regulated at the molecular level in mammals remains to be further studied. In addition, given the beneficial impacts of UPR^mt as a defense mechanism induced by proteolysis dysfunction, it is important to investigate pharmaceutical approaches to target UPR^mt, in a context that life span in higher organisms would be improved. It would shed new insights into promising therapeutic success to treat age-related diseases.

Mitophagy

Mitochondrial homeostasis is also achieved by selective autophagic elimination of mitochondria (mitophagy), which is active during cellular programming and differentiation. One example is the clearance of redundant mitochondria during erythrocyte differentiation [95]. Another instance is evident during embryogenesis, where the offspring mitochondria are exclusively inherited maternally and the paternal mitochondria must be removed by mitophagy [96].

In general, nonselective bulk autophagy is achieved via five characteristic stages: (i) isolation membrane initiation, (ii) phagophore expansion, (iii) autophagosome maturation, (iv) auto-lysosome fusion and (v) lysosomal degradation [32, 97–100]. During mitophagy (selective autophagy), the mitochondria are presumably targeted as autophagic cargoes, in line with these hierarchical steps for mitophagosome formation [36, 38, 101–104]. Intriguingly, the organelle-localized signals that trigger mitophagy or for bulk autophagy may differ. The question as to how the selective autophagic signaling assemble mitophagy, within the steady-state conditions of the whole cell, remains unclear. In addition, whether mitochondrial fission always serves to promote mitochondrial elimination is not yet completely understood [42].

PINK1/Parkin-dependent mitophagy

Mitophagy is differentially activated depending on disparate stimuli and manifested via specific routes. PINK1/Parkin-mediated mitophagy is the most prevalent mitophagy pathway (Fig. 2A). Under basal conditions, PTEN-induced putative kinase 1 (PINK1) is constitutively imported from the cytosol into the mitochondrial intermembrane space, where it is rapidly degraded by mitochondrial proteases and proteasome [105]. However, under stress conditions, mitochondrial depolarization prevents PINK1 import, allowing PINK1 to instead be stabilized on the OMM [34]. As a mitochondria serine/threonine kinase, PINK1 subsequently

phosphorylates mitochondrial ubiquitin and the E3 ligase Parkin [106, 107]. In a feed-forward mechanism, phosphorylated Parkin further stimulates Parkin recruitment and activation [34, 108], allowing Parkin to target and ubiquitinate OMM proteins, including Mfn1 [109], Mfn2 [40, 109], translocase of outer mitochondrial membrane 20 (Tom20), and voltage-dependent anion channel [110] for degradation via the ubiquitin–proteasome system [111, 112]. These ubiquitinated OMM proteins yield more substrates for PINK1 phosphorylation, which in turn further activates Parkin in a positive amplification loop. Finally, autophagy receptors sequestosome-1 (p62/SQSTM1) [113], optineurin (OPTN) [114] and calcium-binding and coiled-coil domain-containing protein 2 (CALCOCO2/NDP52) recognize ubiquitin-tagged OMM proteins, and are recruited to sequester the mitochondria as autophagic cargo [37]. These autophagy adapters contain an LC3 interacting region (LIR), which directly interacts with autophagosomal LC3, and instigates mitochondrial elimination via mitophagosome trafficking and delivery into lysosome [115].

Despite plenty of evidence demonstrating the necessity of PINK1 and Parkin in maintaining mitochondrial fidelity, most studies have used in vitro models of ectopic Parkin overexpression and induced mitochondrial damage with the mitochondrial uncoupler, carbonyl cyanide m-chlorophenyl hydrazine (CCCP) at high doses of 10–20 μM [34, 109, 116, 117]. Less is known about the mitochondrial "vulnerability" threshold to exogenous toxins, consequently undergoing autophagic clearance. Of note, a low dose of CCCP at 5 μM, the time-course of Parkin translocation at 1.5 h, degradation of the OMM proteins and mitochondrial removal at 16 h, can be readily visualized and tracked [65]. Somewhat surprisingly, the OMM proteins possess disparate modulation in the early versus the late stage of mitophagy. For example, Mfn2 was found to brake mitophagy at an early phase [118] but positively serves for mitophagy at a later stage of PINK1/Parkin-dependent mitophagy [65]. Remarkably, our recent study showed that MiD51 depletion, which induces mitochondrial fusion, confers susceptibility to Parkin recruitment and is associated with rapid clearance of the mitochondria [65]. This study was the first to illustrate a novel action of MiD51, and thus functionally segregate MiD51 from MiD49. More importantly, this finding highlighted that mitochondrial fission is not always indispensable for mitochondrial turnover [65].

PINK1/Parkin-independent mitophagy

Mitophagy receptor-mediated mitophagy

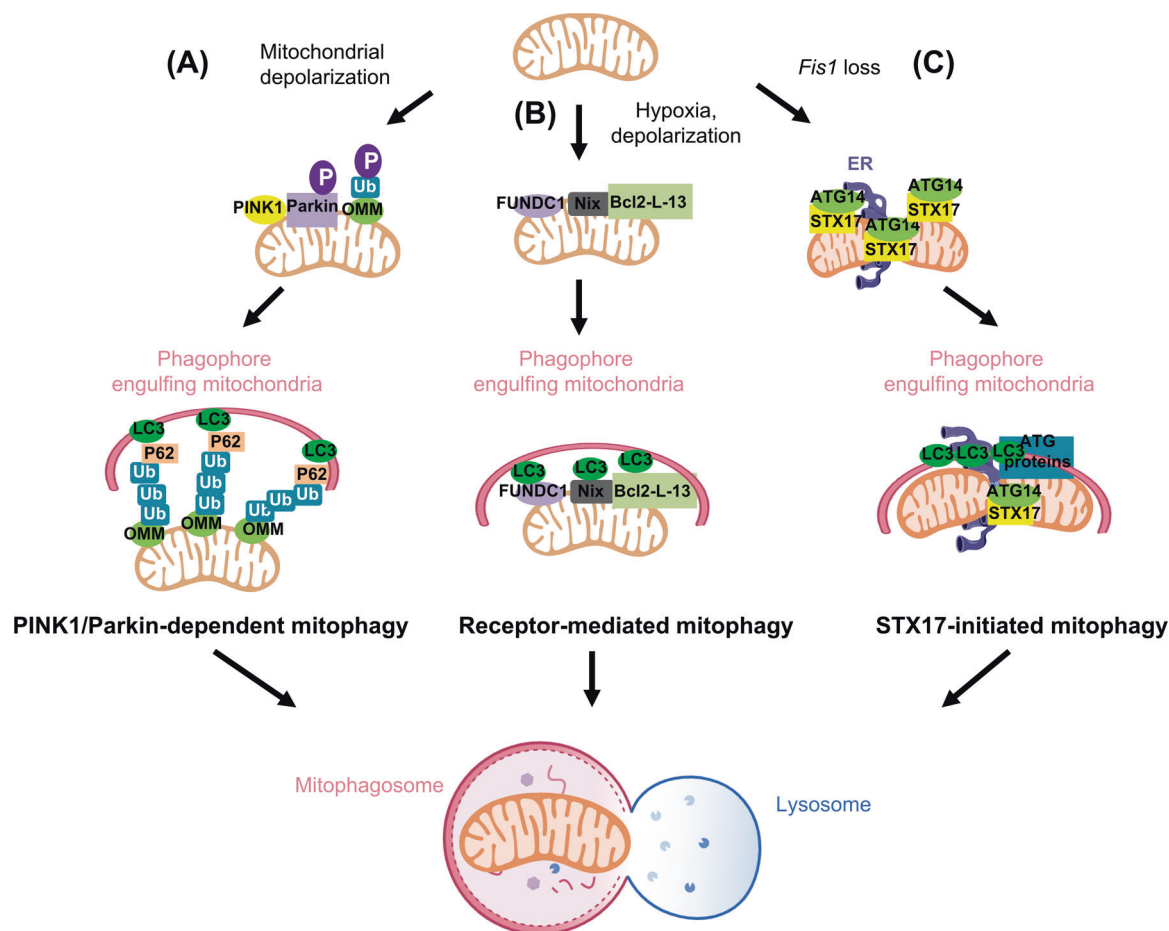Recent intensive studies on alternative PINK1/Parkin-independent mitophagy have made great progress in

Fig. 2 Mammalian mitophagy machinery. A During PINK1/Parkin-dependent mitophagy, ectopic toxins (such as CCCP) cause mitochondrial damage, in which PINK1 cleavage and import fail. PINK1 thus stabilizes on the outer mitochondrial membrane (OMM) and phosphorylates ubiquitin and Parkin. The attached OMM proteins are subsequently ubiquitinated by the E3 ligase, Parkin. These ubiquitinated OMM proteins serve as binding partners for P62. P62 further recruits LC3 and assembles the isolation membrane for selective autophagic mitochondrial removal. **B** During receptor-mediated mitophagy, in which cells are under hypoxic or mitochondrial membrane potential dissipation conditions, FUNDC1, Nix or Bcl-L-13 on

OMM directly attracts LC3 via an LIR motif for mitophagosome formation. **C** STX17-induced mitophagy upon Fis1 loss participates in autonomous mitochondrial elimination through a hierarchical autophagic route. Under basal conditions, Fis1 interacts with STX17, preventing the over-translocation of STX17 onto mitochondria, governing the initiation of mitophagy. Fis1 loss primes the dynamic shuffling of STX17 onto mitochondria-associated membranes (MAM) and mitochondrial pools. Mitochondrial STX17 then self-oligomerizes and recruits ATG14. Subsequently, downstream autophagy modulators assemble on the mitochondria to ensure commitment to mitochondrial clearance.

understanding mitochondrial quality control in cells devoid of Parkin activity [45, 95, 119–122]. Studies have shown that mitophagy receptors directly interact with and recruit Microtubule-associated protein 1A/1B-light chain 3 (LC3) [119, 120] or GABA Type A Receptor-Associated Protein (GABARAP) [122], which are key components of autophagosome membrane, via the LIR motif to help sequester mitochondria for autophagic degradation. These receptors thus serve as a degradation "eat-me" signal for damaged mitochondria (Fig. 2B). Several OMM proteins have been identified as mitophagy receptors, including Bcl2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) [123], NIX (also known as BNIP3L) [95], Fun14 Domain-containing 1 (FUNDC1) [119], FK506-binding protein 8

(FKBP8) [120], and Bcl2-like protein 13 (Bcl2-L-13) [45, 46].

In response to hypoxia, BNIP3 and NIX are transcriptionally upregulated, and mediated by Hypoxia-inducible factor 1-alpha (HIF1α) [124, 125] and Forkhead box protein O3 (FOXO3) [125]. They play crucial complementary roles to govern mitochondrial quality and avoid abnormal reactive oxygen species (ROS) accumulation [122, 126]. Moreover, NIX regulates red blood cells development by removing redundant mitochondria [95]. The phosphorylation of BNIP3 and NIX drives mitophagy. The phosphorylation of Ser17 and Ser24 flanking the BNIP3 LIR motif promotes its binding to ATG8 members [127]. The phosphorylated Ser34/35 juxtaposed to the NIX

LIR enhances its affinity to LC3A/B [128], and the phosphorylation of NIX at Ser212 accounts for its dimerization and robust recruitment of autophagosome onto mitochondria [129]. Moreover, upon hypoxia, FUNDC1 is phosphorylated and associated with LC3 [119], whereas FKBP8 strongly associates with lipidated LC3A upon mitochondrial depolarization [120]. Consequently, mitochondria are engulfed by autophagosome for autophagic elimination. Mammalian Bcl2-L-13, a homolog of yeast protein ATG32, induces mitochondrial fission and mitophagy by interacting LC3 in HEK293 cells after CCCP treatment [45]. In addition to the mechanisms mentioned above, a novel Parkin- or LC3B-independent but p62/LC3C-dependent piecemeal-type basal mitophagy has also been revealed recently [102]. In this pathway, it is suggested that lysosomal targeting of MTX1 by LC3C is required for the maintenance of mitochondrial network when cells undergo oxidative phosphorylation; however, how exactly MTX1 is recognized by LC3C has not yet been characterized [102].

Interestingly, the phospholipid cardiolipin, synthesized on the IMM, also contains a unique LIR motif and can initiate mitochondrial engulfment by LC3 via its externalization from the IMM to the OMM upon mitochondrial depolarization [130]. In primary cortical neurons and SH-SY5Y cells, rotenone induces the redistribution of cardiolipin onto OMM, and serves as an "eat-me" signal to recruit autophagosome onto mitochondria [130]. Given by the different extent of mitochondrial membrane potential loss caused by rotenone and CCCP treatment, cardiolipin was proposed to have a complementary role of Parkin for mitophagy [131]. The cardiolipin-mediated mitophagy is induced by mild stress caused by rotenone treatment, but CCCP incubation primes cells to PINK1/Parkin-dependent mitophagy. To this end, it would be very interesting to examine whether cardiolipin could function in the Parkin-depleted cells.

Collectively, mitophagy receptors are inactive under resting conditions, and their activity is elicited upon signals triggering mitochondrial damage. These receptors then exhibit a preferential association with LC3 family members, to recruit autophagosome that encapsulates mitochondria. As a consequence, mitochondria are removed via the autophagic route. Over the past several years, this field has gained fruitful achievements in understanding the various mitophagy receptors at the molecular level, particularly focusing on the autophagosome recruitment step. However, questions such as what signal exactly triggers the phagophore to engulf mitochondria would need to be further explored.

Mitophagy receptor-independent mitophagy

Most of the mitophagic pathways described above have been shown using acute and extreme stress signals, such as inducing mitochondrial depolarization with CCCP [34, 45], or mitochondrial respiration damage with oligomycin plus antimycin A [37], or hypoxia [119]. We, however, recently identified an additional mitophagy mechanism without using ectopic inductions [39]. Specifically, we showed that the SNARE protein, Syntaxin 17 (STX17), initiates mitophagy via a macroautophagic pathway that is triggered by the loss of the OMM protein, Fis1 [39]. Under basal conditions, Fis1 acts as a "gatekeeper" to prevent the dynamic trafficking of STX17 from the endoplasmic reticulum to the mitochondria and restraining STX17 self-oligomerization. As a result, basal mitophagy in the resting conditions is minimal. Conversely, loss of Fis1 through genetic approaches disables this protective gatekeeper from the mitochondria, resulting in priming of STX17 to actively translocate onto mitochondria-associated membranes (MAM) and the mitochondria. STX17 further recruits ATG14 onto the mitophagosome formation site and assembles the isolation membrane involving a group of proteins including DFCP1, WIPI-1, ATG5, and ATG16 on mitochondria (Fig. 2C). Subsequently, Rab7 is recruited onto the mitophagosome. As a small GTPase protein, Rab7 cycles between two nucleotide-bound states, a GDP-bound inactive state and a GTP-bound active state [132]. In the presence of an active GTP-bound form, Rab7 drives mitophagosome-lysosome fusion to ensure mitochondrial elimination [39, 133]. In demand of mitophagy activation upon Fis1 deficiency, STX17 also initiates the nuclear translocation of transcription factor EB (TFEB), a master regulator of autophagy and lysosome biogenesis [134]. Consequently, the nuclear localization and transcriptional activity of TFEB serve for the need of mitochondria turnover via autophagy [135].

More surprisingly, we also found that Drp1-modulated mitochondrial fission makes little contribution to the mechanistic regulation of STX17-induced mitophagy. The hyper-fused mitochondria from the loss of Drp1 can still undergo mitophagy [39]. Strikingly, this notion that fused mitochondria are permissible to autophagic clearance casts doubt to the mainstream concept that mitochondrial fission is preliminary for mitophagy [21, 22]. We seek to address this observation by illustrating the potential interplay between mitochondria dynamics and mitophagy; adapting to stress, mitochondrial dynamics and mitophagy are intimately integrated and coordinated to maintain mitochondrial homeostasis. Of note, dominant-negative mutant of Drp1, which facilitates mitochondrial fusion, abrogates mitophagy [41]. A predominant notion in this field is that mitochondrial fission represents an effort to favor mitophagy, given by that smaller mitochondria are easier to be encapsulated by autophagosome to proceed mitophagy [21, 22] (Fig. 3B). However, mitochondrial functions
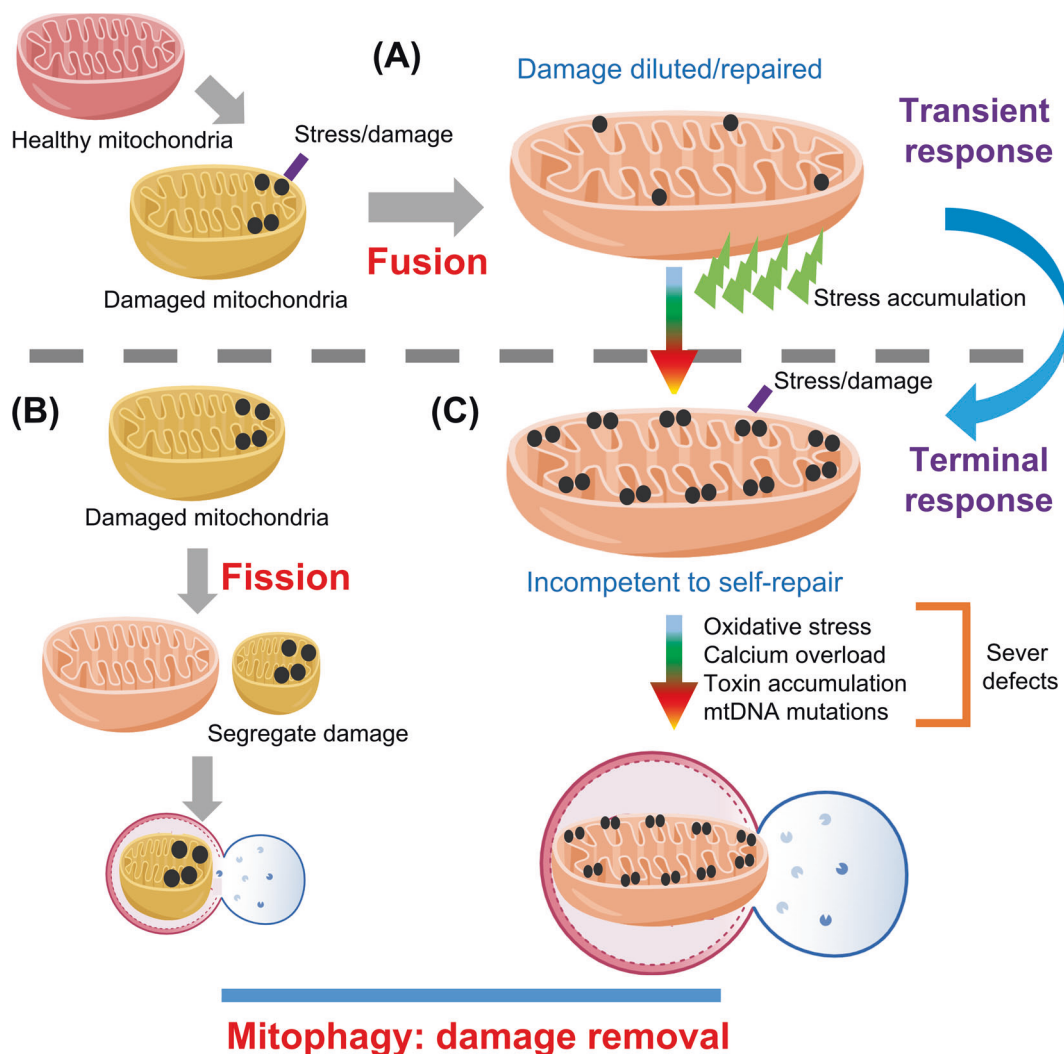
Fig. 3 A schematic illustration about interplay between mitochondrial dynamics and mitophagy. **A** As a first line of defense to toxins, mitochondrial fusion works as a "transient response", by mixing and sharing mitochondrial contents, to dilute and buffer mitochondrial damage (black dots), as well as to recover bad mitochondria back to healthy mitochondria. **B** When deleterious damage accumulates in the mitochondria, fission results in the segregation of impaired mitochondria from healthy ones. Damaged mitochondria in small sizes are destined for autophagic removal. **C** In response to acute stress, mitochondria fuse in self-repair mechanism as a first-aid. Simultaneously, stress cumulates on the mitochondria. When the damage reaches a threshold at which "transient response" (fusion) is incompetent to repair, in the case that mitochondrial fission is retarded by mitochondria dysfunction or restrained by genetic ablation of fission machinery, mitochondria undergo autophagic elimination at a hyper-fused state. Fused mitochondria are permissible to mitophagy.

involve beyond the morphological side. In face of stress, mitochondrial fusion may be an initial response to aid in buffering and diluting mitochondrial defects (Fig. 3A). But when the damage reaches to a certain threshold that fusion is incompetent to repair, mitochondria are destined to be cleared wholesale through the autophagic route. Under intense damage such as calcium overload, oxidative stress or toxin accumulation, acute shift to mitochondrial fission may be retarded (Fig. 3B). Consequently, small sizes of mitochondria fail to be achieved. Instead, fused mitochondria acutely undergo mitophagy to terminate and remove the damage. In this case, mitochondrial fusion is permissible

to cope with damage removal via mitophagic pathway (Fig. 3C).

By tethering an autophagy molecule (STX17) and an OMM protein (Fis1), our work is the first to bridge mitochondria and hierarchical autophagic route in a perfect coalescence, in which autonomous mitophagy regulation independent of ectopic mitochondrial damages is achieved. The ER-resident protein STX17 has controversial roles in PINK1/Parkin-dependent mitophagy; while it modulates the localization of PGAM5 and the association between PGAM5 and FUNDC1 to facilitate mitophagy [136], STX17 is also reported to be dispensable for depolarized

mitochondria removal mediated by PINK1/Parkin [137]. Given a novel role of STX17 in PINK1/Parkin-independent mitophagy [39], future investigations concerning the role of ER for mitophagy are needed. It is also unclear how the spatial position of MAM allows for mitophagosome formation. Another important piece of puzzle at the mechanistic level is what mitochondrial dysfunction intrinsically initiates this type of autonomous mitophagy. Furthermore, subsequent advances in pathological impacts of STX17-induced mitophagy will promise more in-depth clues of mitochondria-related diseases.

Bulk autophagy versus mitophagy

Bulk autophagy is an evolutionarily conserved "self-eating" process, regulated by genetic programming. It is a highly hierarchical pathway that involves the de novo formation of vesicles characterized as "autophagosomes", which engulf regions of the cytoplasm, damaged or unwanted organelles, protein aggregates, and invading pathogens [32, 33, 100]. In particular, mitophagy is a selective form of autophagy: numerous studies have illustrated that mitophagy employs general autophagic mediators, such as ULK1 [37, 46, 138], FIP200, and ATG13 [46, 104, 139], which are recruited onto damaged mitochondria. It has been reported that Bcl2-L-13, the mammalian homolog of Atg32, is an essential mitophagy receptor in yeast and relies on the ULK1 complex to regulate mitochondrial elimination [46]. However, little is known regarding whether mitophagic formation is distinguishable from the hierarchy of bulk autophagy. Indeed, based on our study of STX17-initiated mitophagy upon Fis1 loss, the mitophagic process directly recruits ATG14 and PI3P (phosphatidylinositol-3-phosphate) binding proteins, but independent of upstream proteins ULK1 and ATG9A [39]. Therefore, we suggest that mitophagy is activated by a specific "organelle-localized" signaling on mitochondria, that differs from the "global signaling-triggered" bulk autophagy. ULK1 is activated at the early stage of bulk autophagy. However, the "organelle-localized" mitophagy does not require ULK1, which is indispensable for "global signaling-triggered" bulk autophagy, though a well-established bulk autophagy modulator ATG13 displays an oscillatory dynamic translocation onto mitochondria and accounts for mitochondrial clearance [104]. Greater insights into the specific mitophagic machinery, that is unique from bulk autophagic machinery may allow for a better understanding of selective autophagy.

Physiological roles of mitophagy

Dysregulated mitophagy is highly implicated in various pathologies, including those affecting neurons [101, 140–142] and muscle [143], as well as aging [144, 145] and cancer

[146, 147]. PINK1/Parkin-dependent mitophagy is highly emphasized in neurodegenerative diseases, such as Parkinson's disease (PD) [101, 140, 148], Alzheimer's disease (AD) [142], and Huntington's disease (HD) [149]. Mutations of PINK1 and Parkin have been linked to autosomal recessive PD [101, 140, 141]. Gene mutations cause the inactivity of PINK1 [148] or Parkin [141, 150], which consequently decelerates mitophagy in neuron cells. Lack of mitophagy causes the accumulation of dysfunctional mitochondria, which result in loss of dopaminergic neurons at the early onset of PD [141]. In addition, key research on PINK1/Parkin-mediated mitophagy has led to an explosion of knowledge regarding its significance in AD [142] and HD [149]. While the overexpression of Parkin in AD mice restored activity-dependent synaptic plasticity and rescued behavior abnormalities, including decreasing β-amyloid load [142], mitophagy was found to be defective in the HD mouse model [149]. Clearly, the specific mechanism of mitophagy among different models of neurodegenerative diseases requires to be further explored. How exactly mitophagy dysregulation contributes to diseases is still enigmatic. Furthermore, the effects of mitophagy are prominent in skeletal muscle development. During myogenesis process from immature myoblasts to mature myotubes, mitophagy is upregulated to ensure the metabolic shift from glycolysis to OXPHOS, in support of the increased energetic demand of contractile muscle [143]. Also, dysfunction of mitophagy by depletion of ATG5 or P62 in C2C12 cells retards myotube development [143]. Moreover, the critical role of mitophagy in aging has been manifested by life span analyses conducted in *Drosophila* [144, 145] and *C. elegans* [151] models, in which mitophagy prolonged longevity but declined along with aging, most likely because that mitophagy removes dysfunctional mitochondria coupled with mtDNA mutations [152].

In the other spectrum, whether mitophagy positively regulates tumorigenesis remains debatable [124, 146, 153, 154]. Parkin loss is closely associated with cancer progression in various tissues [153], as Parkin knockout mice show spontaneous tumor growth, suggesting that the accumulated dysfunctional mitochondria, as a result of mitophagy defect, generates high ROS levels. Increased ROS production leads to increased transcriptional activation of genes involved in glycolysis, which facilitates the Warburg effect and is optimal for cancer cell survival as well as development [146]. Moreover, the mitophagy receptor BNIP3 is responsible for tumor suppression, supported by that Bnip3 depletion in mice model enables breast cancer metastasis in the lung, liver, and bone [147]. Nevertheless, mitophagy can also confer a supportive role in oncology because hypoxia, a pro-survival microenvironment for cancer cells, induces mitophagy [124]. Up to now, we are still in the early stages of understanding the mechanistic actions of specific molecules in the pathological level,

mostly focusing on Parkin. Thus, the precise relevance of mitophagy in potential therapeutic treatments requires more exploration.

Crosstalk between mitochondrial dynamics and mitophagy

Mitochondrial dynamics closely links to mitochondrial quality control, especially mitophagy. A large body of studies have proposed that mitochondrial fission is necessary for the initiation of mitophagy, but fusion serves as a "rescue" mechanism preventing mitophagy [20, 21, 41]. A simple rationale is that mitochondria fission segregates dysfunctional mitochondria into small sizes to be easily cleared (Fig. 3B). Conversely, fusion acts as a "transient response" adapting to mitochondrial stress and dilutes impaired mitochondrial components (Fig. 3A). Depolarization of mitochondria is a well-established driving force for mitophagy, involved in PINK1/Parkin [34], NIX [126], and Bcl2-L-13 [45]-mediated mitochondrial elimination. Clearly, mitochondrial fragmentation is coupled with mitochondrial membrane potential loss and precedes mitophagosome formation [34, 45, 126]. Upon hypoxic stress, FUNDC1-dependent mitophagy also associates with mitochondrial fission [43]. In support of this positive coherence between fission and mitophagy, genetic manipulation of the Drp1 through overexpression of dominant-negative form [41] or Drp1 deficiency [42, 109] both retarded mitophagy. Nevertheless, it still remains debatable whether mitochondrial fission is indeed a precursor for mitochondrial elimination. Recently, it was proposed that mitochondrial division is dispensable for mitophagy [155]. Consistently, our recent studies also found that certain OMM proteins that mediate mitochondrial dynamics do not necessarily involve in mitophagy formation via fission–fusion [39, 65]. As discussed, MiD51 depletion even primes cells for PINK1/Parkin-mediated mitochondrial removal, despite that MiD51 loss triggers mitochondrial fusion. We elucidated that the modulation of mitochondrial quality control uncouples from mitochondrial dynamics [65]. In line with this, we also reveal that over-fusion of mitochondria, resulted from Drp1 or Mff silencing using RNA interference, has no effect on STX17-initiated mitophagy upon Fis1 loss, further substantiating the idea that mitochondrial fission–fusion dynamics is not a prerequisite for and may be split from mitophagy [39]. Undoubtedly, more studies are needed to define the crosstalk between mitochondrial dynamics and mitophagy. The key question as to how tubular mitochondria are directly pinched off from main mitochondrial bodies engulfed by autophagy isolation membrane remains to be answered. Furthermore, autonomous mitochondrial damage at the genetic level, not induced by ectopic toxins, may be a driving force for mitophagy, and closer investigations of how specific OMM proteins engage in regulating mitochondrial homeostasis in this specific context is also necessary. We consider that future work which focuses on developing pathological models, based on the physiological contributions by these mechanisms, will yield a better understanding of translational significances related to mitochondrial functions.

Of note, MAM, the interface between ER and mitochondria, has been highly emphasized in mitochondrial dynamics and mitophagy [156–160], and is responsible for mitochondrial constriction [161]. Mitochondrial Drp1 receptors and Drp1 oligomers assemble on MAM, whereby ER wraps around mitochondria, to form a fission site [68, 162]. In addition, Mfn2 enriched on MAM tightens the juxtaposition of mitochondria and ER, and positively regulates mitochondrial calcium influx [163]. It was reported that Mfn2 ablation in cells disrupted ER morphology and loosened ER and mitochondria interactions. The increased distance between ER and mitochondria couples with mitochondrial fragmentation [163]. In addition, the GTPase protein S-OPA1 also accumulates and localizes on MAM to accelerate fission [164]. All these studies support that MAM is critical to mitochondrial dynamics. On the other hand, the ER-resident protein STX17, shuffles among ER, MAM, and mitochondria in response to nutrient levels, conferring important roles in switching between mitochondrial dynamics and autophagosome formation [158, 165]. Closer investigations of STX17 on MAM have demonstrated that MAM is involved in mitophagy [39, 136, 137], implying a broad role of MAM in mitochondrial homeostasis. Currently, we still lack a comprehensive picture of the coordination between fission and mitophagy initiation on MAM. It will be intriguing to answer whether the Drp1-mediated fission on MAM is a "trigger" or "brake" for mitophagy initiation. Is the site that Drp1 severs mitochondria also accounting for mitophagosome formation? An important question is how exactly fission and mitophagy are orchestrated remains to be elucidated.

Conclusion

In summary, the advent of studies about the multi-facets of mitochondrial behaviors usher in the exciting areas concerning the crosstalk among these actions. OMM proteins distribute on the interface between mitochondria and cytosol, or ER, in a geographic advantage that they crucially play for the interplay of various mitochondrial signaling pathways. Up to now, exciting breakthroughs into deciphering OMM proteins in mitochondrial dynamics and mitophagy have informatively shed light into mitochondrial homeostasis (Table 1). But greater insights into the

Table 1 Lessons from OMM proteins: mitochondrial fission does not essentially favor mitophagy.

Protein	Action on mitochondrial dynamics	Role in mitophagy
Drp1	A GTPase protein that accounts for mitochondrial fission.	1. Facilitates PINK1/Parkin-dependent mitophagy [42, 109] and FUNDC1-mediated mitophagy [43]. 2. No effect on STX17-initiated mitophagy [39].
Mff	An OMM protein; A Drp1 receptor to support mitochondrial division.	1. Facilitates PINK1/Parkin-dependent mitophagy [166]. 2. No effect on STX17-initiated mitophagy [39].
Fis1	An OMM protein; A controversial role in fission–fusion.	1. Promotes mitophagosome biogenesis for PINK1/Parkin-mediated mitophagy [133]. 2. Retards mitophagy by governing the over-assembly of STX17 on mitochondria. Loss of Fis1 primes cells for STX17-induced mitophagy [39].
MiD49	An OMM protein; A Drp1 receptor to support mitochondrial division.	Positively regulates PINK1/Parkin-dependent mitophagy. Loss of MiD49 decelerates PINK1/Parkin-dependent mitophagy [65].
MiD51	An OMM protein; A Drp1 receptor to support mitochondrial division.	Restrains PINK1/Parkin-dependent mitophagy. MiD51 loss accelerates Parkin translocation onto depolarized mitochondria [65] and mitophagy.
Mfn1	An OMM protein; GTPase activity required for mitochondrial fusion.	1. Substrate of UPS induced by Parkin, which is preliminary for PINK1/Parkin-dependent mitophagy [109]; 2. Required for Gp78-dependent mitophagy upon mitochondrial depolarization [167].
Mfn2	An OMM protein; GTPase activity required for mitochondrial fusion.	1. Substrate of UPS induced by Parkin, which is preliminary for PINK1/Parkin-dependent mitophagy [109]; 2. At the early stage of mitochondrial depolarization, Mfn2 functions as an ER-mitochondria tether to prevent PINK1/Parkin-mediated mitophagy [118]; 3. At the late stage of PINK1/Parkin-mediated mitophagy, the UPS activation of Mfn2 is indispensable for mitophagy [65].
OPA1	An IMM protein; GTPase activity required for mitochondrial fission or fusion (depending on disparate OPA1 isoforms).	1. Negatively regulates basal mitophagy [168]; 2. A negative role to gate FUNDC1-mediated mitophagy [43].

OMM outer mitochondrial membrane, *IMM* inner mitochondrial membrane, *UPS* ubiquitin–proteasome system.

significance of mitochondrial functions and mitochondria-associated diseases are still needed for further investigation. Given the promising advances of more metabolic and genomic approaches, more in-depth understanding into animal disease models and pathological causes will allow for a better prospect in rational therapeutic application.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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