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Mitochondrial fission and fusion: A dynamic role in aging and potential target for age-related disease

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ABSTRACT

The mitochondria is the major hub to convert energy for cellular processes. Dysregulation of mitochondrial function is one of the classical hallmarks of aging, and mitochondrial interventions have repeatedly been shown to improve outcomes in age-related diseases. Crucial to mitochondrial regulation is the dynamic nature of their network structure. Mitochondria separate and merge using fission and fusion processes in response to changes in energy and stress status. While many mitochondrial processes are already characterized in relation to aging, specific evidence in multicellular organisms causally linking mitochondrial dynamics to the regulation of lifespan is limited. There does exist, however, a large body of evidence connecting mitochondrial dynamics to other aging-related cellular processes and implicates them in a number of human diseases. Here, we discuss the mechanisms of mitochondrial fission and fusion, the current evidence of their role in aging of multicellular organisms, and how these connect to cell cycle regulation, quality control, and transmission of energy status. Finally, we discuss the current evidence implicating these processes in age-related human pathologies, such as neurodegenerative or cardio-metabolic diseases. We suggest that deeper understanding of the regulatory mechanisms within this system and downstream implications could benefit in understanding and intervention of these conditions.

1. The basics of mitochondrial structure

Mitochondria are dynamically interconnected, allowing them to share membranes, solutes, metabolites and proteins, as well as electrochemical gradients. Each mitochondria is organized into two phospholipid bilayers: the outer mitochondrial membrane (OMM), which separates the intermembrane space from the cytosol, and the inner mitochondrial membrane (IMM), which forms cristae into the matrix (Tilokani et al., 2018). While the OMM is mostly permeable to ions and larger molecules, the IMM is less so. Across the IMM an electrochemical gradient is formed, allowing ATP formation through oxidative phosphorylation, heat production through proton leaking, and ROS formation through oxygen reduction (Vafai and Mootha, 2012). Beyond interactions with one another, mitochondria can also connect and exchange materials with other cellular organelles, such as the endoplasmic reticulum (ER) and the lysosomes (Marchi et al., 2014; Soto-Heredero et al., 2017).

2. Fusion and fission proteins and processes

Fusion occurs when two adjacent mitochondria join, while fission separates one mitochondria into two (Sebastián and Zorzano, 2018) (Fig. 1). These two events permanently counterbalance each other; the inactivation of one leads to unopposed action by the other and the subsequent imbalance controls mitochondrial structure (Scorrano, 2013). The molecular mechanisms of these two processes have been previously reviewed in great detail (Tilokani et al., 2018), but here we will briefly describe the conserved proteins (Table 1) and mechanisms that control these processes.

2.1. Fusion

In mammalian cells, fusion is coordinated by the OMM-located mitofusin (MFN) 1, MFN2 and optic atrophy 1 (OPA1), located on the IMM, in separable sequential events (Malka et al., 2005; Song et al., 2009). The mitofusins are dynamin-like GTPases that contain conserved catalytic GTP-binding domains at the N termini, and are anchored to

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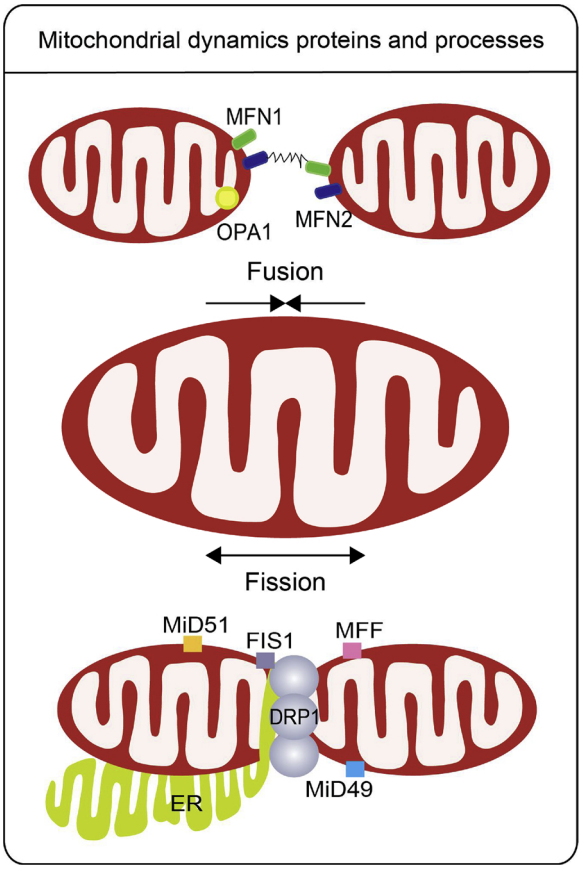

Fig. 1. Simplified model of mitochondrial fusion and fission in human cells. Mitochondrial fusion joins two mitochondria together, while fission separates one into two. Fusion is coordinated on the OMM by the mitofusins (MFN1 and MFN2), and on the IMM by optic atrophy 1 (OPA1). Fission begins when the endoplasmic reticulum (ER) is recruited to the constriction site, marked by mtDNA. Next, multiple OMM-bound proteins (FIS1, MFF, MiD49 and MiD51) recruit DRP1 to the surface of the mitochondria, aiding in ER-mediated constriction.

Table 1
Fusion and fission orthologs.

	Mammalian	C. elegans	D. melanogaster
Fusion proteins	MFN1	FZO-1	FZO
	MFN2		Marf
	OPA1	EAT-3	Opa1
Fission proteins	DRP1	DRP-1	Drp1
	FIS1	FIS-1; FIS-2	Fis
	MFF		Dmel
	MID49		
	MID51		
	DNM2		

the OMM by C-terminal transmembrane domains (Wai and Langer, 2016). They each contain two hydrophobic heptad repeats which, during fusion, interact between adjacent mitochondria (Koshiba et al., 2004). The fusion of the OMMs is driven by GTP hydrolysis, which induces a conformational change to bring the opposing membranes in contact with one another (Cao et al., 2017; Qi et al., 2016). *MFN1* and *MFN2* share approximately 80% similarity (Santel et al., 2003), which is likely the reason that, when overexpressed, each protein is able to rescue the loss of the other to promote fusion (Chen et al., 2003). MFN2 is also present in the ER and controls tethering of the ER to the mitochondria (Basso et al., 2018; de Brito and Scorrano, 2008; Naon et al., 2016), which, as discussed later, aids in the mitochondrial constriction of the fission process (Cohen et al., 2018).

OPA1 is a dynamin-like GTPase anchored to the IMM by an N-terminal transmembrane domain and is responsible for the fusion of inner mitochondrial membranes (Delettre et al., 2000). Alternative splicing of OPA1 gives rise to long forms (L-OPA1) that can be proteolytically cleaved to short forms (S-OPA1). This cleavage is executed by two IM peptidases: OMA1 and YME1L (Anand et al., 2014). In addition to OPA1, cardiolipin, a mitochondria-specific lipid, is critical to IMM fusion (Ban et al., 2017; Tilokani et al., 2018). The interaction between L-OPA1 and cardiolipin on either side of the membrane tethers the two IMM, which fuse following OPA1-dependent GTP hydrolysis (Liesa et al., 2009). S-OPA1 has been proposed to act as an enhancer of OPA1-CL interaction and fusion (DeVay et al., 2009; Rujiviphat et al., 2009). Mitofusin synthesis is regulated both transcriptionally and with post-transcriptional mechanisms, while their degradation is controlled by ubiquitylation and phosphorylation. OPA1 is regulated post-transcriptionally and post-translationally (Wai and Langer, 2016). Specifically, proteolytic processing plays a large role in regulation of mitochondrial dynamics, as reviewed by (Dietz et al., 2019). A deficiency or loss of fusion proteins leads to mitochondrial fragmentation (Ichishita et al., 2008; Kanazawa et al., 2008).

2.2. Fission

To begin the process of mitochondrial fission, replication of mtDNA in the matrix marks the site for recruitment of the endoplasmic reticulum (ER) (Friedman et al., 2011; Lewis et al., 2016). OMM constriction begins at the mitochondria-ER contact sites, before the oligomerization of DRP1. A number of mitochondrial-bound proteins then aid in the recruitment of DRP1 to the mitochondria, including FIS1, MFF, MiD49, and MiD51, though some of these proteins are known to perform overlapping functions (Loson et al., 2013). Recently, FIS1 was also shown to be involved in lysosomal marking of the mitochondrial fission sites (Wong et al., 2018), thereby further demonstrating inter-organelle communication as an important component of this process and as a point of interest for future study. GTP hydrolysis causes conformational changes, which enhance the ER-mediated constriction (Labrousse et al., 1999; Smirnova et al., 2001).

Interestingly, while FIS1 is not required for DRP1 recruitment to the OMM and therefore fission induction, overexpression of FIS1 can induce mitochondrial fragmentation in the absence of DRP1 (Liesa et al., 2019). Recent evidence demonstrates, in fact, that FIS1 promotes mitochondrial fragmentation both by activating fission and inhibiting fusion (Yu et al., 2019). Human FIS1 blocks fusion machinery by preventing the GTPase activity of MFN1, MFN2, and OPA1 (Yu et al., 2019). This recent work demonstrates how closely connected fission and fusion processes are, and suggests there might be other mechanisms by which one process inactivates the other.

OMM constriction has been well documented, but the mechanism of IMM division is still unclear (Tilokani et al., 2018). Recent work has suggested that IMM constriction is Ca^{2+}-dependent and occurs at mitochondria-ER contact sites, even suggesting a possible role for S-OPA1 in untethering the OMM from the IMM during fission (Chakrabarti et al., 2018; Cho et al., 2017). However, further study is necessary to confirm these results and fully understand the fission process of the IMM.

Mitochondria in cells lacking *DRP1* adopt a hypertubular configuration with a highly connected and elongated network in yeast, worms and mammals (Labrousse et al., 1999; Weir et al., 2017). It should be noted that both DRP1 and its receptors also localize to the peroxisomal membranes where they perform membrane fission (Schrader et al., 2016; Waterham et al., 2007). Therefore, studies that ablate *DRP1* may also affect cellular processes outside of mitochondrial fission alone. DRP1 can be both activated and inactivated by phosphorylation, depending on the phosphorylated residue, and further regulated by ubiquitylation and SUMOylation (Galvan et al., 2019; Jhun et al., 2018;

van der Bliek et al., 2013). DRP1 phosphorylation can be regulated by a number of factors, including exercise (Moore et al., 2019) and circadian rhythm (Schmitt et al., 2018) though the mechanisms between these processes and the phosphorylation remain unknown.

3. Mitochondrial dynamics in aging

Deterioration in mitochondrial function is one of the nine currently established hallmarks of aging (Lopez-Otin et al., 2013). Over recent years, mild mitochondrial perturbations in various animal models including mice, *Drosophila melanogaster*, and *Caenorhabditis elegans* have been shown to delay aging and age-related functional declines (Cho et al., 2011; Dell'agnello et al., 2007; Dillin et al., 2002; Houtkooper et al., 2013; Lee et al., 2003; Liu et al., 2005). Under these conditions, not only is mitochondrial function affected, but also affect mitochondrial form, seemingly via mitochondrial fission and fusion.

However, the role of mitochondrial dynamics in lifespan regulation is not well elucidated. The yeast field has provided some solid connections, yet there is currently limited evidence causally connecting these two processes in higher organisms. Studies in *Saccharomyces cerevisiae* have shown that fission inhibition increases longevity, while unopposed fission shortens lifespan (Scheckhuber et al., 2007). In line with these observations, studies in *C. elegans and D. melanogaster* showed that increased mitochondrial fusion is associated with increased longevity (Chaudhari and Kipreos, 2017; Rana et al., 2017), and in worms, fragmentation of the mitochondrial network correlates with age (Houtkooper et al., 2013; Jiang et al., 2015; Regmi et al., 2014) (Table 2). However, yeast and worms yield opposite effects on longevity upon simultaneous ablation of both fission and fusion processes. In yeast, doing so shortens replicative lifespan (Bernhardt et al., 2015) while in worms a frozen mitochondrial network promotes longevity (Weir et al., 2017). Though these differences between unicellular and multicellular organisms are interesting, and certainly warrant future study, the subsections presented below focus on complex, multicellular animal models.

A number of studies have shown that mitochondrial dynamics are required for lifespan extension in distinct long-lived conditions, including TORC1-mediated longevity, AMPK-mediated longevity, and upon dietary restriction (Burkewitz et al., 2015; Weir et al., 2017; Zhang et al., 2019) (Table 2). Similarly, in mice, caloric restriction (CR) caused increased mitochondrial length and width in muscle fibers, and this effect was dependent on the mitochondrial biogenesis transcriptional coactivator, PGC-1α (Finley et al., 2012). However, more study is necessary to understand these connections, as different longevity regimens cause different cellular responses involving distinct molecular mechanisms. While AMPK-mediated longevity requires both fission and fusion (Weir et al., 2017), longevity induced via TORC1 specifically requires mitochondrial fusion (Zhang et al., 2019). Considering this context dependence, it will be necessary to unravel the mechanisms further to understand how these processes are required for specific lifespan extension interventions.

While much remains to be studied to causally connect mitochondrial dynamics with lifespan per se, there already exists a strong body of evidence in multicellular animal organisms tying mitochondrial dynamics to specific cellular and molecular hallmarks of aging. We discuss below how mitochondrial dynamics specifically affect cell viability, senescence, mitochondrial health, bioenergetics, quality control and intracellular signaling. Each of these processes plays an important role in aging, tying even more tightly together the connections between mitochondrial form and function with longevity.

3.1. Mitochondrial function and energy states

Different mitochondrial network states are associated with specific nutrient states. A nutrient-rich environment tends to accompany a fragmented mitochondrial network, whereas starvation leads to elongated and fused mitochondria (Liesa and Shirihai, 2013; Rossignol et al., 2004; Tondera et al., 2009). While these effects are not universal, and do not lead to unopposed fission or fusion, imbalance of the system has led to these observations. The network exhibits a high level of plasticity, allowing rapid rescue if nutrient status changes (Schrepfer and Scorrano, 2016). Mitochondrial fusion tends to lead to an increase in bioenergetics efficiency, maintaining ATP production even upon limited nutrients and therefore allowing the cell to maintain viability (Gomes et al., 2011; Rambold et al., 2011). Meanwhile, mitochondrial fragmentation is associated with increased oxidative stress, mitochondrial depolarization, and reduced ATP production (Jheng et al., 2012). The decreased bioenergetics efficiency may serve as a protective mechanism from the detrimental effects associated with nutrient overload (Liesa and Shirihai, 2013).

These metabolic inputs regulate the proteins and processes of fission and fusion. DRP1 particularly seems to play a large role. Under starvation conditions, PKA phosphorylates DRP1, thereby blunting the fission process (Gomes et al., 2011; Rambold et al., 2011). Conversely, excess of glucose is also dependent on DRP1 to fragment mitochondria and increase levels of ROS (Yu et al., 2006), suggesting a potential role for DRP1 in treatment of metabolic diseases, as discussed below.

Upon *MFN2* deletion, mammalian cells have decreased oxygen consumption, increased proton leak, reduced mitochondrial membrane potential, increased production of ROS, thereby leading to reduced glucose, pyruvate and fatty acid oxidation (Bach et al., 2003; Mourier et al., 2015; Sebastian et al., 2012). Interestingly, one study in this cell model demonstrated that insufficient coenzyme Q levels could explain the deficient respiratory chain activity (Mourier et al., 2015). Similarly, knockdown of *OPA1* reduces mitochondrial membrane potential and increases proton leak, leading to overall reduction in basal, ATP-coupled, and maximal respiration (Buck et al., 2016; Chen et al., 2005; Zhang et al., 2011). Contrary to *Mfn2* deletion, an increase in mitochondrial respiration and ROS production is observed in POMC neurons with ablated *Mfn1* (Ramirez et al., 2017). However, the effect was not conserved in mice missing *Opa1* in POMC neurons (Ramirez et al., 2017), suggesting the effect is specific to *Mfn1*, not mitochondrial fusion.

3.2. Cell viability and senescence

Cell proliferation requires a great deal of energy, and these energy states seem, at least in part, to be regulated by the mitochondrial network. Mitochondria elongate in the G1 and S phases, creating an energy-conservative state to provide enough ATP for cell replication (Mitra et al., 2009; Schieke et al., 2008; Schrepfer and Scorrano, 2016). Entry into S phase can be induced by *Drp1* knockdown via increased cyclin E expression (Mitra et al., 2009), demonstrating the balance between mitochondrial fission and fusion, even in the context of cell cycle regulation.

In the G2/M phases, mitochondria tend to fragment, presumably to ensure equal distribution of mitochondria between daughter cells (Mitra et al., 2009; Taguchi et al., 2007). Knockdown of *FIS1* causes replicative stress and G2/M arrest (Lee et al., 2014; Qian et al., 2012; Salazar-Roa and Malumbres, 2017). Regulation of mitochondrial dynamics and cell cycling has been reviewed previously in more depth (Horbay and Bilyy, 2016; Salazar-Roa and Malumbres, 2017).

Cellular senescence, whereby cells cease division and enter a quiescent state, characterized by the secretion of inflammatory signaling factors, is a well-described hallmark of aging (Lopez-Otin et al., 2013). Senescent cells have a decreased capacity for mitochondrial biogenesis and ATP synthesis (Liesa and Shirihai, 2013). Aged organisms and tissues tend to accumulate senescent cells, and their clearance increases lifespan (Baker et al., 2016, 2011; Gorgoulis et al., 2019; Xu et al., 2018). Senescent cells have reduced *FIS1* and *DRP1* expression, with slightly increased MFN protein levels (Gomes et al., 2011; Lee et al., 2007; Yoon et al., 2006). Knockdown of *FIS1* in human cells also

Table 2
Summary of mitochondrial morphological alterations in aging and aging-related diseases. Specific examples are discussed more elaborately in the main text.

Disease/lifespan phenotypes		Mitochondrial network	Mitochondrial dynamics proteins	References
Neurodegenerative disease	CMT2A: peripheral neuropathy	Fragmented	MFN2 mutation in humans	(Vance, 2000; Zuchner et al., 2004)
	DOA: loss of RGCs	Fragmented	OPA1 mutation in humans	(Votruba et al., 1998)
	PD: dopaminergic neurodegeneration	Fragmented	DRP1-mediated excessive fragmentation	(Dagda et al., 2009; Lutz et al., 2009)
	AD: ubiquitous neurodegeneration	Fragmented	DRP1 activation through S-nitrosylation	(Cho et al., 2009)
	HD: neurodegeneration in basal ganglia and cerebral cortex	Fragmented	Elevated GTPase DRP1 activity	(Shirendeb et al., 2011)
Cardiac dysfunction	Cardiomyopathy and heart failure in mice	Fragmented	*Mfn-1/Mfn-2* knockout in mouse heart	(Jin et al., 2011)
	Cardiomyopathy in mice	Fragmented	Heterozygous OPA1 mice	(Chen et al., 2012)
	Dilated cardiomyopathy and cardiomyocyte necrosis in mice	Mitochondrial enlargement	*Drp1* knockout in mouse heart	(Song et al., 2015)
	Cardiac hypertrophy in mice	Heterogenous size	*Mfn1/Mfn2/Drp1* triple knockout in mouse heart	(Song et al., 2017)
Metabolic dysfunction	Obese Zucker rats and obese humans	Fragmented	Reduced *Mfn2* expression	(Bach et al., 2003)
	Glucose intolerance and insulin resistance in both liver and muscle in mice	Fragmented	*Mfn2* deletion in mice liver	(Sebastian et al., 2012)
	Obese mice	Fragmented	Increased protein level of DRP1	(Jheng et al., 2012)
Longevity model	Lifespan extension of wild type *C. elegans*	Tubular mitochondria	*drp-1;fzo-1* double mutations	(Weir et al., 2017)
	Longevity model of insulin/IGF signaling inhibition in *C. elegans, daf-2(e1370)*	Increased fusion compared to wild type	Increased protein level of EAT-3	(Chaudhari and Kipreos, 2017)
	Lifespan extension of *daf-2(e1370)*	Giant globular mitochondria	*drp-1* mutation	(Yang et al., 2011)
	Dietary restriction model in *C. elegans, eat-2(ad1116)*	Increased fusion compared to wild type	unknown	(Chaudhari and Kipreos, 2017; Weir et al., 2017)
	Longevity model of LET-363/TOR inhibition in *C. elegans, let-363* RNAi, null mutations in *raga-1* (RagA homolog) or *rsks-1* (S6K homolog)	Increased fusion compared to wild type	unknown	(Chaudhari and Kipreos, 2017; Zhang et al., 2019)
	Lifespan extension in *D. melanogaster*	Increased fission in midlife of animals	*Drp1* or *p62* overexpression in midlife of animals	(Aparicio et al., 2019; Rana et al., 2017)

triggers premature senescence-associated phenotypes, such as lysosomal accumulation, which can be reversed by abrogation of mitochondrial dynamics through additional knockdown of *OPA1* (Lee et al., 2007). Additionally, while senescence is related to hyper-tubular mitochondrial networks, apoptosis is associated with mitochondrial fragmentation (Frank et al., 2001). Altogether, these data suggest that an individual cell's life cycles are marked by distinct mitochondrial network structures, responding in large part to balance specific energy states. However, there is limited recent evidence tying together the role of mitochondrial dynamics and cellular senescence. This would be an interesting topic for future research as it connects two well-established hallmarks of aging.

3.3. Mitochondrial quality control mechanisms

3.3.1. Mitochondrial proteostasis

Aging is accompanied by a gradual loss of proteostasis and interventions that maintain proteostasis, such as by increasing molecular chaperone expression or promoting protein turnover, have been implicated in health and longevity in animals (Jensen and Jasper, 2014). For example, the mitochondrial unfolded protein response (UPR^{mt}) is a mitochondria-to-nucleus retrograde signaling cascade that limits protein import and induces expression of chaperone and protease genes to maintain mitochondrial protein homeostasis (Haynes and Ron, 2010). Studies in *C. elegans* have shown that moderate mitochondrial dysfunction resulting from inhibition of mitochondrial translation or mitochondrial electron transport chain activate the UPR^{mt} to promote longevity (Durieux et al., 2011; Houtkooper et al., 2013).

The instrumental role of mitochondrial dynamics in mitochondrial proteostasis lies in the concept of fusion-mediated content mixing and fission-mediated separation. Fusion allows the exchange of mitochondrial contents between adjacent mitochondria which facilitates functional complementation in the face of mitochondrial deficits (Liu et al., 2009). In contrast, fission allows an equal distribution of the mitochondrial proteome and mtDNA in two daughter mitochondria during mitochondrial biogenesis (Mishra and Chan, 2014). Fission also functions by segregating dysfunctional and superfluous mitochondria for degradation through mitochondrial autophagy (mitophagy, discussed below). A direct link between the mitochondrial network and mitochondrial proteome homeostasis has been suggested by studies in *C. elegans,* where genetically blocking fission or fusion evokes protein misfolding stress, thereby activating the UPR^{mt} (Zhang et al., 2018). Moreover, loss of mitochondrial protein homeostasis coincides with dysregulation of mitochondrial dynamics and abnormal mitochondrial morphology during aging (Houtkooper et al., 2013; Leduc-Gaudet et al., 2015; Moehle et al., 2019; Sebastian et al., 2016). It will be interesting in the future to test if rebalancing fission and fusion will revert the decline of mitochondrial protein homeostasis so as to benefit longevity and health in aged animals.

3.3.2. Mitochondrial DNA integrity

Loss of mtDNA integrity and stability is a major cause of mitochondrial dysfunction and the accumulation of mtDNA mutations with age has been implicated in cellular dysfunction (Kujoth et al., 2005; Linnane et al., 1989; Trifunovic et al., 2004). Knock-in mice expressing a proofreading-deficient form of polymerase POLGγ, the so-called 'mutator mice', significantly accumulate mtDNA mutations in various tissues and exhibit premature aging phenotypes such as hair loss, graying, sarcopenia, and deafness (Kujoth et al., 2005).

Mitochondrial fusion is important for maintaining mtDNA levels and mtDNA fidelity (Chen et al., 2010; Papanicolaou et al., 2012a). Patients with OPA1 mutations harbor mtDNA deletions in their skeletal muscle, suggesting an association between fusion and mtDNA instability (Amati-Bonneau et al., 2008; Hudson et al., 2008). In addition, reducing mitochondrial fusion by conditionally ablating mitofusins in mouse skeletal muscle or heart results in profound reductions in mtDNA

content, great accumulations of mtDNA mutations, and development of mitochondrial myopathy in both muscle and heart (Chen et al., 2010; Papanicolaou et al., 2012a). Moreover, fusion also confers high tolerance to mtDNA lesions in cells through content mixing, thereby suppressing expression of mitochondrial dysfunction-related disease phenotypes in mice (Nakada et al., 2001; Ono et al., 2001). Conversely, blocking fission in mouse embryonic fibroblasts does not have a significant effect on mtDNA levels (Ishihara et al., 2009). Overall, these results demonstrate the beneficial effects of fusion in safeguarding mtDNA integrity, thereby highlighting fusion as a potential therapeutic target for aging and mtDNA-related diseases (Chen et al., 2010; Nakada et al., 2009).

3.3.3. Mitochondrial-derived vesicles

Mitochondrial-derived vesicles (MDVs) recently emerged as a mitochondrial quality control pathway that acts to remove oxidized proteins and lipids in mitochondria. This pathway provides a fine-tuned mitochondrial repair system before accumulation of too much damage, thereby preventing complete elimination of mitochondria by mitophagy. Although investigation of the factors constituting MDVs transport system is just begun, it seems that some essential components of the mitophagy process also participate in lysosome-targeted MDV formation (Sugiura et al., 2014). For example, mitochondrial ROS induced by the uncoupler CCCP and the complex III inhibitor antimycin A in immortalized human cells evokes formation of MDVs in a PINK1- and Parkin-dependent manner (McLelland et al., 2014). Mechanistically, instead of relying on the established DRP1-involved fission machinery, new mediators, so far undescribed, sever MDVs from mitochondria (McLelland et al., 2014; Neuspiel et al., 2008; Soubannier et al., 2012a). This conclusion is supported by ultrastructural analysis: the size of MDVs is between 70 nm–150 nm, whereas the diameter of the yeast mitochondrial dynamin (Dnm1) spirals that drive mitochondrial constrictions is restricted to 100 nm (Ingerman et al., 2005; Soubannier et al., 2012a, b). Therefore, DRP1-formed spirals are too large to constrict a MDV neck, meaning another mediator is required.

Given the connection between mitophagy and MDVs, dysfunction of MDVs is speculated to trigger premature mitophagy, which consequently impairs the hierarchical surveillance network of mitochondrial quality control mechanisms, encompassing the UPR^{mt}, mitochondrial fission and fusion, MDVs, and mitophagy (Sugiura et al., 2014). As such, deficiency in MDVs may contribute to aggregation of global cellular damage and dysfunctional mitochondria during aging (Sugiura et al., 2014). Understanding the molecular mechanisms required for formation and trafficking of MDVs will foster our understanding about how cargoes are specifically incorporated into MDVs, the role of MDVs in mitochondrial quality control, and also how defects in MDVs pathways are implicated in human diseases.

3.3.4. Mitophagy

Mitophagy is a specific form of autophagy that exclusively eliminates damaged and superfluous mitochondria in cells (Ding and Yin, 2012). A functional decline in mitophagy results in the accumulation of dysfunctional mitochondria, a shared hallmark of aging and aging-related pathologies (Lopez-Otin et al., 2013; Sun et al., 2016). Many mechanistic aspects of mitophagy were resolved in yeast (for a comprehensive overview we refer the reader to (Furukawa et al., 2019; Kanki et al., 2015)), but the links between mitophagy and animal aging are less clear.

Several mitophagy signaling cascades are differentially activated in response to various stimuli under distinct cellular contexts in mammalian cells (Palikaras et al., 2017; Wei et al., 2015). Depending on whether ubiquitin (Ub) is required for the recognition of cargoes for degradation, mitophagy pathways can be classified into ubiquitin-dependent and mitochondrial receptor-mediated mechanisms (Khaminets et al., 2016; Pickles et al., 2018) (Fig. 2). Much of what is known about ubiquitin-dependent mitophagy involves PINK1 and Parkin that, when mutated, can cause familial Parkinson's diseases (Kitada et al., 1998; Valente et al., 2004). Upon stresses such as mitochondrial depolarization or mitochondrial proteotoxicity, PINK1 accumulates on the mitochondrial surface and recruits ubiquitin E3 ligase Parkin, which ubiquitinates outer mitochondrial membrane (OMM) proteins to facilitate mitochondria removal (Harper et al., 2018; Matsuda et al., 2010; Ordureau et al., 2014). Mitochondrial receptor-mediated mitophagy occurs in response to specific stresses such as hypoxia or during erythropoiesis. Upon activation, the OMM proteins, such as BCL-2-like protein 13 (BCL2L13), NIX (also called BCL2/adenovirus E1B-interacting protein 3-like, BNIP3L), BNIP3, and FUNDC1 (FUN14 domain-containing protein 1), serve as mitophagy receptors to interact with autophagosomes through their LC3-interacting region (LIR) motifs and promote mitochondrial degradation (Gatica et al., 2018; Hamacher-Brady et al., 2007; Liu et al., 2012; Murakawa et al., 2015; Quinsay et al., 2010; Rogov et al., 2017).

Mitochondrial dynamics is a common target of various mitophagy pathways to initiate the degradation process. Upon mitochondrial depolarization, MFN1 and MFN2 are ubiquitinated by Parkin, which promotes their degradation, thereby abolishing fusion, promoting mitochondrial fragmentation, and facilitating mitophagy (Gegg et al., 2010; Ziviani et al., 2010). In addition, in most cancer cells where Parkin is not expressed, the E3 ubiquitin-protein ligase ARIH1 ubiquitinates MFN2 and promotes its degradation through the proteasome upon CCCP-induced mitophagy (Villa et al., 2017). Moreover, MFN2 is phosphorylated by PINK1 to recruit Parkin to impaired mitochondria upon depolarization-induced mitophagy in mouse cardiac myocytes (Chen and Dorn, 2013). PINK1 also upregulates DRP1 activity in mitophagy by preventing its phosphorylation from protein kinase A (PKA), which promotes segregation of damaged mitochondria for

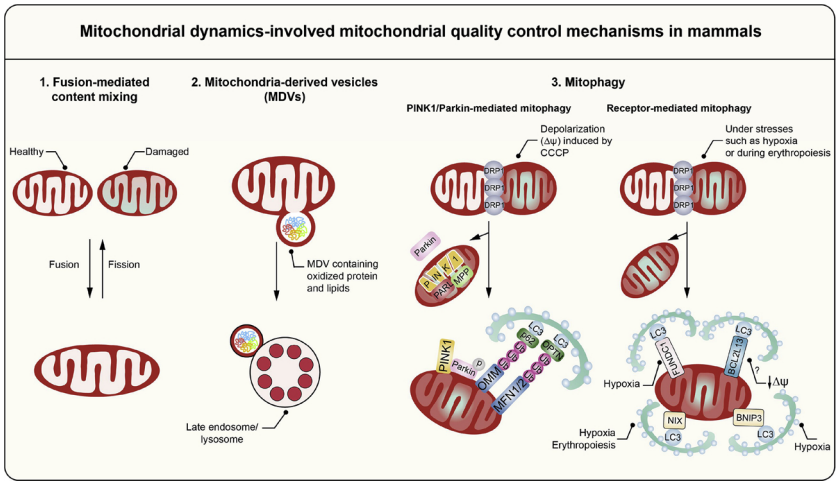

Fig. 2. Mitochondrial quality control mechanisms involving mitochondrial dynamics. Mitochondria harbor a network of surveillance mechanisms encompassing (1) fusion-mediated function complementation, (2) mitochondria-derived vesicles, and (3) mitophagy processes to protect mitochondrial homeostasis from increasing degrees of damage. Specifically, fusion-mediated functional complementation and mitochondria-derived vesicles constitute the first line of defense against mild mitochondrial impairment. Upon an increase in the impairment within the mitochondria, damaged compartments are segregated from the mitochondrial network through fission and subsequently undergo mitophagy. According to the type of stress, different molecular machineries are responsible for mitophagy. For instance, PINK1/Parkin mediates mitophagy in the face of mitochondrial depolarization while, in mitophagy induced by hypoxia or during erythropoiesis, the connection of damaged mitochondria to nascent autophagosomes is built by mitochondrial receptors such as NIX, BNIP3, FUNDC1, and BCL2L13 through interaction with LC3.

degradation (Pryde et al., 2016). Additionally, under the stress of hypoxia in Hela cells, FUNDC1 activated DRP1 in mitophagy (Chen et al., 2016; Liu et al., 2012). Collectively, these data show that mitochondrial fragmentation is necessary in mitophagy pathways.

Conventionally, the role of mitochondrial division in mitophagy is thought to fit long and tubular mitochondria into nascent autophagosomes (Gomes et al., 2011; Kageyama et al., 2014; Rambold et al., 2011; Tanaka et al., 2010). Indeed, a number of studies have provided evidence in support of the necessity of fission in the induction of mitophagy (Gomes et al., 2011; Ikeda et al., 2015; Kageyama et al., 2014; Kanki et al., 2009; Rambold et al., 2011; Tanaka et al., 2010; Twig et al., 2008). However, some forms of mitophagy, for instance when induced by hypoxia, occur independent of mitochondrial division (Yamashita et al., 2016). In addition, studies in yeast also found that Dnm1 is dispensable for mitophagy (Bernhardt et al., 2015; Kanki et al., 2009; Mendl et al., 2011; Yamashita et al., 2016). Therefore, it is still controversial whether fragmentation mediated by the canonical core components of mitochondrial fission machinery is a prerequisite for mitophagy.

It should be noted that the current understanding of the role of mitochondrial division in mitophagy described above is based predominately on experimental evidence obtained after massive induction of mitophagy, such as using mitochondrial membrane potential uncouplers. This causes severe impairments of mitochondrial and cellular functions, which does not represent situations under physiological conditions. One study instead activated PINK1-Parkin-mediated mitophagy by expressing the mitochondrial-localized mutant ornithine transcarbamylase (ΔOTC) in mammalian cells to better represent physiological conditions (Burman et al., 2017). They reported that rather than being required for mitophagy, DRP1 selectively segregated mitochondrial subdomains that contain accumulated misfolded protein aggregates for elimination through mitophagy (Burman et al., 2017). Furthermore, a recent study revealed a novel function of DRP1 in affecting mitochondrial membrane potential (Cho et al., 2019). Specifically, under normal conditions, DRP1 can transiently reduce mitochondrial membrane potential at division sites in mammalian cells (Cho et al., 2019). This reduction in mitochondrial membrane potential was rapidly restored in healthy mitochondria, whereas damaged mitochondria failed to do so and therefore underwent mitophagy (Cho et al., 2019). This is proposed as a routine surveillance mechanism and negative selection pressure to maintain mitochondrial quality (Cho et al., 2019). It is necessary in future studies to determine the functions of DRP1 and DRP1-mediated fission in mitophagy in different physiological contexts to gain a comprehensive understanding of the significance of mitochondrial fission in mitochondrial homeostasis.

Mitophagy maintains mitochondrial homeostasis and its decline with age contributes to an accumulation of dysfunctional mitochondria, a cause of numerous diseases of old age (Lopez-Otin et al., 2013; Sun et al., 2016; Wallace, 2005). Interventions that boost mitophagy benefit health and longevity in multiple model organisms ranging from yeasts to mice (Aparicio et al., 2019; Palikaras et al., 2015; Rana et al., 2017; Ryu et al., 2016; Schiavi et al., 2015). For example, studies in *C. elegans* reveal an important role of mitophagy in longevity assurance (Palikaras et al., 2015; Schiavi et al., 2015). Inhibiting mitophagy through loss of the mitophagy regulators *dct-1* (NIX/BNIP3L homolog) or *pink-1* (PINK1 homolog) leads to an accumulation of dysfunctional mitochondria and compromises animals' resistance to various types of stress such as oxidative stress, heat stress, and starvation (Palikaras et al., 2015). Moreover, in long-lived *C. elegans* such as the insulin/IGF1 receptor mutant *daf-2* and animals with moderate mitochondrial dysfunction, induction of mitophagy through *dct-1* or *pink-1* is key to their longevity assurance (Palikaras et al., 2015; Schiavi et al., 2015). Studies in *D. melanogaster* provide further support of a direct role of mitophagy in lifespan determination (Aparicio et al., 2019; Rana et al., 2017). Upregulation of an autophagy receptor p62 (also known as Sequestosome 1) in middle-aged flies promotes mitochondrial fission and mitophagy to prolong lifespan. In addition, *Drp1* overexpression in aging flies reverses age-related mitochondrial enlargement, restores mitochondrial respiratory function, and facilitates mitophagy, so as to delay age-onset pathology and prolong lifespan (Rana et al., 2017). Moreover, pharmacological activation of mitophagy through dietary supplementation of urolithin A also prolongs *C. elegans* lifespan (Ryu et al., 2016). Urolithin A treatment in *C. elegans* induces mitochondrial fragmentation and autophagy-dependent mitochondrial removal (Ryu et al., 2016). In aged mice, urolithin A stimulates autophagy in gastrocnemius muscle and prevents age-related decline of muscle function (Ryu et al., 2016). In summary, these findings suggest that targeting mitochondrial fission-mitophagy axis provides promising therapeutic choices to benefit organismal health and lifespan.

3.4. Bioenergetics and metabolic signaling pathways

Nutrients are vital for life. Therefore, it is not surprising that the prime signaling pathways that function in sensing, absorbing, and consuming nutrients also modulate the rate of aging. These include the insulin/insulin-like growth factor 1 (IIS) signaling pathway, mammalian target of rapamycin (mTOR), and AMP-activated kinase (AMPK) pathways (Houtkooper et al., 2010; Templeman and Murphy, 2018).

An increasing body of evidence suggests the importance of mitochondrial morphology in these energy-sensing signaling pathways to influence metabolism, health, and longevity (Fig. 3). Studies in *C. elegans* show that genetically suppressing the IIS receptor DAF-2 increases

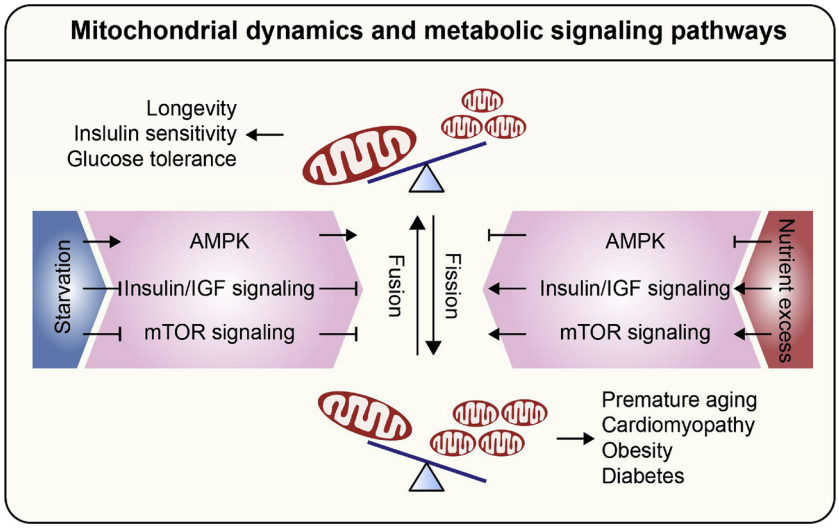

Fig. 3. The role of mitochondrial fission and fusion in metabolic signaling pathways. Generalized and simplified summary of the main pathways linking nutritional state with mitochondrial dynamics and their ultimate phenotypic outcome. AMPK, insulin/IGF, and mTOR nutrient signaling pathways constitute a core network in mammalian cells to coordinate metabolism and regulate lifespan. Depending on the availability of nutrients, these signaling pathways are differentially switched on or off, corresponding to specific mitochondrial morphologies. For example, under the condition of starvation, AMPK is activated, while insulin/IGF and mTOR signaling are suppressed. This change typically favors mitochondrial fusion, which is associated with major beneficial effects such as prolonged lifespan, improved insulin sensitivity, and enhanced glucose tolerance. In contrast, nutrient excess activates insulin/IGF and mTOR signaling but represses AMPK. This leads to an activation of mitochondrial fission, which is associated with a number of human pathologies such as aging, cardiomyopathy, obesity, and diabetes. It should be noted that these responses are not uniform and are highly context-dependent.

the level of mitochondrial fusion by preventing degradation of EAT-3 (OPA1 homolog in *C. elegans*), and the fused mitochondrial network is required for DAF-2 inhibition-mediated longevity (Chaudhari and Kipreos, 2017). Conversely, promoting mitochondrial fusion by depleting the fission gene *drp-1* amplifies the effect of reduced insulin signaling on longevity (Yang et al., 2011). Inhibiting LET-363/TOR in *C. elegans* also engenders a fused mitochondrial network, which is necessary for its beneficial effects on longevity (Chaudhari and Kipreos, 2017). Furthermore, inhibiting mTOR abrogates translation of its target gene mitochondrial fission process 1 (MTFP1) in mouse embryonic fibroblasts, thereby causing mitochondrial hyperfusion and protecting cells from apoptosis (Morita et al., 2017). In contrast to the pro-fission effect of insulin signaling, as described above, studies in cultured rat cardiomyocytes reported that a 3 h treatment of insulin upregulates OPA1 at the protein level and leads to an interconnected mitochondrial network partially through the Akt/PKB-mTOR signaling pathway (Parra et al., 2014). A similar disconnect involving bimodal effects on mitochondrial dynamics appears to happen upon CR. CR is by far the most effective and non-invasive way to improve health and deaccelerate aging in most organisms through an AMPK-dependent mechanism (Fontana et al., 2010). An increase in mitochondrial size has been reported in skeletal muscle from caloric restricted mice, which may contribute to CR-mediated improvement of mitochondrial function (Finley et al., 2012). Moreover, CR and constitutively active AAK2 (AMPKα2 homolog) was shown to prolong lifespan in *C. elegans* by maintaining mitochondrial network connectivity (Weir et al., 2017). Overexpressing of constitutively active AMPK in human endothelial cells also promoted mitochondrial fusion by lowering the protein level of DRP1 (Wang et al., 2017). In contrast, upon acute mitochondrial stress such as inhibition of mitochondrial electron transport chain through treatment of rotenone or antimycin A, AMPK mediated mitochondrial fragmentation in cultured human cells (Toyama et al., 2016). Short-term pharmacological (1 h) activation of AMPK was also sufficient for mitochondrial fragmentation in cultured human cells (Toyama et al., 2016). The apparent discrepancy regarding the effect of insulin and AMPK signaling on mitochondrial network might be, at least partially, explained by the varied type (acute vs mild) and duration (long-term vs short-term) of stress used in cell lines or animal models. Together, these results highlight that the adaptation of the mitochondrial network is required by these nutrient-sensing pathways to exert beneficial effects on longevity. Future studies are warranted to determine the mechanism by which mitochondrial morphology engages in lifespan regulation upon activation of various nutrient-sensing signaling pathways. In this sense, it will be interesting to evaluate whether the outputs of fission and fusion such as mitochondrial respiration, mitophagy, and ROS production are associated with longevity mediated by nutrient-sensing signaling pathways.

4. Implications of mitochondrial dynamics in human pathology

Defects in mitochondrial dynamics lead to mitochondrial dysfunction, which is an unequivocal culprit in the pathogenesis of various human diseases (Table 2). Some disorders linked to mitochondrial dynamics are caused by monogenic mutations that directly alter fusion or division activity, while many other diseases associated with mitochondrial dynamics result from diverse environmental and genetic factors, such as cardiovascular diseases, neurodegenerative diseases, and metabolic disorders.

4.1. Mutations in mitochondrial dynamics genes as the primary cause of neurodegenerative diseases

The importance of mitochondrial dynamics in the neural system was first corroborated by genetic studies that identified mutations of mitochondrial fission and fusion machinery in human neurodegenerative diseases (Alexander et al., 2000; Delettre et al., 2000; Kijima et al., 2005; Waterham et al., 2007; Zuchner et al., 2004). A mutation in *MFN2* causes Charcot-Marie-Tooth Type 2A (CMT2A) disease with clinical manifestations of the peripheral neuropathy (Vance, 2000; Zuchner et al., 2004). According to the functions of MFN2, several mechanisms have been proposed to be responsible for the pathogenesis of CMT2A. Firstly, due to the importance of mitochondrial fusion in maintaining mtDNA integrity, inhibiting this process results in mtDNA depletion and thus dysfunction of mitochondrial respiratory chain, which renders neurons more susceptible to death (Chen et al., 2005; Ono et al., 2001). In line with this hypothesis, the absolute mtDNA copy numbers in CMT2A patient skeletal muscle biopsies were reduced approximately two-fold when compared to healthy controls (Vielhaber et al., 2013). MFN2 is also related to the pathogenesis of CMT2A through compromised mitochondrial transport in nerve cells. This is currently considered the major cause of neuronal degeneration in CMT2A, according to findings from previous animal studies (Baloh et al., 2007; El Fissi et al., 2018; Misko et al., 2010). Mutation of *MFN2* disrupts proper mitochondrial positioning which undermines the ability of mitochondria to fulfill the local energetic needs within axons, thus resulting in axonal degeneration (Misko et al., 2010).

Heterozygous mutation in the fusion gene *OPA1* results in autosomal dominant optic atrophy (DOA), an inherited neuropathy characterized by preferential loss of retinal ganglion cells (RGCs) and optic nerve fibers (Delettre et al., 2000; Votruba et al., 1998). In addition, heterozygous *OPA1* mutations are also associated with other symptoms including deafness, ataxia, axonal sensory-motor polyneuropathy, and mitochondrial myopathy (Amati-Bonneau et al., 2008; Hudson et al., 2008; Payne et al., 2004). Although different individuals with autosomal dominant optic atrophy may present varied clinical phenotypes, visual loss resulting from the retinal ganglion cells degeneration is the major clinical manifestation (Yu-Wai-Man and Newman, 2017).

In contrast to neuropathies resulting from mutations in *MFN2* and *OPA1,* which are late-onset disorders and have localized pathogenic effects, patients with dominant-negative mutation in *DRP1* present more severe and fatal clinical abnormalities with a prenatal-onset including microcephaly, abnormal brain development, optic atrophy, and hypoplasia (Waterham et al., 2007). This result suggests that mitochondrial fission plays a more critical role than does mitochondrial fusion in human health, which may be due to the fact that DRP1 mutations also led to impaired peroxisome fission which additionally exacerbates the severity of symptoms (Waterham et al., 2007).

4.2. Neurodegenerative diseases associated with imbalanced mitochondrial dynamics

Abnormal, fragmented mitochondrial networks have been implicated in many other neurodegenerative diseases that are not primarily caused by mutations in fission- or fusion-related genes, such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD). For example, loss of PINK1 or Parkin in human SH-SY5Y cells, associated with PD, results in excessive mitochondrial fragmentation mediated by DRP1 (Dagda et al., 2009; Lutz et al., 2009). Blocking the fission process attenuates dopaminergic neuronal degeneration and restored striatal dopamine release in both a PINK1 deletion PD mouse model and an environmental PD mouse model (Rappold et al., 2014). In addition, beta-amyloid, believed to be the primary cause of Alzheimer's disease, increases neuronal nitric oxide, which triggers mitochondrial fragmentation and neuronal damage by activating DRP1 through S-nitrosylation (Cho et al., 2009). Consistent with this observation, the level of S-nitrosylated DRP1 is also elevated in brains of human AD, suggesting mitochondrial fragmentation as a contributor to the pathogenesis of AD (Cho et al., 2009). Accordingly, inhibiting mitochondrial fission pharmacologically alleviates beta-amyloid-caused neuronal apoptosis (Kim et al., 2016). In addition, Tau and mutant huntingtin were shown to directly interact with and activate DRP1, consequently augmenting fission and sensitizing neurons to

apoptosis observed in patients with HD (Shirendeb et al., 2011) or AD (Manczak and Reddy, 2012). Collectively, these data highlight mitochondrial fragmentation as an important contributor to the pathogenesis of these neurodegenerative diseases and suggest that restoring homeostasis of mitochondrial morphology genetically and/or pharmaceutically is a potentially viable and appealing therapeutic strategy to treat these diseases.

4.3. Mitochondrial dynamics and cardiovascular disease

The heart is rich in mitochondria due to high energy demands for the excitation-contraction cycle. Decreases in mitochondrial density, OXPHOS, and mitochondrial fusion proteins including MFN1 and OPA1 have been found in failing hearts in humans (Ahuja et al., 2013; Rosca and Hoppel, 2010). Conditional combined *Mfn1/Mfn2* knockout in adult mouse heart leads to overall fragmentation of the mitochondrial network, dysfunction of cardiomyocytes, and eventually overt heart failure after seven to eight weeks of tamoxifen induction of the knockout (Jin et al., 2011). Interestingly, although MFN1 and MFN2 share high sequence similarities in mammals and are both abundant in the heart (Santel and Fuller, 2001), individual knockout of either *Mfn1* or *Mfn2* leads to distinct effects on cardiac functions (Papanicolaou et al., 2011, 2012b). Conditional knockout of *Mfn1* in mouse heart results in fragmented mitochondria. However, in this context, mitochondrial respiration is normal and the hearts of *Mfn1* knockout mice present no gross abnormalities (Papanicolaou et al., 2012b). In contrast, *Mfn2*-deficient mice develop modest cardiac hypertrophy and *Mfn2* deficiency in adult cardiomyocytes leads to mitochondrial enlargement with increased production of mitochondrial ROS (Papanicolaou et al., 2011). These results indicate that, in addition to mitochondrial fragmentation in the heart, some functions of MFN2 possibly contribute to heart dysfunction, such as its role in ER-mitochondria tethering and mitophagy, as discussed above. In addition, heterozygous *Opa1* mice develop late-onset cardiomyopathy (Chen et al., 2012). These results point to the importance of mitochondrial fusion genes in preserving heart function.

In addition to heart dysfunction resulting from fusion deficiency, mitochondrial fission-related genes are also essential to the heart. Conditionally ablating *Drp1* in adult mouse hearts results in lethal dilated cardiomyopathy and cardiomyocyte necrosis by generating enlarged mitochondria and activating mitochondrial permeability transition pores (Song et al., 2015). These data illustrate the significance of balanced fission and fusion in heart functions and the loss of either one will result in heart dysfunction.

Growing evidence supports the importance of balanced mitochondrial dynamics in cardiac functions. A concomitant depletion of *Mfn1* and a mitochondrial fission gene (*Mff*), remarkably rescued *Mff* deletion-caused mitochondrial respiration deficiency, cardiac-associated dysfunction, and lifespan shortening in mice (Chen et al., 2015). In addition, mice with *Mfn1/Mfn2/Drp1* triple knockout specifically in the heart have less severe cardiac defects and survive longer compared to mice with respective cardiac knockout of *Mfn1/Mfn2* and *Drp1* (Song et al., 2017). In summary, these data demonstrate that fusion and division coordinately sustain cardiac function and suggest that preserving the balance of fusion and division might be a promising therapeutic strategy for cardiac disease.

4.4. Mitochondrial dynamics and metabolic disorders

Mitochondrial morphology reacts to distinct metabolic cues. A growing body of evidence suggests that mitochondrial network dysfunction is tightly associated with metabolic disorders including obesity, insulin resistance, and diabetes (Fig. 3). For example, in obese Zucker rats and obese humans, skeletal muscle mitochondria are smaller and fragmented, along with reduced *Mfn2* expression (Bach et al., 2003). *Mfn2* deletion in mouse liver evokes glucose intolerance and results in insulin resistance in both liver and muscle (Sebastian et al., 2012). Studies in rat models show that *Mfn2* overexpression improves insulin sensitivity by reducing accumulation of lipid intermediates in skeletal muscle (Zhang et al., 2013) and ameliorates high-fat diet induced insulin resistance in liver (Gan et al., 2013). In line with this observation, an increase in fission protein DRP1 and mitochondrial fragmentation has been also reported in skeletal muscle from mice with diet- or leptin-deficient-induced obesity (Jheng et al., 2012). Inhibiting fission by treating diabetic mice with the DRP1 inhibitor mdivi-1 partly alleviates glucose-induced mitochondrial malfunction (Huang et al., 2015). Although these findings suggest the association between mitochondrial fragmentation and development of insulin resistance, the mechanism underlying the alteration of mitochondrial morphology during the development of insulin resistance or metabolic syndromes is still elusive. In this context, more studies should focus on the regulation of mitochondrial dynamics proteins at the transcriptional, translational, and posttranslational levels in an attempt to answer if they are regulated by pathways of insulin signaling, and glucose and fatty acid metabolism.

In contrast with metabolic inflexibility induced by *Mfn2* deletion in mouse liver and skeletal muscle, adipose-specific *Mfn2* knockout mice were resistant to high-fat diet-induced insulin resistance (Boutant et al., 2017). These results suggest that the functions of MFN2 in energy homeostasis and metabolism are highly context dependent. Similarly, deletion of *Mfn1* in mouse liver protects against insulin resistance induced by high-fat diet, despite mitochondrial fragmentation, which is opposite to the findings obtained in mice with *Mfn2* deletion in the liver (Kulkarni et al., 2016). This discrepancy can be partly reconciled by considering that in addition to mediating fusion, MFN2 is also involved in tethering the ER and mitochondria (de Brito and Scorrano, 2009). Indeed, liver-specific ablation of *Mfn2* rather than *Mfn1* in mice evokes ER stress (Kulkarni et al., 2016; Sebastian et al., 2012). Future studies are warranted to elucidate the precise role of mitochondrial dynamics proteins in different tissues in relation to these metabolic disorders.

5. Concluding remarks

Mitochondria are major crossroads of catabolic and anabolic metabolism and signaling hubs that integrate diverse cellular signals to regulate cell growth, differentiation, vitality, and death. As such, mitochondrial dysfunction is one of the classical hallmarks of aging (Lopez-Otin et al., 2013). Although knowledge of how mitochondria affect and are affected by aging has grown considerably in recent decades, there is still much to untangle with regards to how the mitochondria influences health and aging in complex organisms. Considering this question from the perspective of mitochondria network dynamics, the following conclusions emerge: (1) mitochondrial form and function are closely interlinked, and the dynamic nature of mitochondrial morphology permits mitochondria to adjust their functions in response to intrinsic and extrinsic signals through a prompt morphological rearrangement; (2) divergent cellular signaling pathways that control the rate of aging such as insulin/IIS, LET-363/TOR, AMPK, and mitochondrial dysfunction-mediated longevity pathways correspond to specific mitochondrial forms, ranging from hyperfused to fragmented patterns (Chaudhari and Kipreos, 2017; Lee et al., 2003; Morita et al., 2017; Trewin et al., 2018); (3) mitochondrial fission and fusion are integral to mitochondrial behavior, but the significance of each process to mitochondrial and cellular functions is highly context-dependent. We propose that remodeling mitochondrial morphology is likely the common strategy adopted by various signaling pathways to impinge on mitochondrial activities and therefore exert their influences on cellular bioenergetic homeostasis. However, more questions remain regarding the regulation of mitochondrial dynamics by cellular signaling pathways and even more so when considering implications in health and aging (see Outstanding Questions). In this regard, future investigations should focus on revealing regulatory mechanisms

underpinning mitochondrial morphological changes in aging and aging-related pathologies as well as the downstream implications of the mitochondrial network in aging contexts. A better understanding of these principles will provide a promising opportunity to slow the progress of age-related diseases by targeting the mitochondrial network.

Outstanding questions:

1 A large body of evidence connects mitochondrial dynamics to aging in yeast. However, some findings, such as lifespan shortening when fission and fusion are both impaired, are opposite to those observed in multicellular organisms. How can we reconcile this for processes we expect to be conserved?
2 Besides enzymes such as AMPK, PKA, and calcineurins that alter the mitochondrial network by directly modifying mitochondrial dynamics proteins in mammalian cells, are there more enzymes, yet unknown, that also participate in this process?
3 How do mitochondrial morphology and dynamics proteins change with age in mammals? Are these changes cell-type or tissue-specific?
4 Are changes throughout lifespan aging-associated defects or protective, adaptive, mechanisms? Accordingly, what are the upstream signaling pathways that regulate these mitochondrial network alterations during aging?
5 What are the downstream metabolic effects of mitochondrial network remodeling in different longevity paradigms such as insulin/IIS, LET-363/TOR, AMPK, and mitochondria dysfunction-mediated longevity pathways?
6 What role does inter-organelle communication play during aging, such as that between mitochondria, ER, and lysosomes? How are mitochondrial dynamics related to these processes?

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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References

Ahuja, P., Wanagat, J., Wang, Z., Wang, Y., Liem, D.A., Ping, P., Antoshechkin, I.A., Margulies, K.B., Maclellan, W.R., 2013. Divergent mitochondrial biogenesis responses in human cardiomyopathy. Circulation 127, 1957–1967.
Alexander, C., Votruba, M., Pesch, U.E., Thiselton, D.L., Mayer, S., Moore, A., Rodriguez, M., Kellner, U., Leo-Kottler, B., Auburger, G., Bhattacharya, S.S., Wissinger, B., 2000. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. Nat. Genet. 26, 211–215.
Amati-Bonneau, P., Valentino, M.L., Reynier, P., Gallardo, M.E., Bornstein, B., Boissiere, A., Campos, Y., Rivera, H., de la Aleja, J.G., Carroccia, R., Iommarini, L., Labauge, P., Figarella-Branger, D., Marcorelles, P., Furby, A., Beauvais, K., Letournel, F., Liguori, R., La Morgia, C., Montagna, P., Liguori, M., Zanna, C., Rugolo, M., Cossarizza, A., Wissinger, B., Verny, C., Schwarzenbacher, R., Martin, M.A., Arenas, J., Ayuso, C., Garesse, R., Lenaers, G., Bonneau, D., Carelli, V., 2008. OPA1 mutations induce mitochondrial DNA instability and optic atrophy' plus' phenotypes. Brain 131, 338–351.
Anand, R., Wai, T., Baker, M.J., Kladt, N., Schauss, A.C., Rugarli, E., Langer, T., 2014. The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. J. Cell Biol. 204, 919–929.
Aparicio, R., Rana, A., Walker, D.W., 2019. Upregulation of the autophagy adaptor p62/SQSTM1 prolongs health and lifespan in middle-aged Drosophila. Cell Rep. 28 (1029–1040), e1025.
Bach, D., Pich, S., Soriano, F.X., Vega, N., Baumgartner, B., Oriola, J., Daugaard, J.R., Lloberas, J., Camps, M., Zierath, J.R., Rabasa-Lhoret, R., Wallberg-Henriksson, H., Laville, M., Palacin, M., Vidal, H., Rivera, F., Brand, M., Zorzano, A., 2003. Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism. A novel regulatory mechanism altered in obesity. J. Biol. Chem. 278, 17190–17197.
Baker, D.J., Wijshake, T., Tchkonia, T., LeBrasseur, N.K., Childs, B.G., van de Sluis, B., Kirkland, J.L., van Deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236.
Baker, D.J., Childs, B.G., Durik, M., Wijers, M.E., Sieben, C.J., Zhong, J., Saltness, R.A., Jeganathan, K.B., Verzosa, G.C., Pezeshki, A., Khazaie, K., Miller, J.D., van Deursen, J.M., 2016. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530, 184–189.
Baloh, R.H., Schmidt, R.E., Pestronk, A., Milbrandt, J., 2007. Altered axonal mitochondrial transport in the pathogenesis of Charcot-Marie-Tooth disease from mitofusin 2 mutations. J. Neurosci. 27, 422–430.
Ban, T., Ishihara, T., Kohno, H., Saita, S., Ichimura, A., Maenaka, K., Oka, T., Mihara, K., Ishihara, N., 2017. Molecular basis of selective mitochondrial fusion by heterotypic action between OPA1 and cardiolipin. Nat. Cell Biol. 19, 856–863.
Basso, V., Marchesan, E., Peggion, C., Chakraborty, J., von Stockum, S., Giacomello, M., Ottolini, D., Debattisti, V., Caicci, F., Tasca, E., Pegoraro, V., Angelini, C., Antonini, A., Bertoli, A., Brini, M., Ziviani, E., 2018. Regulation of ER-mitochondria contacts by Parkin via Mfn2. Pharmacol. Res. 138, 43–56.
Bernhardt, D., Muller, M., Reichert, A.S., Osiewacz, H.D., 2015. Simultaneous impairment of mitochondrial fission and fusion reduces mitophagy and shortens replicative lifespan. Sci. Rep. 5, 7885.
Boutant, M., Kulkarni, S.S., Joffraud, M., Ratajczak, J., Valera-Alberni, M., Combe, R., Zorzano, A., Canto, C., 2017. Mfn2 is critical for brown adipose tissue thermogenic function. EMBO J. 36, 1543–1558.
Buck, M.D., O'Sullivan, D., Klein Geltink, R.I., Curtis, J.D., Chang, C.H., Sanin, D.E., Qiu, J., Kretz, O., Braas, D., van der Windt, G.J., Chen, Q., Huang, S.C., O'Neill, C.M., Edelson, B.T., Pearce, E.J., Sesaki, H., Huber, T.B., Rambold, A.S., Pearce, E.L., 2016. Mitochondrial Dynamics Controls T Cell Fate through Metabolic Programming. Cell 166, 63–76.
Burkewitz, K., Morantte, I., Weir, H.J.M., Yeo, R., Zhang, Y., Huynh, F.K., Ilkayeva, O.R., Hirschey, M.D., Grant, A.R., Mair, W.B., 2015. Neuronal CRTC-1 governs systemic mitochondrial metabolism and lifespan via a catecholamine signal. Cell 160, 842–855.
Burman, J.L., Pickles, S., Wang, C., Sekine, S., Vargas, J.N.S., Zhang, Z., Youle, A.M., Nezich, C.L., Wu, X., Hammer, J.A., Youle, R.J., 2017. Mitochondrial fission facilitates the selective mitophagy of protein aggregates. J. Cell Biol. 216, 3231–3247.
Cao, Y.L., Meng, S., Chen, Y., Feng, J.X., Gu, D.D., Yu, B., Li, Y.J., Yang, J.Y., Liao, S., Chan, D.C., Gao, S., 2017. MFN1 structures reveal nucleotide-triggered dimerization critical for mitochondrial fusion. Nature 542, 372–376.
Chakrabarti, R., Ji, W.K., Stan, R.V., de Juan Sanz, J., Ryan, T.A., Higgs, H.N., 2018. INF2-mediated actin polymerization at the ER stimulates mitochondrial calcium uptake, inner membrane constriction, and division. J. Cell Biol. 217, 251–268.
Chaudhari, S.N., Kipreos, E.T., 2017. Increased mitochondrial fusion allows the survival of older animals in diverse *C. Elegans* longevity pathways. Nat. Commun. 8, 182.
Chen, Y., Dorn 2nd, G.W., 2013. PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. Science 340, 471–475.
Chen, H., Detmer, S.A., Ewald, A.J., Griffin, E.E., Fraser, S.E., Chan, D.C., 2003. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. J. Cell Biol. 160, 189–200.
Chen, H., Chomyn, A., Chan, D.C., 2005. Disruption of fusion results in mitochondrial heterogeneity and dysfunction. J. Biol. Chem. 280, 26185–26192.
Chen, H., Vermulst, M., Wang, Y.E., Chomyn, A., Prolla, T.A., McCaffery, J.M., Chan, D.C., 2010. Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. Cell 141, 280–289.
Chen, L., Liu, T., Tran, A., Lu, X., Tomilov, A.A., Davies, V., Cortopassi, G., Chiamvimonvat, N., Bers, D.M., Votruba, M., Knowlton, A.A., 2012. OPA1 mutation and late-onset cardiomyopathy: mitochondrial dysfunction and mtDNA instability. J. Am. Heart Assoc. 1, e003012.
Chen, H., Ren, S., Clish, C., Jain, M., Mootha, V., McCaffery, J.M., Chan, D.C., 2015. Titration of mitochondrial fusion rescues Mff-deficient cardiomyopathy. J. Cell Biol. 211, 795–805.
Chen, M., Chen, Z., Wang, Y., Tan, Z., Zhu, C., Li, Y., Han, Z., Chen, L., Gao, R., Liu, L., Chen, Q., 2016. Mitophagy receptor FUNDC1 regulates mitochondrial dynamics and mitophagy. Autophagy 12, 689–702.
Cho, D.H., Nakamura, T., Fang, J., Cieplak, P., Godzik, A., Gu, Z., Lipton, S.A., 2009. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 324, 102–105.
Cho, J., Hur, J.H., Walker, D.W., 2011. The role of mitochondria in Drosophila aging. Exp. Gerontol. 46, 331–334.
Cho, B., Cho, H.M., Jo, Y., Kim, H.D., Song, M., Moon, C., Kim, H., Kim, K., Sesaki, H., Rhyu, I.J., Kim, H., Sun, W., 2017. Constriction of the mitochondrial inner compartment is a priming event for mitochondrial division. Nat. Commun. 8, 15754.
Cho, H.M., Ryu, J.R., Jo, Y., Seo, T.W., Choi, Y.N., Kim, J.H., Chung, J.M., Cho, B., Kang, H.C., Yu, S.W., Yoo, S.J., Kim, H., Sun, W., 2019. Drp1-Zip1 interaction regulates mitochondrial quality surveillance system. Mol. Cell 73 (364–376), e368.
Cohen, S., Valm, A.M., Lippincott-Schwartz, J., 2018. Interacting organelles. Curr. Opin. Cell Biol. 53, 84–91.
Dagda, R.K., Cherra 3rd, S.J., Kulich, S.M., Tandon, A., Park, D., Chu, C.T., 2009. Loss of

PINK1 function promotes mitophagy through effects on oxidative stress and mitochondrial fission. J. Biol. Chem. 284, 13843–13855.
de Brito, O.M., Scorrano, L., 2008. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature 456, 605–610.
de Brito, O.M., Scorrano, L., 2009. Mitofusin-2 regulates mitochondrial and endoplasmic reticulum morphology and tethering: the role of Ras. Mitochondrion 9, 222–226.
Delettre, C., Lenaers, G., Griffoin, J.M., Gigarel, N., Lorenzo, C., Belenguer, P., Pelloquin, L., Grosgeorge, J., Turc-Carel, C., Perret, E., Astarie-Dequeker, C., Lasquellec, L., Arnaud, B., Ducommun, B., Kaplan, J., Hamel, C.P., 2000. Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. Nat. Genet. 26, 207–210.
Dell'agnello, C., Leo, S., Agostino, A., Szabadkai, G., Tiveron, C., Zulian, A., Prelle, A., Roubertoux, P., Rizzuto, R., Zeviani, M., 2007. Increased longevity and refractoriness to Ca(2+)-dependent neurodegeneration in Surf1 knockout mice. Hum. Mol. Genet. 16, 431–444.
DeVay, R.M., Dominguez-Ramirez, L., Lackner, L.L., Hoppins, S., Stahlberg, H., Nunnari, J., 2009. Coassembly of Mgm1 isoforms requires cardiolipin and mediates mitochondrial inner membrane fusion. J. Cell Biol. 186, 793–803.
Dietz, J.V., Bohovych, I., Viana, M.P., Khalimonchuk, O., 2019. Proteolytic regulation of mitochondrial dynamics. Mitochondrion 49, 289–304.
Dillin, A., Hsu, A.L., Arantes-Oliveira, N., Lehrer-Graiwer, J., Hsin, H., Fraser, A.G., Kamath, R.S., Ahringer, J., Kenyon, C., 2002. Rates of behavior and aging specified by mitochondrial function during development. Science 298, 2398–2401.
Ding, W.X., Yin, X.M., 2012. Mitophagy: mechanisms, pathophysiological roles, and analysis. Biol. Chem. 393, 547–564.
Durieux, J., Wolff, S., Dillin, A., 2011. The cell-non-autonomous nature of electron transport chain-mediated longevity. Cell 144, 79–91.
El Fissi, N., Rojo, M., Aouane, A., Karatas, E., Poliacikova, G., David, C., Royet, J., Rival, T., 2018. Mitofusin gain and loss of function drive pathogenesis in Drosophila models of CMT2A neuropathy. EMBO Rep. 19.
Finley, L.W., Lee, J., Souza, A., Desquiret-Dumas, V., Bullock, K., Rowe, G.C., Procaccio, V., Clish, C.B., Arany, Z., Haigis, M.C., 2012. Skeletal muscle transcriptional coactivator PGC-1alpha mediates mitochondrial, but not metabolic, changes during calorie restriction. Proc. Natl. Acad. Sci. U. S. A. 109, 2931–2936.
Fontana, L., Partridge, L., Longo, V.D., 2010. Extending healthy life span–from yeast to humans. Science 328, 321–326.
Frank, S., Gaume, B., Bergmann-Leitner, E.S., Leitner, W.W., Robert, E.G., Catez, F., Smith, C.L., Youle, R.J., 2001. The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. Dev. Cell 1, 515–525.
Friedman, J.R., Lackner, L.L., West, M., DiBenedetto, J.R., Nunnari, J., Voeltz, G.K., 2011. ER tubules mark sites of mitochondrial division. Science 334, 358–362.
Furukawa, K., Innokentev, A., Kanki, T., 2019. Regulatory mechanisms of mitochondrial autophagy: lessons from yeast. Front. Plant Sci. 10, 1479.
Galvan, D.L., Long, J., Green, N., Chang, B.H., Lin, J.S., Schumacker, P., Truong, L.D., Overbeek, P., Danesh, F.R., 2019. Drp1S600 phosphorylation regulates mitochondrial fission and progression of nephropathy in diabetic mice. J. Clin. Invest. 129, 2807–2823.
Gan, K.X., Wang, C., Chen, J.H., Zhu, C.J., Song, G.Y., 2013. Mitofusin-2 ameliorates high-fat diet-induced insulin resistance in liver of rats. World J. Gastroenterol. 19, 1572–1581.
Gatica, D., Lahiri, V., Klionsky, D.J., 2018. Cargo recognition and degradation by selective autophagy. Nat. Cell Biol. 20, 233–242.
Gegg, M.E., Cooper, J.M., Chau, K.Y., Rojo, M., Schapira, A.H., Taanman, J.W., 2010. Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Hum. Mol. Genet. 19, 4861–4870.
Gomes, L.C., Di Benedetto, G., Scorrano, L., 2011. During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. Nat. Cell Biol. 13, 589–598.
Gorgoulis, V., Adams, P.D., Alimonti, A., Bennett, D.C., Bischof, O., Bishop, C., Campisi, J., Collado, M., Evangelou, K., Ferbeyre, G., Gil, J., Hara, E., Krizhanovsky, V., Jurk, D., Maier, A.B., Narita, M., Niedernhofer, L., Passos, J.F., Robbins, P.D., Schmitt, C.A., Sedivy, J., Vougas, K., von Zglinicki, T., Zhou, D., Serrano, M., Demaria, M., 2019. Cellular senescence: defining a path forward. Cell 179, 813–827.
Hamacher-Brady, A., Brady, N.R., Logue, S.E., Sayen, M.R., Jinno, M., Kirshenbaum, L.A., Gottlieb, R.A., Gustafsson, A.B., 2007. Response to myocardial ischemia/reperfusion injury involves Bnip3 and autophagy. Cell Death Differ. 14, 146–157.
Harper, J.W., Ordureau, A., Heo, J.M., 2018. Building and decoding ubiquitin chains for mitophagy. Nat. Rev. Mol. Cell Biol. 19, 93–108.
Haynes, C.M., Ron, D., 2010. The mitochondrial UPR - protecting organelle protein homeostasis. J. Cell. Sci. 123, 3849–3855.
Horbay, R., Bilyy, R., 2016. Mitochondrial dynamics during cell cycling. Apoptosis 21, 1327–1335.
Houtkooper, R.H., Williams, R.W., Auwerx, J., 2010. Metabolic networks of longevity. Cell 142, 9–14.
Houtkooper, R.H., Mouchiroud, L., Ryu, D., Moullan, N., Katsyuba, E., Knott, G., Williams, R.W., Auwerx, J., 2013. Mitonuclear protein imbalance as a conserved longevity mechanism. Nature 497, 451–457.
Huang, S., Wang, Y., Gan, X., Fang, D., Zhong, C., Wu, L., Hu, G., Sosunov, A.A., McKhann, G.M., Yu, H., Yan, S.S., 2015. Drp1-mediated mitochondrial abnormalities link to synaptic injury in diabetes model. Diabetes 64, 1728–1742.
Hudson, G., Amati-Bonneau, P., Blakely, E.L., Stewart, J.D., He, L., Schaefer, A.M., Griffiths, P.G., Ahlqvist, K., Suomalainen, A., Reynier, P., McFarland, R., Turnbull, D.M., Chinnery, P.F., Taylor, R.W., 2008. Mutation of OPA1 causes dominant optic atrophy with external ophthalmoplegia, ataxia, deafness and multiple mitochondrial DNA deletions: a novel disorder of mtDNA maintenance. Brain 131, 329–337.
Ichishita, R., Tanaka, K., Sugiura, Y., Sayano, T., Mihara, K., Oka, T., 2008. An RNAi screen for mitochondrial proteins required to maintain the morphology of the organelle in *Caenorhabditis elegans*. J. Biochem. 143, 449–454.
Ikeda, Y., Shirakabe, A., Maejima, Y., Zhai, P., Sciarretta, S., Toli, J., Nomura, M., Mihara, K., Egashira, K., Ohishi, M., Abdellatif, M., Sadoshima, J., 2015. Endogenous Drp1 mediates mitochondrial autophagy and protects the heart against energy stress. Circ. Res. 116, 264–278.
Ingerman, E., Perkins, E.M., Marino, M., Mears, J.A., McCaffery, J.M., Hinshaw, J.E., Nunnari, J., 2005. Dnm1 forms spirals that are structurally tailored to fit mitochondria. J. Cell Biol. 170, 1021–1027.
Ishihara, N., Nomura, M., Jofuku, A., Kato, H., Suzuki, S.O., Masuda, K., Otera, H., Nakanishi, Y., Nonaka, I., Goto, Y., Taguchi, N., Morinaga, H., Maeda, M., Takayanagi, R., Yokota, S., Mihara, K., 2009. Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. Nat. Cell Biol. 11, 958–966.
Jensen, M.B., Jasper, H., 2014. Mitochondrial proteostasis in the control of aging and longevity. Cell Metab. 20, 214–225.
Jheng, H.F., Tsai, P.J., Guo, S.M., Kuo, L.H., Chang, C.S., Su, I.J., Chang, C.R., Tsai, Y.S., 2012. Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. Mol. Cell. Biol. 32, 309–319.
Jhun, B.S., J.O.U, Adaniya, S.M., Cypress, M.W., Yoon, Y., 2018. Adrenergic regulation of Drp1-Driven mitochondrial fission in cardiac physio-pathology. Antioxidants Basel (Basel) 7.
Jiang, H.C., Hsu, J.M., Yen, C.P., Chao, C.C., Chen, R.H., Pan, C.L., 2015. Neural activity and CaMKII protect mitochondria from fragmentation in aging *Caenorhabditis elegans* neurons. Proc. Natl. Acad. Sci. U. S. A. 112, 8768–8773.
Jin, C., Li, J., Green, C.D., Yu, X., Tang, X., Han, D., Xian, B., Wang, D., Huang, X., Cao, X., Yan, Z., Hou, L., Liu, J., Shukeir, N., Khaitovich, P., Chen, C.D., Zhang, H., Jenuwein, T., Han, J.D., 2011. Histone demethylase UTX-1 regulates *C. Elegans* life span by targeting the insulin/IGF-1 signaling pathway. Cell Metab. 14, 161–172.
Kageyama, Y., Hoshijima, M., Seo, K., Bedja, D., Sysa-Shah, P., Andrabi, S.A., Chen, W., Hoke, A., Dawson, V.L., Dawson, T.M., Gabrielson, K., Kass, D.A., Iijima, M., Sesaki, H., 2014. Parkin-independent mitophagy requires Drp1 and maintains the integrity of mammalian heart and brain. EMBO J. 33, 2798–2813.
Kanazawa, T., Zappaterra, M.D., Hasegawa, A., Wright, A.P., Newman-Smith, E.D., Buttle, K.F., McDonald, K., Mannella, C.A., van der Bliek, A.M., 2008. The *C. Elegans* Opa1 homologue EAT-3 is essential for resistance to free radicals. PLoS Genet. 4, e1000022.
Kanki, T., Wang, K., Baba, M., Bartholomew, C.R., Lynch-Day, M.A., Du, Z., Geng, J., Mao, K., Yang, Z., Yen, W.L., Klionsky, D.J., 2009. A genomic screen for yeast mutants defective in selective mitochondria autophagy. Mol. Biol. Cell 20, 4730–4738.
Kanki, T., Furukawa, K., Yamashita, S., 2015. Mitophagy in yeast: molecular mechanisms and physiological role. Biochim. Biophys. Acta 1853, 2756–2765.
Khaminets, A., Behl, C., Dikic, I., 2016. Ubiquitin-dependent and independent signals in selective autophagy. Trends Cell Biol. 26, 6–16.
Kijima, K., Numakura, C., Izumino, H., Umetsu, K., Nezu, A., Shiiki, T., Ogawa, M., Ishizaki, Y., Kitamura, T., Shozawa, Y., Hayasaka, K., 2005. Mitochondrial GTPase mitofusin 2 mutation in Charcot-Marie-Tooth neuropathy type 2A. Hum. Genet. 116, 23–27.
Kim, D.I., Lee, K.H., Gabr, A.A., Choi, G.E., Kim, J.S., Ko, S.H., Han, H.J., 2016. Abeta-Induced Drp1 phosphorylation through Akt activation promotes excessive mitochondrial fission leading to neuronal apoptosis. Biochim. Biophys. Acta 1863, 2820–2834.
Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y., Shimizu, N., 1998. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392, 605–608.
Koshiba, T., Detmer, S.A., Kaiser, J.T., Chen, H., McCaffery, J.M., Chan, D.C., 2004. Structural basis of mitochondrial tethering by mitofusin complexes. Science 305, 858–862.
Kujoth, G.C., Hiona, A., Pugh, T.D., Someya, S., Panzer, K., Wohlgemuth, S.E., Hofer, T., Seo, A.Y., Sullivan, R., Jobling, W.A., Morrow, J.D., Van Remmen, H., Sedivy, J.M., Yamasoba, T., Tanokura, M., Weindruch, R., Leeuwenburgh, C., Prolla, T.A., 2005. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. Science 309, 481–484.
Kulkarni, S.S., Joffraud, M., Boutant, M., Ratajczak, J., Gao, A.W., Maclachlan, C., Hernandez-Alvarez, M.I., Raymond, F., Metairon, S., Descombes, P., Houtkooper, R.H., Zorzano, A., Canto, C., 2016. Mfn1 deficiency in the liver protects against diet-induced insulin resistance and enhances the hypoglycemic effect of metformin. Diabetes 65, 3552–3560.
Labrousse, A.M., Zappaterra, M.D., Rube, D.A., van der Bliek, A.M., 1999. *C. Elegans* dynamin-related protein DRP-1 controls severing of the mitochondrial outer membrane. Mol. Cell 4, 815–826.
Leduc-Gaudet, J.P., Picard, M., St-Jean Pelletier, F., Sgarioto, N., Auger, M.J., Vallee, J., Robitaille, R., St-Pierre, D.H., Gouspillou, G., 2015. Mitochondrial morphology is altered in atrophied skeletal muscle of aged mice. Oncotarget 6, 17923–17937.
Lee, S.S., Lee, R.Y., Fraser, A.G., Kamath, R.S., Ahringer, J., Ruvkun, G., 2003. A systematic RNAi screen identifies a critical role for mitochondria in *C. Elegans* longevity. Nat. Genet. 33, 40–48.
Lee, S., Jeong, S.Y., Lim, W.C., Kim, S., Park, Y.Y., Sun, X., Youle, R.J., Cho, H., 2007. Mitochondrial fission and fusion mediators, hFis1 and OPA1, modulate cellular

senescence. J. Biol. Chem. 282, 22977–22983.
Lee, S., Park, Y.Y., Kim, S.H., Nguyen, O.T., Yoo, Y.S., Chan, G.K., Sun, X., Cho, H., 2014. Human mitochondrial Fis1 links to cell cycle regulators at G2/M transition. Cell. Mol. Life Sci. 71, 711–725.
Lewis, S.C., Uchiyama, L.F., Nunnari, J., 2016. ER-mitochondria contacts couple mtDNA synthesis with mitochondrial division in human cells. Science 353 aaf5549.
Liesa, M., Shirihai, O.S., 2013. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab. 17, 491–506.
Liesa, M., Palacin, M., Zorzano, A., 2009. Mitochondrial dynamics in mammalian health and disease. Physiol. Rev. 89, 799–845.
Liesa, M., Van der Bliek, A., Shirihai, O.S., 2019. To Fis or not to Fuse? This is the question!. EMBO J. 38.
Linnane, A.W., Marzuki, S., Ozawa, T., Tanaka, M., 1989. Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. Lancet 1, 642–645.
Liu, X., Jiang, N., Hughes, B., Bigras, E., Shoubridge, E., Hekimi, S., 2005. Evolutionary conservation of the clk-1-dependent mechanism of longevity: loss of mclk1 increases cellular fitness and lifespan in mice. Genes Dev. 19, 2424–2434.
Liu, X., Weaver, D., Shirihai, O., Hajnoczky, G., 2009. Mitochondrial' kiss-and-run': interplay between mitochondrial motility and fusion-fission dynamics. EMBO J. 28, 3074–3089.
Liu, L., Feng, D., Chen, G., Chen, M., Zheng, Q., Song, P., Ma, Q., Zhu, C., Wang, R., Qi, W., Huang, L., Xue, P., Li, B., Wang, X., Jin, H., Wang, J., Yang, F., Liu, P., Zhu, Y., Sui, S., Chen, Q., 2012. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat. Cell Biol. 14, 177–185.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Loson, O.C., Song, Z., Chen, H., Chan, D.C., 2013. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol. Biol. Cell 24, 659–667.
Lutz, A.K., Exner, N., Fett, M.E., Schlehe, J.S., Kloos, K., Lammermann, K., Brunner, B., Kurz-Drexler, A., Vogel, F., Reichert, A.S., Bouman, L., Vogt-Weisenhorn, D., Wurst, W., Tatzelt, J., Haass, C., Winklhofer, K.F., 2009. Loss of parkin or PINK1 function increases Drp1-dependent mitochondrial fragmentation. J. Biol. Chem. 284, 22938–22951.
Malka, F., Guillery, O., Cifuentes-Diaz, C., Guillou, E., Belenguer, P., Lombes, A., Rojo, M., 2005. Separate fusion of outer and inner mitochondrial membranes. EMBO Rep. 6, 853–859.
Manczak, M., Reddy, P.H., 2012. Abnormal interaction between the mitochondrial fission protein Drp1 and hyperphosphorylated tau in Alzheimer's disease neurons: implications for mitochondrial dysfunction and neuronal damage. Hum. Mol. Genet. 21, 2538–2547.
Marchi, S., Patergnani, S., Pinton, P., 2014. The endoplasmic reticulum-mitochondria connection: one touch, multiple functions. Biochim. Biophys. Acta 1837, 461–469.
Matsuda, N., Sato, S., Shiba, K., Okatsu, K., Saisho, K., Gautier, C.A., Sou, Y.S., Saiki, S., Kawajiri, S., Sato, F., Kimura, M., Komatsu, M., Hattori, N., Tanaka, K., 2010. PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. J. Cell Biol. 189, 211–221.
McLelland, G.L., Soubannier, V., Chen, C.X., McBride, H.M., Fon, E.A., 2014. Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. EMBO J. 33, 282–295.
Mendl, N., Occhipinti, A., Muller, M., Wild, P., Dikic, I., Reichert, A.S., 2011. Mitophagy in yeast is independent of mitochondrial fission and requires the stress response gene WHI2. J. Cell. Sci. 124, 1339–1350.
Mishra, P., Chan, D.C., 2014. Mitochondrial dynamics and inheritance during cell division, development and disease. Nat. Rev. Mol. Cell Biol. 15, 634–646.
Misko, A., Jiang, S., Wegorzewska, I., Milbrandt, J., Baloh, R.H., 2010. Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with the Miro/Milton complex. J. Neurosci. 30, 4232–4240.
Mitra, K., Wunder, C., Roysam, B., Lin, G., Lippincott-Schwartz, J., 2009. A hyperfused mitochondrial state achieved at G1-S regulates cyclin E buildup and entry into S phase. Proc. Natl. Acad. Sci. U. S. A. 106, 11960–11965.
Moehle, E.A., Shen, K., Dillin, A., 2019. Mitochondrial proteostasis in the context of cellular and organismal health and aging. J. Biol. Chem. 294, 5396–5407.
Moore, T.M., Zhou, Z., Cohn, W., Norheim, F., Lin, A.J., Kalajian, N., Strumwasser, A.R., Cory, K., Whitney, K., Ho, T., Ho, T., Lee, J.L., Rucker, D.H., Shirihai, O., van der Bliek, A.M., Whitelegge, J.P., Seldin, M.M., Lusis, A.J., Lee, S., Drevon, C.A., Mahata, S.K., Turcotte, L.P., Hevener, A.L., 2019. The impact of exercise on mitochondrial dynamics and the role of Drp1 in exercise performance and training adaptations in skeletal muscle. Mol. Metab. 21, 51–67.
Morita, M., Prudent, J., Basu, K., Goyon, V., Katsumura, S., Hulea, L., Pearl, D., Siddiqui, N., Strack, S., McGuirk, S., St-Pierre, J., Larsson, O., Topisirovic, I., Vali, H., McBride, H.M., Bergeron, J.J., Sonenberg, N., 2017. mTOR controls mitochondrial dynamics and cell survival via MTFP1. Mol. Cell 67 (922–935), e925.
Mourier, A., Motori, E., Brandt, T., Lagouge, M., Atanassov, I., Galinier, A., Rappl, G., Brodesser, S., Hultenby, K., Dieterich, C., Larsson, N.G., 2015. Mitofusin 2 is required to maintain mitochondrial coenzyme Q levels. J. Cell Biol. 208, 429–442.
Murakawa, T., Yamaguchi, O., Hashimoto, A., Hikoso, S., Takeda, T., Oka, T., Yasui, H., Ueda, H., Akazawa, Y., Nakayama, H., Taneike, M., Misaka, T., Omiya, S., Shah, A.M., Yamamoto, A., Nishida, K., Ohsumi, Y., Okamoto, K., Sakata, Y., Otsu, K., 2015. Bcl-2-like protein 13 is a mammalian Atg32 homologue that mediates mitophagy and mitochondrial fragmentation. Nat. Commun. 6, 7527.
Nakada, K., Inoue, K., Ono, T., Isobe, K., Ogura, A., Goto, Y.I., Nonaka, I., Hayashi, J.I., 2001. Inter-mitochondrial complementation: mitochondria-specific system preventing mice from expression of disease phenotypes by mutant mtDNA. Nat. Med. 7, 934–940.
Nakada, K., Sato, A., Hayashi, J., 2009. Mitochondrial functional complementation in mitochondrial DNA-based diseases. Int. J. Biochem. Cell Biol. 41, 1907–1913.
Naon, D., Zaninello, M., Giacomello, M., Varanita, T., Grespi, F., Lakshminaranayan, S., Serafini, A., Semenzato, M., Herkenne, S., Hernandez-Alvarez, M.I., Zorzano, A., De Stefani, D., Dorn 2nd, G.W., Scorrano, L., 2016. Critical reappraisal confirms that Mitofusin 2 is an endoplasmic reticulum-mitochondria tether. Proc. Natl. Acad. Sci. U. S. A. 113, 11249–11254.
Neuspiel, M., Schauss, A.C., Braschi, E., Zunino, R., Rippstein, P., Rachubinski, R.A., Andrade-Navarro, M.A., McBride, H.M., 2008. Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. Curr. Biol. 18, 102–108.
Ono, T., Isobe, K., Nakada, K., Hayashi, J.I., 2001. Human cells are protected from mitochondrial dysfunction by complementation of DNA products in fused mitochondria. Nat. Genet. 28, 272–275.
Ordureau, A., Sarraf, S.A., Duda, D.M., Heo, J.M., Jedrychowski, M.P., Sviderskiy, V.O., Olszewski, J.L., Koerber, J.T., Xie, T., Beausoleil, S.A., Wells, J.A., Gygi, S.P., Schulman, B.A., Harper, J.W., 2014. Quantitative proteomics reveal a feedforward mechanism for mitochondrial PARKIN translocation and ubiquitin chain synthesis. Mol. Cell 56, 360–375.
Palikaras, K., Lionaki, E., Tavernarakis, N., 2015. Coordination of mitophagy and mitochondrial biogenesis during ageing in *C. Elegans*. Nature 521, 525–528.
Palikaras, K., Daskalaki, I., Markaki, M., Tavernarakis, N., 2017. Mitophagy and age-related pathologies: development of new therapeutics by targeting mitochondrial turnover. Pharmacol. Ther. 178, 157–174.
Papanicolaou, K.N., Khairallah, R.J., Ngoh, G.A., Chikando, A., Luptak, I., O'Shea, K.M., Riley, D.D., Lugus, J.J., Colucci, W.S., Lederer, W.J., Stanley, W.C., Walsh, K., 2011. Mitofusin-2 maintains mitochondrial structure and contributes to stress-induced permeability transition in cardiac myocytes. Mol. Cell. Biol. 31, 1309–1328.
Papanicolaou, K.N., Kikuchi, R., Ngoh, G.A., Coughlan, K.A., Dominguez, I., Stanley, W.C., Walsh, K., 2012a. Mitofusins 1 and 2 are essential for postnatal metabolic remodeling in heart. Circ. Res. 111, 1012–1026.
Papanicolaou, K.N., Ngoh, G.A., Dabkowski, E.R., O'Connell, K.A., Ribeiro Jr., R.F., Stanley, W.C., Walsh, K., 2012b. Cardiomyocyte deletion of mitofusin-1 leads to mitochondrial fragmentation and improves tolerance to ROS-induced mitochondrial dysfunction and cell death. Am. J. Physiol. Heart Circ. Physiol. 302, H167–179.
Parra, V., Verdejo, H.E., Iglewski, M., Del Campo, A., Troncoso, R., Jones, D., Zhu, Y., Kuzmicic, J., Pennanen, C., Lopez-Crisosto, C., Jana, F., Ferreira, J., Noguera, E., Chiong, M., Bernlohr, D.A., Klip, A., Hill, J.A., Rothermel, B.A., Abel, E.D., Zorzano, A., Lavandero, S., 2014. Insulin stimulates mitochondrial fusion and function in cardiomyocytes via the Akt-mTOR-NFkappaB-Opa-1 signaling pathway. Diabetes 63, 75–88.
Payne, M., Yang, Z., Katz, B.J., Warner, J.E., Weight, C.J., Zhao, Y., Pearson, E.D., Treft, R.L., Hillman, T., Kennedy, R.J., Meire, F.M., Zhang, K., 2004. Dominant optic atrophy, sensorineural hearing loss, ptosis, and ophthalmoplegia: a syndrome caused by a missense mutation in OPA1. Am. J. Ophthalmol. 138, 749–755.
Pickles, S., Vigie, P., Youle, R.J., 2018. Mitophagy and quality control mechanisms in mitochondrial maintenance. Curr. Biol. 28, R170–R185.
Pryde, K.R., Smith, H.L., Chau, K.Y., Schapira, A.H., 2016. PINK1 disables the anti-fission machinery to segregate damaged mitochondria for mitophagy. J. Cell Biol. 213, 163–171.
Qi, Y., Yan, L., Yu, C., Guo, X., Zhou, X., Hu, X., Huang, X., Rao, Z., Lou, Z., Hu, J., 2016. Structures of human mitofusin 1 provide insight into mitochondrial tethering. J. Cell Biol. 215, 621–629.
Qian, W., Choi, S., Gibson, G.A., Watkins, S.C., Bakkenist, C.J., Van Houten, B., 2012. Mitochondrial hyperfusion induced by loss of the fission protein Drp1 causes ATM-dependent G2/M arrest and aneuploidy through DNA replication stress. J. Cell. Sci. 125, 5745–5757.
Quinsay, M.N., Thomas, R.L., Lee, Y., Gustafsson, A.B., 2010. Bnip3-mediated mitochondrial autophagy is independent of the mitochondrial permeability transition pore. Autophagy 6, 855–862.
Rambold, A.S., Kostelecky, B., Elia, N., Lippincott-Schwartz, J., 2011. Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. Proc. Natl. Acad. Sci. U. S. A. 108, 10190–10195.
Ramirez, S., Gomez-Valades, A.G., Schneeberger, M., Varela, L., Haddad-Tovolli, R., Altirriba, J., Noguera, E., Drougard, A., Flores-Martinez, A., Imbernon, M., Chivite, I., Pozo, M., Vidal-Itriago, A., Garcia, A., Cervantes, S., Gasa, R., Nogueiras, R., Gama-Perez, P., Garcia-Roves, P.M., Cano, D.A., Knauf, C., Servitja, J.M., Horvath, T.L., Gomis, R., Zorzano, A., Claret, M., 2017. Mitochondrial dynamics mediated by mitofusin 1 is required for POMC neuron glucose-sensing and insulin release control. Cell Metab. 25 (1390–1399), e1396.
Rana, A., Oliveira, M.P., Khamoui, A.V., Aparicio, R., Rera, M., Rossiter, H.B., Walker, D.W., 2017. Promoting Drp1-mediated mitochondrial fission in midlife prolongs healthy lifespan of *Drosophila melanogaster*. Nat. Commun. 8, 448.
Rappold, P.M., Cui, M., Grima, J.C., Fan, R.Z., de Mesy-Bentley, K.L., Chen, L., Zhuang, X., Bowers, W.J., Tieu, K., 2014. Drp1 inhibition attenuates neurotoxicity and dopamine release deficits in vivo. Nat. Commun. 5, 5244.
Regmi, S.G., Rolland, S.G., Conradt, B., 2014. Age-dependent changes in mitochondrial morphology and volume are not predictors of lifespan. Aging (Albany NY) 6, 118–130.
Rogov, V.V., Suzuki, H., Marinkovic, M., Lang, V., Kato, R., Kawasaki, M., Buljubasic, M.,

Sprung, M., Rogova, N., Wakatsuki, S., Hamacher-Brady, A., Dotsch, V., Dikic, I., Brady, N.R., Novak, I., 2017. Phosphorylation of the mitochondrial autophagy receptor Nix enhances its interaction with LC3 proteins. Sci. Rep. 7, 1131.
Rosca, M.G., Hoppel, C.L., 2010. Mitochondria in heart failure. Cardiovasc. Res. 88, 40–50.
Rossignol, R., Gilkerson, R., Aggeler, R., Yamagata, K., Remington, S.J., Capaldi, R.A., 2004. Energy substrate modulates mitochondrial structure and oxidative capacity in cancer cells. Cancer Res. 64, 985–993.
Rujiviphat, J., Meglei, G., Rubinstein, J.L., McQuibban, G.A., 2009. Phospholipid association is essential for dynamin-related protein Mgm1 to function in mitochondrial membrane fusion. J. Biol. Chem. 284, 28682–28686.
Ryu, D., Mouchiroud, L., Andreux, P.A., Katsyuba, E., Moullan, N., Nicolet-Dit-Felix, A.A., Williams, E.G., Jha, P., Lo Sasso, G., Huzard, D., Aebischer, P., Sandi, C., Rinsch, C., Auwerx, J., 2016. Urolithin A induces mitophagy and prolongs lifespan in *C. Elegans* and increases muscle function in rodents. Nat. Med. 22, 879–888.
Salazar-Roa, M., Malumbres, M., 2017. Fueling the cell division cycle. Trends Cell Biol. 27, 69–81.
Santel, A., Fuller, M.T., 2001. Control of mitochondrial morphology by a human mitofusin. J. Cell. Sci. 114, 867–874.
Santel, A., Frank, S., Gaume, B., Herrler, M., Youle, R.J., Fuller, M.T., 2003. Mitofusin-1 protein is a generally expressed mediator of mitochondrial fusion in mammalian cells. J. Cell. Sci. 116, 2763–2774.
Scheckhuber, C.Q., Erjavec, N., Tinazli, A., Hamann, A., Nystrom, T., Osiewacz, H.D., 2007. Reducing mitochondrial fission results in increased life span and fitness of two fungal ageing models. Nat. Cell Biol. 9, 99–105.
Schiavi, A., Maglioni, S., Palikaras, K., Shaik, A., Strappazzon, F., Brinkmann, V., Torgovnick, A., Castelein, N., De Henau, S., Braeckman, B.P., Cecconi, F., Tavernarakis, N., Ventura, N., 2015. Iron-starvation-Induced mitophagy mediates lifespan extension upon mitochondrial stress in *C. Elegans*. Curr. Biol. 25, 1810–1822.
Schieke, S.M., McCoy Jr., J.P., Finkel, T., 2008. Coordination of mitochondrial bioenergetics with G1 phase cell cycle progression. Cell Cycle 7, 1782–1787.
Schmitt, K., Grimm, A., Dallmann, R., Oettinghaus, B., Restelli, L.M., Witzig, M., Ishihara, N., Mihara, K., Ripperger, J.A., Albrecht, U., Frank, S., Brown, S.A., Eckert, A., 2018. Circadian control of DRP1 activity regulates mitochondrial dynamics and bioenergetics. Cell Metab. 27 (657–666), e655.
Schrader, M., Costello, J.L., Godinho, L.F., Azadi, A.S., Islinger, M., 2016. Proliferation and fission of peroxisomes - an update. Biochim. Biophys. Acta 1863, 971–983.
Schrepfer, E., Scorrano, L., 2016. Mitofusins, from mitochondria to metabolism. Mol. Cell 61, 683–694.
Scorrano, L., 2013. Keeping mitochondria in shape: a matter of life and death. Eur. J. Clin. Invest. 43, 886–893.
Sebastian, D., Hernandez-Alvarez, M.I., Segales, J., Sorianello, E., Munoz, J.P., Sala, D., Waget, A., Liesa, M., Paz, J.C., Gopalacharyulu, P., Oresic, M., Pich, S., Burcelin, R., Palacin, M., Zorzano, A., 2012. Mitofusin 2 (Mfn2) links mitochondrial and endoplasmic reticulum function with insulin signaling and is essential for normal glucose homeostasis. Proc. Natl. Acad. Sci. U. S. A. 109, 5523–5528.
Sebastian, D., Sorianello, E., Segales, J., Irazoki, A., Ruiz-Bonilla, V., Sala, D., Planet, E., Berenguer-Llergo, A., Munoz, J.P., Sanchez-Feutrie, M., Plana, N., Hernandez-Alvarez, M.I., Serrano, A.L., Palacin, M., Zorzano, A., 2016. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. EMBO J. 35, 1677–1693.
Sebastián, D., Zorzano, A., 2018. Mitochondrial dynamics and metabolic homeostasis. Curr. Opin. Physiol. 3, 34–40.
Shirendeb, U.P., Calkins, M.J., Manczak, M., Anekonda, V., Dufour, B., McBride, J.L., Mao, P., Reddy, P.H., 2011. Mutant huntingtin's interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington's disease. Hum. Mol. Genet. 21, 406–420.
Smirnova, E., Griparic, L., Shurland, D.L., van der Bliek, A.M., 2001. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Mol. Biol. Cell 12, 2245–2256.
Song, Z., Ghochani, M., McCaffery, J.M., Frey, T.G., Chan, D.C., 2009. Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion. Mol. Biol. Cell 20, 3525–3532.
Song, M., Mihara, K., Chen, Y., Scorrano, L., Dorn 2nd, G.W., 2015. Mitochondrial fission and fusion factors reciprocally orchestrate mitophagic culling in mouse hearts and cultured fibroblasts. Cell Metab. 21, 273–286.
Song, M., Franco, A., Fleischer, J.A., Zhang, L., Dorn 2nd, G.W., 2017. Abrogating mitochondrial dynamics in mouse hearts accelerates mitochondrial senescence. Cell Metab. 26 (872–883), e875.
Soto-Heredero, G., Baixauli, F., Mittelbrunn, M., 2017. Interorganelle communication between mitochondria and the endolysosomal system. Front. Cell Dev. Biol. 5, 95.
Soubannier, V., McLelland, G.L., Zunino, R., Braschi, E., Rippstein, P., Fon, E.A., McBride, H.M., 2012a. A vesicular transport pathway shuttles cargo from mitochondria to lysosomes. Curr. Biol. 22, 135–141.
Soubannier, V., Rippstein, P., Kaufman, B.A., Shoubridge, E.A., McBride, H.M., 2012b. Reconstitution of mitochondria derived vesicle formation demonstrates selective enrichment of oxidized cargo. PLoS One 7, e52830.
Sugiura, A., McLelland, G.L., Fon, E.A., McBride, H.M., 2014. A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J. 33, 2142–2156.
Sun, N., Youle, R.J., Finkel, T., 2016. The mitochondrial basis of aging. Mol. Cell 61, 654–666.
Taguchi, N., Ishihara, N., Jofuku, A., Oka, T., Mihara, K., 2007. Mitotic phosphorylation of dynamin-related GTPase Drp1 participates in mitochondrial fission. J. Biol. Chem. 282, 11521–11529.
Tanaka, A., Cleland, M.M., Xu, S., Narendra, D.P., Suen, D.F., Karbowski, M., Youle, R.J., 2010. Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. J. Cell Biol. 191, 1367–1380.
Templeman, N.M., Murphy, C.T., 2018. Regulation of reproduction and longevity by nutrient-sensing pathways. J. Cell Biol. 217, 93–106.
Tilokani, L., Nagashima, S., Paupe, V., Prudent, J., 2018. Mitochondrial dynamics: overview of molecular mechanisms. Essays Biochem. 62, 341–360.
Tondera, D., Grandemange, S., Jourdain, A., Karbowski, M., Mattenberger, Y., Herzig, S., Da Cruz, S., Clerc, P., Raschke, I., Merkwirth, C., Ehses, S., Krause, F., Chan, D.C., Alexander, C., Bauer, C., Youle, R., Langer, T., Martinou, J.C., 2009. SLP-2 is required for stress-induced mitochondrial hyperfusion. EMBO J. 28, 1589–1600.
Toyama, E.Q., Herzig, S., Courchet, J., Lewis Jr., T.L., Loson, O.C., Hellberg, K., Young, N.P., Chen, H., Polleux, F., Chan, D.C., Shaw, R.J., 2016. Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. Science 351, 275–281.
Trewin, A.J., Berry, B.J., Wojtovich, A.P., 2018. Exercise and mitochondrial dynamics: keeping in shape with ROS and AMPK. Antioxidants Basel (Basel) 7.
Trifunovic, A., Wredenberg, A., Falkenberg, M., Spelbrink, J.N., Rovio, A.T., Bruder, C.E., Bohlooly, Y.M., Gidlof, S., Oldfors, A., Wibom, R., Tornell, J., Jacobs, H.T., Larsson, N.G., 2004. Premature ageing in mice expressing defective mitochondrial DNA polymerase. Nature 429, 417–423.
Twig, G., Elorza, A., Molina, A.J., Mohamed, H., Wikstrom, J.D., Walzer, G., Stiles, L., Haigh, S.E., Katz, S., Las, G., Alroy, J., Wu, M., Py, B.F., Yuan, J., Deeney, J.T., Corkey, B.E., Shirihai, O.S., 2008. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. EMBO J. 27, 433–446.
Vafai, S.B., Mootha, V.K., 2012. Mitochondrial disorders as windows into an ancient organelle. Nature 491, 374–383.
Valente, E.M., Abou-Sleiman, P.M., Caputo, V., Muqit, M.M., Harvey, K., Gispert, S., Ali, Z., Del Turco, D., Bentivoglio, A.R., Healy, D.G., Albanese, A., Nussbaum, R., Gonzalez-Maldonado, R., Deller, T., Salvi, S., Cortelli, P., Gilks, W.P., Latchman, D.S., Harvey, R.J., Dallapiccola, B., Auburger, G., Wood, N.W., 2004. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 304, 1158–1160.
van der Bliek, A.M., Shen, Q., Kawajiri, S., 2013. Mechanisms of mitochondrial fission and fusion. Cold Spring Harb. Perspect. Biol. 5.
Vance, J.M., 2000. The many faces of Charcot-Marie-Tooth disease. Arch. Neurol. 57, 638–640.
Vielhaber, S., Debska-Vielhaber, G., Peeva, V., Schoeler, S., Kudin, A.P., Minin, I., Schreiber, S., Dengler, R., Kollewe, K., Zuschratter, W., Kornblum, C., Zsurka, G., Kunz, W.S., 2013. Mitofusin 2 mutations affect mitochondrial function by mitochondrial DNA depletion. Acta Neuropathol. 125, 245–256.
Villa, E., Proics, E., Rubio-Patino, C., Obba, S., Zunino, B., Bossowski, J.P., Rozier, R.M., Chiche, J., Mondragon, L., Riley, J.S., Marchetti, S., Verhoeyen, E., Tait, S.W.G., Ricci, J.E., 2017. Parkin-independent mitophagy controls chemotherapeutic response in Cancer cells. Cell Rep. 20, 2846–2859.
Votruba, M., Moore, A.T., Bhattacharya, S.S., 1998. Clinical features, molecular genetics, and pathophysiology of dominant optic atrophy. J. Med. Genet. 35, 793–800.
Wai, T., Langer, T., 2016. Mitochondrial dynamics and metabolic regulation. Trends Endocrinol. Metab. 27, 105–117.
Wallace, D.C., 2005. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. Annu. Rev. Genet. 39, 359–407.
Wang, Q., Zhang, M., Torres, G., Wu, S., Ouyang, C., Xie, Z., Zou, M.H., 2017. Metformin Suppresses Diabetes-Accelerated Atherosclerosis via the Inhibition of Drp1-Mediated Mitochondrial Fission. Diabetes 66, 193–205.
Waterham, H.R., Koster, J., van Roermund, C.W., Mooyer, P.A., Wanders, R.J., Leonard, J.V., 2007. A lethal defect of mitochondrial and peroxisomal fission. N. Engl. J. Med. 356, 1736–1741.
Wei, H., Liu, L., Chen, Q., 2015. Selective removal of mitochondria via mitophagy: distinct pathways for different mitochondrial stresses. Biochim. Biophys. Acta 1853, 2784–2790.
Weir, H.J., Yao, P., Huynh, F.K., Escoubas, C.C., Goncalves, R.L., Burkewitz, K., Laboy, R., Hirschey, M.D., Mair, W.B., 2017. Dietary restriction and AMPK increase lifespan via mitochondrial network and peroxisome remodeling. Cell Metab. 26 (884–896), e885.
Wong, Y.C., Ysselstein, D., Krainc, D., 2018. Mitochondria-lysosome contacts regulate mitochondrial fission via RAB7 GTP hydrolysis. Nature 554, 382–386.
Xu, M., Pirtskhalava, T., Farr, J.N., Weigand, B.M., Palmer, A.K., Weivoda, M.M., Inman, C.L., Ogrodnik, M.B., Hachfeld, C.M., Fraser, D.G., Onken, J.L., Johnson, K.O., Verzosa, G.C., Langhi, L.G.P., Weigl, M., Giorgadze, N., LeBrasseur, N.K., Miller, J.D., Jurk, D., Singh, R.J., Allison, D.B., Ejima, K., Hubbard, G.B., Ikeno, Y., Cubro, H., Garovic, V.D., Hou, X., Weroha, S.J., Robbins, P.D., Niedernhofer, L.J., Khosla, S., Tchkonia, T., Kirkland, J.L., 2018. Senolytics improve physical function and increase lifespan in old age. Nat. Med. 24, 1246–1256.
Yamashita, S.I., Jin, X., Furukawa, K., Hamasaki, M., Nezu, A., Otera, H., Saigusa, T., Yoshimori, T., Sakai, Y., Mihara, K., Kanki, T., 2016. Mitochondrial division occurs concurrently with autophagosome formation but independently of Drp1 during mitophagy. J. Cell Biol. 215, 649–665.
Yang, C.C., Chen, D., Lee, S.S., Walter, L., 2011. The dynamin-related protein DRP-1 and the insulin signaling pathway cooperate to modulate *Caenorhabditis elegans* longevity. Aging Cell 10, 724–728.
Yoon, Y.S., Yoon, D.S., Lim, I.K., Yoon, S.H., Chung, H.Y., Rojo, M., Malka, F., Jou, M.J., Martinou, J.C., Yoon, G., 2006. Formation of elongated giant mitochondria in DFO-

induced cellular senescence: involvement of enhanced fusion process through modulation of Fis1. J. Cell. Physiol. 209, 468–480.
Yu, T., Robotham, J.L., Yoon, Y., 2006. Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. Proc. Natl. Acad. Sci. U. S. A. 103, 2653–2658.
Yu, R., Jin, S.B., Lendahl, U., Nister, M., Zhao, J., 2019. Human Fis1 regulates mitochondrial dynamics through inhibition of the fusion machinery. EMBO J. 38.
Yu-Wai-Man, P., Newman, N.J., 2017. Inherited eye-related disorders due to mitochondrial dysfunction. Hum. Mol. Genet. 26, R12–R20.
Zhang, Z., Wakabayashi, N., Wakabayashi, J., Tamura, Y., Song, W.J., Sereda, S., Clerc, P., Polster, B.M., Aja, S.M., Pletnikov, M.V., Kensler, T.W., Shirihai, O.S., Iijima, M., Hussain, M.A., Sesaki, H., 2011. The dynamin-related GTPase Opa1 is required for glucose-stimulated ATP production in pancreatic beta cells. Mol. Biol. Cell 22, 2235–2245.
Zhang, X., Wang, C., Song, G., Gan, K., Kong, D., Nie, Q., Ren, L., 2013. Mitofusion-2-mediated alleviation of insulin resistance in rats through reduction in lipid intermediate accumulation in skeletal muscle. J. Biomed. Sci. 20, 45.
Zhang, Q., Wu, X., Chen, P., Liu, L., Xin, N., Tian, Y., Dillin, A., 2018. The Mitochondrial Unfolded Protein Response Is Mediated Cell-Non-autonomously by Retromer-Dependent Wnt Signaling. Cell 174 (870-883), e817.
Zhang, Y., Lanjuin, A., Chowdhury, S.R., Mistry, M., Silva-Garcia, C.G., Weir, H.J., Lee, C.L., Escoubas, C.C., Tabakovic, E., Mair, W.B., 2019. Neuronal TORC1 modulates longevity via AMPK and cell nonautonomous regulation of mitochondrial dynamics in *C. Elegans*. Elife 8.
Ziviani, E., Tao, R.N., Whitworth, A.J., 2010. Drosophila parkin requires PINK1 for mitochondrial translocation and ubiquitinates mitofusin. Proc. Natl. Acad. Sci. U. S. A. 107, 5018–5023.
Zuchner, S., Mersiyanova, I.V., Muglia, M., Bissar-Tadmouri, N., Rochelle, J., Dadali, E.L., Zappia, M., Nelis, E., Patitucci, A., Senderek, J., Parman, Y., Evgrafov, O., Jonghe, P.D., Takahashi, Y., Tsuji, S., Pericak-Vance, M.A., Quattrone, A., Battaloglu, E., Polyakov, A.V., Timmerman, V., Schroder, J.M., Vance, J.M., 2004. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat. Genet. 36, 449–451.