HHS Public Access

Author manuscript

Toxicology. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Toxicology. 2017 November 01; 391: 42–53. doi:10.1016/j.tox.2017.07.019.

Mitochondrial fusion, fission, and mitochondrial toxicity Submitted for consideration for the Special Issue of Toxicology on "Chemical Mitochondrial Toxicity"

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Abstract

Mitochondrial dynamics are regulated by two sets of opposed processes: mitochondrial fusion and fission, and mitochondrial biogenesis and degradation (including mitophagy), as well as processes such as intracellular transport. These processes maintain mitochondrial homeostasis, regulate mitochondrial form, volume and function, and are increasingly understood to be critical components of the cellular stress response. Mitochondrial dynamics vary based on developmental stage and age, cell type, environmental factors, and genetic background. Indeed, many mitochondrial homeostasis genes are human disease genes. Emerging evidence indicates that deficiencies in these genes often sensitize to environmental exposures, yet can also be protective under certain circumstances. Inhibition of mitochondrial dynamics also affects elimination of irreparable mitochondrial DNA (mtDNA) damage and transmission of mtDNA mutations. We briefly review the basic biology of mitodynamic processes with a focus on mitochondrial fusion and fission, discuss what is known and unknown regarding how these processes respond to chemical and other stressors, and review the literature on interactions between mitochondrial toxicity and genetic variation in mitochondrial fusion and fission genes. Finally, we suggest areas for future research, including elucidating the full range of mitodynamic responses from low to high-level exposures, and from acute to chronic exposures; detailed examination of the physiological consequences of mitodynamic alterations in different cell types; mechanism-based testing of mitotoxicant interactions with interindividual variability in mitodynamics processes; and incorporating other environmental variables that affect mitochondria, such as diet and exercise.

Keywords

Mitochondrial fusion; mitochondrial fission; mitochondrial dynamics; mitochondrial toxicity; gene-environment interactions; mitochondrial homeostasis; mitochondrial DNA; biomarker

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Conflict of interest

The authors declare no conflict of interest.

1. Mitochondrial dynamics: fusion and fission, transport, biogenesis and mitophagy

Mitochondrial dynamics are critical in regulating morphology, number, subcellular distribution, and function. They are also critical in maintaining mitochondrial homeostasis in response to stress. The degree to which mitochondria are networked results from a dynamic equilibrium between fusion and fission, facilitated by movement of mitochondria within the cell. Similarly, the total mitochondrial content of a cell is a dynamic equilibrium between mitochondrial biogenesis (henceforth referred to as mitobiogenesis) and mitochondrial degradation, including mitophagy and other forms of mitochondrial recycling. Mitochondrial dynamics vary based on developmental stage and age, cell type, environmental factors, disease state, and genetic background. In this section, we provide a brief overview of these processes, with the goal of providing context for the subsequent sections; more detail can be found in the cited reviews. Many of the most critical proteins involved in these processes are important human disease genes; an incomplete list including the subset of these genes that is highlighted in this review is provided in Table 1. These diseases often exhibit variable severity and progression, suggesting a role for environmental factors (i.e., gene-environment interactions). Altered mitochondrial dynamics and morphology also occur in a variety of other diseases (Archer 2013; Babbar and Sheikh 2013), although causality is less clear in those cases.

1.1. Mitochondrial fusion and fission

Mitochondria fuse in a process that requires inner- and outer-mitochondrial membrane (IMM and OMM) GTPases (Van der Bliek et al. 2014). In humans, these proteins are named Optic atrophy 1 (OPA1; IMM) and Mitofusins 1 and 2 (MFN1 and MFN2; OMM). Loss of mitofusins blocks fusion of both the OMM and IMM, while loss of OPA1 blocks fusion of the IMM, but not the OMM (Song et al. 2009). Mitochondrial fission is mediated by several proteins, but the GTPase Dynamin related protein 1 (DRP1) is the most central, or at least best understood (Chan 2012). Fission does not require membrane potential (Twig et al. 2008a), and in fact can be triggered by low membrane potential (Section 2). The inner but not outer membrane fusion process is mitochondrial membrane potential-dependent (Van der Bliek et al. 2014), although loss of membrane potential may also lead to PARK2-mediated degradation of mitofusins, ultimately preventing fusion of mitochondria with low membrane potential with other healthier ones (Narendra et al. 2012). Regulation of mitochondrial fusion and fission has been reviewed in detail (Narendra et al. 2012; Van der Bliek et al. 2014). It should be noted that while our focus is on mitochondrial dynamics, these proteins may play roles in other cellular processes. For example, MFN2 is also involved in mitophagy (Chen and Dorn 2013) and in tethering mitochondria both to the endoplasmic reticulum, which is important for early stages of mitochondrial fission (de Brito and Scorrano 2008; Friedman et al. 2011), and to microtubules, permitting mitochondrial transport in neurons (Pareyson et al. 2015); OPA1 contributes to maintenance of cristae structure (Olichon et al. 2003) and may help anchor nucleoids to the IMM (Elachouri et al. 2011); and several fission proteins may also play a role in peroxisomal division (Chan 2012).

In cell culture, fusion and fission can occur within minutes or even seconds, particularly in the case of rapid stress-induced fission or transient, partial fusion events described as “kiss-and-run” (Dalmasso et al. 2017; Duarte et al. 2012; Liu et al. 2009). At the cellular level, mixing of contents between mitochondria can occur within an hour (Youle and van der Bliek 2012); however, there is also evidence that heterogeneous mitochondrial sub-populations persist within cells in some cases (Wikstrom et al. 2009). Genetic loss of mitochondrial fusion results in insufficient mixing of mitochondria within cells, causing dramatic mitochondrial heterogeneity in protein, mtDNA, and membrane potential (Mishra and Chan 2016). Fusion and fission may also serve to permit subcellular specialization of mitochondria, e.g. such that perinuclear mitochondria function differently than axonal mitochondria (Kowald and Kirkwood 2011). The relative rates of these two processes at any given time in specific tissues are not well understood (Mishra and Chan 2016), but presumably act in an integrated fashion to regulate both morphology and the potential rate at which morphology can be altered. This may also relate to the rate of movement of mitochondria in the cells, estimated to be ~0.1–0.2 μm/second in the perinuclear region and up to ~0.7 μm/second in the cytosol and in axons (Dalmasso et al. 2017).

In general, it appears that more-networked mitochondria are more efficient at generating ATP, particularly by aerobic metabolism, although there are some exceptions to this (Benard et al. 2010; Correia-Melo and Passos 2015; Mishra and Chan 2016; Westermann 2012; Youle and van der Bliek 2012); there is also evidence that fusion is important for other processes, such as steroid and coenzyme Q synthesis (Duarte et al. 2012; Mourier et al. 2015b). Fusion can also be beneficial by permitting “functional complementation”: if specific mitochondria carry a high level of damaged components or mutated mtDNA, the deleterious effects of these dysfunctional components may be compensated for by functional components from other mitochondria (Nakada et al. 2001; Schon and Gilkerson 2010). The kinetics of functional complementation may be limited by the fact that mixing of OMM, intermembrane space and matrix components is faster than mixing of IMM components (including mtDNA, which is anchored in nucleoids to the IMM: (Wikstrom et al. 2009), apparently because of cristae structure (Busch et al. 2014), the details of which remain disputed (Zick et al. 2009). Fission permits distribution of mitochondria throughout a cell (e.g., transport down axons or to permit allocation prior to cell division), and facilitates apoptosis via release of cytochrome C under some circumstances (Mishra and Chan 2014). Finally, fission may allow identification of dysfunctional daughter mitochondria and their subsequent removal via lysosomal degradation (i.e., mitophagy), when combined with inhibition of fusion (which, as a mitochondrial membrane-dependent process, is inhibited in damaged mitochondria) (Mouli et al. 2009; Youle and van der Bliek 2012).

Overall, fusion and fission maintain mtDNA copy number, integrity (i.e., removal of damaged and mutated mtDNA), and distribution (Amati-Bonneau et al. 2008; Elachouri et al. 2011; Rouzier et al. 2012; Vidoni et al. 2013), yet also permit tolerance of mtDNA mutations (Kowald and Kirkwood 2011; Lin et al. 2016), presumably via the processes of complementation and mitophagy as described above.

1.2 Biological variability in fusion and fission

Mitochondrial morphology is highly variable in different biological contexts, and much remains to be learned about this variability (Zick et al. 2009). We summarize some of the better-characterized patterns; a number of specific examples are reviewed by Kuznetsov et al. (Kuznetsov et al. 2009). In stem cells, mitochondria are fragmented and spherical, predominantly perinuclearly located, and exhibit less oxidative phosphorylation, more glycolysis, low oxidative damage to macromolecules, and other functional changes (Bukowiecki et al. 2014). In dividing cells, mitochondria tend to fuse during G1-S stages, presumably to provide energy for division, and divide prior to mitosis, presumably to enable distribution into daughter cells (Mishra and Chan 2014). Mitochondria may also exhibit tissue-specific forms and functions. For example, mitochondria in cardiomyocytes are relatively lacking in dynamics and non-networked, yet still express fusion and fission proteins which appear to have important quality-control functions (Shirihai et al. 2015) and may have developed alternate mechanism for content exchange (Huang et al. 2013). Mitochondria in differentiating T cells employ undergo both biogenesis and dramatic metabolic remodeling (Ron-Harel et al. 2016). In addition, mitochondrial morphology may be altered by and influence disease processes. For instance, inhibition of mitochondrial fission can impede cancerous processes (Rehman et al. 2012; Wang et al. 2012; Zhao et al. 2013), perhaps by opposing the glycolytic and proliferative phenotypes of cancerous cells. Mitochondrial dynamics may be altered in some cell types by circadian rhythms (Manella and Asher 2016) and as a function of age (Seo et al. 2010). Finally, recent modeling efforts suggest that low mitochondrial mass impedes production of a more-networked morphology, again illustrating the interdependence of mitochondrial parameters (Dalmasso et al. 2017).

Mitochondrial fusion and fission are regulated transcriptionally and non-transcriptionally (including proteolytic degradation and post-translational modification of proteins) by a multitude of factors, including metabolic status and energetic status, mitochondrial membrane potential, redox status, and cellular stress (Hoppins 2014; Mishra and Chan 2016; Toyama et al. 2016; Van der Bliek et al. 2014; Willems et al. 2015). Transcriptional regulation is relatively poorly understood, and post-translational regulation is quite complex (Dhingra and Kirshenbaum 2014). Reported environmental regulation of mitochondrial fusion, fission and morphology are reviewed in Section 2.

1.3 Mitochondrial biogenesis and mitochondrial degradation

Just as fusion and fission dynamically regulate mitochondrial morphology, mitochondrial production (mitobiogenesis) and removal dynamically regulate mitochondrial quantity and quality (Ploumi et al. 2017). Mitobiogenesis is a regulated process permitting a coordinated, increased production of nuclear and mitochondrial-encoded proteins, mtDNA (addressed in detail by Chan (this issue), and other components (reviewed in (Dominy and Puigserver 2013)). Mitobiogenesis is stimulated by many factors including exercise, diet, hormones, and stressors. Regulation of mitobiogenesis varies among tissues, but often involves the peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α), AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR) kinase, sirtuins (e.g. SIRT1), nuclear respiratory factors (NRF1 and NRF2), nuclear factor-erythroid 2-like 2 (NFE2L2; also referred to as Nrf2), and estrogen-related receptors (ERR-α, ERR-β, ERR-γ)

(Ploumi et al. 2017). In the context of stressors, mitobiogenesis may be upregulated either to increase mitochondrial function in general, or to compensate for increased rates of removal of damaged mitochondria (Dorn et al. 2015). Mitobiogenesis has been viewed as occurring largely in the perinuclear region (Davis and Clayton 1996), but the number of cells in which this has been tested is limited and there may be some exceptions (Amiri and Hollenbeck 2008).

Mitochondrial degradation can occur at multiple scales, including removal of damaged molecules by proteases, lipases, and DNA degradation machinery (Bohovych et al. 2015; Scheibye-Knudsen et al. 2015); removal of more localized or minor damage by small mitochondria-derived vesicles (recently termed “micro-mitophagy”), and mitophagy (Lemasters 2014; Sugiura et al. 2014). Of these, only mitophagy requires mitochondrial fission, as elongated mitochondrial are somewhat recalcitrant to mitophagy. Of note, fission may facilitate mitophagy not just by physically reducing mitochondria to a size amenable to autophagosomal encapsulation, but may also segregate dysfunctional fractions of mitochondrial networks that can be identified as such by loss of membrane potential. This process is mediated in part by PTEN-induced putative kinase 1 (PINK1), a mitochondrial kinase that accumulates on dysfunctional mitochondria and recruits and activates proteins including Parkin (PARK2), a ubiquitin ligase; both are involved in some forms of mitophagy as well as micro-mitophagy (Lemasters 2014; Narendra et al. 2012; Palikaras and Tavernarakis 2014). In addition to PINK1 and Parkin, a large and increasing number of other proteins are being identified as capable of participating in mitophagy (Ploumi et al. 2017; Wei et al. 2017). Many forms of mitochondrial degradation are inducible by stimuli including nutrient or caloric deprivation and loss of membrane potential.

Perhaps unsurprisingly, regulation of mitobiogenesis and mitophagy is frequently coordinated, often by the same transcription factors, thus permitting increased turnover without a decrease in mass under stressed conditions; an imbalance in these processes underlies some disease states (Ploumi et al. 2017). In most cases, initiation of mitophagy is somewhat slower than fusion and fission, occurring over minutes to hours, although some forms of mitophagy are faster than others (Lemasters 2014). Mitobiogenesis is slower yet, requiring hours or more (Dalmasso et al. 2017). Finally, as was the case for fusion and fission genes, many proteins involved in these processes also participate in other biological functions. For example, there is evidence that Parkin directly protects and stimulates repair of mtDNA (Rothfuss et al. 2009), while PINK1 can regulate mitochondrial transport in axons (Liu et al. 2012), complex I activity, and more (Voigt et al. 2016).

1.4 Biological variability in mitobiogenesis and mitochondrial degradation

Alterations in replication of mtDNA result in multiple pathologies, as described by Chan (this issue). Mitobiogenesis is highly variable during very early development; two bottlenecks (i.e., very low numbers per cell) of mtDNA per cell occur, first during the progression of primordial germ cells to oocytes, and then during progression of the embryo to the blastocyst stage (Mishra and Chan 2014). To our knowledge, developmental differences in damage-induced mitochondrial degradation pathways have been less well characterized, although mitophagy is critical for removal of mitochondria from sperm and

developing erythrocytes (Palikaras and Tavernarakis 2014). There are also important roles in cellular differentiation and cell type-specific differences (Lu et al. 2013; Scarpulla 2011). In a particularly remarkable example, while mitophagy is generally viewed as a process that occurs within cells, recent evidence indicates that in some cases, mitochondria may be exported to another cell or extracellular space via “exosomes” (Torralba et al. 2016) or “exophers” (Melentijevic et al. 2017), potentially rescuing function in a damaged cell. For example, astrocytes can digest mitochondria from neighboring axons (“transcellular mitophagy”) (Davis et al. 2014). Finally, there are alterations associated with disease. For example, PINK1 and PARK2 mutations result in early-onset Parkinson’s Disease (Truban et al. 2016), and a variety of mitophagy defects result in pathological changes in other neuronal populations, liver, heart, and possibly cancer (Lu et al. 2013; Roberts et al. 2016).

1.5 Relationship to other mitochondrial parameters

Mitochondrial parameters are closely linked. As mentioned above, more-networked mitochondria are generally associated with higher ATP production. Loss of MFN2 is associated with lower mitochondrial membrane potential, proton leak, glucose oxidation, and Krebs cycle activity; these same parameters are increased upon MFN2 overexpression (Schrepfer and Scorrano 2016). These deficiencies appear to result at least in part from depletion of coenzyme Q (Mourier et al. 2015a). Loss of membrane potential, which contributes to mitophagy via PINK1-mediated Parkin activation, can also inhibit mitochondrial fusion and mobility because Parkin can also ubiquinate mitofusins and Miro1 (involved in mitochondrial transport), leading to their degradation (Narendra et al. 2012), and loss of membrane potential leads to OPA1 degradation (Head et al. 2009). Additional mitochondrial parameters can also be altered, including energetics and calcium homeostasis (Archer 2013; Benard et al. 2007; Dalmasso et al. 2017; Mishra and Chan 2016). Thus, experimental manipulation of one parameter may cause other deleterious or compensatory responses. For example, loss of OPA1 or MFN2 can result in either reduced (Belenguer and Pellegrini 2013; Rouzier et al. 2011) or increased (Sitarz et al. 2012; Yu-Wai-Man et al. 2010) mtDNA, and loss of PINK1 is reported in some (Anichtchik et al. 2008; Dagda et al. 2009) but not all (Gautier et al. 2008) cases to cause increased oxidative stress. Many mitodynamic responses and well as other mitochondrial and cellular functions are regulated by the same signaling cascades (e.g., AMPK: (Garcia and Shaw 2017)). These interactions complicate interpretation of experiments in which one mitochondrial parameter is manipulated, and should be considered during experimental design and interpretation, including of the outcomes that we describe in the following sections.

2. Mitochondrial fusion and fission as stress responses

As mentioned above and as previously reviewed (Youle and van der Bliek 2012), there is reason to expect either mitochondrial fusion and fission after stress. We reviewed the literature on the reported effects of environmental stressors on mitochondrial dynamics with the goal of identifying any patterns. We focus on fusion and fission due to space constraints and the relative paucity of information about these processes relative to mitobiogenesis and (especially) degradation.

2.1. Cellular stress may result in mitochondrial fusion or fission

General stress responses mediated via mitochondrial dynamics are best described in the cases of ROS, diet, and exercise.

While cells at homeostasis maintain a balance of fusion and fission, stressors can tip this balance towards excess fusion via a process termed “stress-induced mitochondrial hyperfusion” (SIMH). SIMH was first observed in multiple mammalian cell lines after short, low-dose exposures to ultraviolet C radiation (UVC), actinomycin D, cycloheximide, anisomycin, hippuristanol, and nutrient deprivation (both carbohydrate and amino acid) (Tondera et al. 2009). Changes in mitochondrial length were observed as early as two to three hours after exposure, reached maximum elongation six to nine hours after exposure, and only persisted if the stressor was not removed. SIMH is mediated through OPA1 and MFN1, but in a manner distinct from normal fusion in terms of some of the molecular machinery involved (Van der Bliek et al. 2014), and is hypothesized to occur in order to maintain OXPHOS and optimal ATP levels to adapt to low levels of stress (van der Bliek 2009; Youle and van der Bliek 2012). Transient increases in fusion were also observed after administration of low levels of hydrogen peroxide (H_2O_2) to human umbilical vein endothelial cells (Jendrach et al. 2008). Starvation also induced mitochondrial elongation, mediated through cAMP-activated protein kinase A leading to phosphorylation of DRP1 and inhibition of mitochondrial fission (Gomes et al. 2011). Conversely, superfluous nutrients can cause increased fragmentation (Molina et al. 2009); these changes are quickly reversible with altered calorie availability (Schrepfer and Scorrano 2016). Additionally, a recent study has demonstrated that the fatty acid metabolite, stearic acid (C18:0), reversed mitochondrial fragmentation by limiting ubiquitination and degradation of mitofusins by HECT, UBA, and WWE domain containing E3 ubiquitin protein ligase (Senyilmaz et al. 2015). However, many of these studies have been carried out *in vitro*, and the extent to which SIMH occurs *in vivo*, and what other factors may regulate its occurrence, are unclear; for example, we recently failed to observed SIMH with chronic, non-lethal arsenic exposure in *Caenorhabditis elegans* (Luz et al. 2017). Mitochondrial fusion may be triggered upon viral infection, and appears to support the innate immune response (Khan et al. 2015).

In contrast, stressors in other experiments resulted in increased mitochondrial fragmentation, resulting both from pathways that activate DRP1 via AMPK phosphorylation of DRP1 (Toyama et al. 2016) and calcium release from the endoplasmic reticulum (Van der Bliek et al. 2014), and inhibition of fusion via cleavage of OPA1 and ubiquitination and degradation of MFN2 (Van der Bliek et al. 2014). As mentioned, at high levels, this can facilitate apoptosis and cell death. However, at low levels, there is evidence that this may also be an adaptive mechanism to avoid cell death. For example, after a brief period of exercise, isolated rat skeletal muscle cells exhibited decreased Mfn1/2 mRNA and protein expression, as well as increased expression of Fis1 mRNA and protein (Ding et al. 2010)(FIS1 is an ancillary mediator of mitochondrial division). This may be due to free radical production, as fragmentation is observed in C2C12 myocytes after acute exposure to H_2O_2 (Fan et al. 2010). However, beginning at three hours post recovery, there was a significant increase in Mfn1 mRNA expression, as well as a significant decrease in Fis1 mRNA and protein levels, implying that after a period of acclimation to an exercise state, mitochondria became

increasingly networked. This is consistent with the observation that long-term exercise may increase mitochondrial networking (Bo et al. 2010; Cartoni et al. 2005; Yan et al. 2012). Finally, increased networking does not always correlate with increased function; in fact, senescent cells exhibit high mitochondrial mass and networking, yet generally decreased function (Correia-Melo et al. 2016; Correia-Melo and Passos 2015).

2.2. General patterns observed in studies of toxicant-induced mitochondrial fusion and fission

Clearly, different levels, duration, and timing of stimuli can have varying impacts on mitochondrial morphology. An emerging literature has begun to describe altered mitochondrial dynamics after exposure to environmental contaminants. Much of the evidence lies in changes in mitochondrial morphology and in expression of proteins that regulate mitochondrial fission and fusion after exposures. We have compiled some of the observations in Table 2, and describe a subset in more detail below. Because the wide range and nonsystematic nature of experimental conditions and stressors employed to date preclude a conclusive integrative analysis, we focused on identifying emerging patterns of fission and fusion in response to environmental toxicants that can be used to generate hypotheses and inform future experiments. We discuss below select studies which are notable in that they either individually employ a range of doses, or in conjunction characterize effects of the same chemical with a range of exposure timing and duration. These features allow us to identify emerging patterns of the effect of multiple doses and timing of dose on mitochondrial dynamics.

A detailed investigation into how toxicant concentration influences mitochondrial dynamics was described in an *in vivo* model testing effects of air pollution on mitochondrial morphology. Changes in expression patterns of proteins that regulate fusion and fission were observed in rat nasal mucosal tissues after *in vivo* inhalation of particulate matter ($PM_{2.5}$) isolated from ambient air samples from Shanghai, China (Guo et al. 2017). *Mnf1* and *Opa1* mRNA and protein expression were increased at low and medium doses of $PM_{2.5}$ (200 and 1000 $\mu g/m^3$), potentially compensating for damage or in response to increased energy demands, but decreased at a high dose $PM_{2.5}$ (3000 $\mu g/m^3$). However, mRNA and protein expression of *Drp1* and *Fis1* were increased only after the high dose exposure. This study emphasizes the complexity in understanding how environmental exposures influence mitochondrial dynamics: at low doses, changes in dynamics due to stress amelioration could be misinterpreted as toxicity and not an adaptive response, when in fact the toxic response may occur only at high levels of exposure when the balance of fission and fusion is disrupted.

Duration and timing of exposure is also important when investigating effects of toxicants on mitochondrial dynamics, as demonstrated by various *in vitro* studies investigating the effects of cigarette smoke extract (CSE) on mitochondrial morphology. Human airway smooth muscle cell mitochondria were highly sensitive to changes in mitochondrial morphology after a 48 hour exposure to 1% CSE, exhibiting decreased branching and branch length, decreased *MFN1*, *MFN2* and *OPA1* expression and increased *DRP1* and *FIS1* expression (Aravamudan et al. 2014). On the other hand, mitochondria in human bronchial epithelial

cells exposed to 10% CSE for three months, followed by three months of control conditions, exhibited increased branching, suggesting mitochondrial fusion occurs in response to a chronic stress scenario (Hoffmann et al. 2013). Finally, even apparently adaptive responses may not preclude longer-term toxicity. For example, acute exposure of developing *Danio rerio* to the mitochondrial uncoupler 2,4-dinitrophenol resulted in an increase in gene expression of *opa1* and *peo1* (mtDNA helicase and twinkle homolog, required for mtDNA replication) immediately following the exposure, as the mitochondria fused and replicated as an initial stress response (Bestman et al. 2015). However, at increasing time intervals following the initial exposure, *opa1, peo1,* and *drp1* expression decreased, followed by a decrease in overall mitochondrial respiratory capacity, as well as motor neuron and retinal developmental defects.

One class of agents with a specific mechanism of action have a very clear effect on mitochondrial dynamics and morphology: uncouplers of oxidative phosphorylation. Specific agents (i.e., FCCP, CCCP, and 2,4-DNP) directly result in mitochondrial uncoupling and lead to loss of mitochondrial membrane potential (MMP), which then leads to an inhibition of fusion. It is therefore important to confirm in future investigations whether environmental compounds that are uncouplers, such as arsenate, triclosan, and pentachlorophenol have the same effect on mitochondrial morphology and dynamics due to this mechanism of action. One could also predict that toxicants that directly or indirectly decrease MMP could have similar effects on mitochondrial morphology. Therefore, in future work, it may be useful to include chemicals that have a clear mechanism of action that could lead to disruption of cellular homeostasis via inhibition of mitochondrial dynamics.

Overall, while limited, available data suggest that patterns of mitodynamic response to chemical stressors are generally similar to responses to other stressors, as previously reviewed (Youle and van der Bliek 2012). Specifically, low level and chronic exposures lead to an increase in fusion and mild increase in fission, resulting in more-networked mitochondria as well as increased turnover of damaged components. Middle-level acute or chronic exposures lead to a similar level of increase in fusion and fission, so that turnover is increased but morphology is not dramatically altered. High level, acute exposure promotes fission and may simultaneously inhibit fusion due to reduced mitochondrial membrane potential.

It is important to distinguish adaptive and compensatory responses from toxic or pathological changes. Generally, it appears that low level and chronic exposures lead to responses that are adaptive in the short term, and in most circumstances also in the long-term, as long as turnover of damaged components is not compromised (note: “exposure levels” are conceptualized here not as specific concentrations of chemical, degree of exercise, etc., but rather relative to the predicted degree of stress and associated morphological response of mitochondria; thus, for example, low levels of “stress” may correspond to adaptive responses). However, if chronic hyperfusion reduces the likelihood of turnover, the risk of a long-term problem may develop. For example, such exposures, if genotoxic, might result in mtDNA mutations, the source of which, as discussed by Meyer and Chen (this issue), is controversial. This long-term trade-off may be particularly marked in the case of persistent mitotoxicants (e.g., metals or persistent organic pollutants) that may

not be removed from mitochondria in the context of a long-term inhibition of fission. We propose that middle range exposures result in both increased turnover of mitochondria and a roughly normally networked morphology via comparable increases in both fusion and fission. Examples of such responses are less common in the literature—perhaps because they may be viewed as negative results if only morphology is examined! These similar increases in fusion and fission would appear to be adaptive in the short-term, with both increased turnover of mitochondria, permitting removal of damaged components, and maintenance of mitochondria that are networked enough to generate ATP efficiently and dynamic enough for functional complementation. A potential downside to simultaneously increased fusion, fission, biogenesis and degradation is increased energy requirement. High-level exposures may result in increased fission, which blocks efficient ATP generation and limits rates of functional complementation, in addition to potentially leading to apoptosis. Highly fragmented mitochondria may be more likely to undergo cellular export (West and Shadel 2017), potentially eliciting an inflammatory response, as discussed by West (this issue). Mitochondrial fission may also inhibit the response to infection (Khan et al. 2015). However, briefly increased fission may also serve a protective role by permitting increased mitochondrial degradation. Additionally, increased fission results in a decrease in oxidative phosphorylation, which could protect the cell if the toxicity of the chemical results in part from inducing mitochondrial ROS generation (e.g., paraquat or rotenone). Finally, apoptosis can be an adaptive stress response if it removes damaged cells with mitochondria damaged beyond full repair capacity. Of note, these potentially adaptive stress responses exist on a longer timeframe, and are thus an additional experimental design parameter that should be considered.

We provide a schematic illustrating these overall patterns, and relating them to other mitochondrial processes (Fig. 1). We highlight two points. First, we view these patterns as hypotheses, which need to be further tested in multiple systems. Second, some researchers have attempted to use endpoints such as mitochondrial morphology or DNA copy number as biomarkers of mitochondrial dynamics. While alterations in mitodynamics are mechanistically informative, the variability in dynamic and morphological responses across doses and timepoints is likely to make the utilization of these endpoints as biomarkers challenging (e.g., note non-monotonic responses illustrated in Figure 1), particularly without additional parameters. Nonetheless, measurement of these mitochondrial endpoints is critically important to test and add detail to the general schematic we present in Figure 1. The model we describe above is based on a rather limited literature, and exceptions exist. For example, a recent investigation of the effects of ozone on mitochondrial morphology identified increased fusion at a high dose, but increased fission at a low dose (Constanzo et al. 2015). Amelioration of fragmentation at the high dose was due to the activation and increased abundance of mitochondrial targeted heat-shock protein 70, a classic adaptive stress response. This provides further motivation to investigate how variation in dose, and/or mechanism of action impacts mitochondrial dynamics; in fact, there are a large number of knowledge gaps regarding environmental contaminants and mitochondrial dynamics, as addressed in the next section.

2.3. Frontiers of knowledge regarding stress-responsive mitochondrial fusion and fission

Many questions remain regarding changes in mitochondrial fission and fusion dynamics in response to direct and indirect mitochondrial toxicants. For example:

- What differences, if any, exist between chemicals and other stressors and environmental factors (e.g., diet, exercise, and infection) in altering mitodynamics? Does this depend on whether the chemical specifically targets mitochondria versus other cellular targets? Does it depend on how persistent the chemical is (in the cell)? How do these factors interact?
- What is the full range of dose-response and time course of the response?
- How long do altered mitodynamics last *in vivo*, and what is the full range of transcriptional and non-transcriptional control mechanisms? What variation exists in mitodynamic response, and the consequences of those changes, across tissue types and developmental stages?
- What are the consequences of changes in mitodynamics, from mitochondrial function to organismal health? Are there long-term organismal-level consequences, or trade-offs, to altered dynamics? How do these relate to reports of “mitohormesis” (Yun and Finkel 2014), and to conditions of nutrient stress, infection, or other environmental stressors?

We hope that researchers will address these questions, as well as design experiments to incorporate wide dose-responses and varied exposure time courses.

Finally, as described, there is strong evidence that mitochondrial fusion and fission play polymorphisms in genes involved these processes in the population, it is also important to consider the possibility that deficiencies in these genes might render some individuals more sensitive to mitotoxicants.

3. Gene-environment interactions: How does genetic variation in mitochondrial dynamics processes affect the response to mitochondrial stress?

3.1. Evidence for interactions between mutations in mitochondrial genes and mitochondrial stressors

To date, the best-characterized examples come from interactions of pharmaceuticals with mutations in mitochondrial genes that function in processes other than mitochondrial dynamics. For example, aminoglycoside antibiotics, which inhibit bacterial protein synthesis via binding to bacterial 16s rRNA, can cause ototoxicity in individuals harboring point mutations in mtDNA-encoded 12s rRNA that render the ribosome more “bacteria-like” in structure [reviewed in (Guan 2011)]. Valproic acid can cause fatal liver hepatotoxicity in individuals with certain inborn errors of metabolism, likely due to inhibition of enzymes involved in fatty acid oxidation [reviewed in (Silva et al. 2008)]. Finally, smoking and heavy drinking can increase the penetrance of Leber’s hereditary optic neuropathy, which is caused

by mutations in mtDNA, from 50 to 93% in males and 10 to 33% in females (Kirkman et al. 2009).

There is also evidence for a role for the environment in the development, progression, and exacerbation of mitochondrial dynamics-related diseases. For example, only 10% of Parkinson's disease (PD) cases have a clear genetic etiology (Klein and Westenberger 2012), while the age of onset (infantile to 50^{+} years of age) and severity of clinical manifestations of CMT2A caused by mutations in *MFN2* vary dramatically, even in patients harboring identical mutations (Choi et al. 2015; Lv et al. 2015). However, mechanistic understanding of how deficiencies in mitochondrial dynamics might sensitize to mitotoxicant exposure is limited; this knowledge gap is particularly apparent for fusion and fission, as is illustrated by the outcome of a recent (July 3, 2017) Pubmed search: "Parkin and toxicity," 252; "Mitofusin and toxicity," 30; "DNM1 and toxicity," 2. Therefore, and because of the relatively high frequency of mutations in mitochondrial fusion genes (Table 1), we focus our review on fusion and fission gene-environment interactions.

3.2 Effects of deficiencies in fusion genes

Numerous drugs are known to worsen preexisting neuropathies, including those caused by Charcot-Marie-Tooth disease [reviewed in (Weimer and Podwall 2006)]. While interactions between neurotoxic drugs and specific genetic defects causative of various CMT subtypes have not been thoroughly investigated, there is some interesting literature. Several case reports of optic atrophies have been reported in patients harboring mutations in mitochondrial fusion genes following administration of ethambutol (EMB), an antimicrobial agent frequently used in the treatment of tuberculosis (Fonkem et al. 2013; Guillet et al. 2010; Pradhan et al. 2010). These include two patients harboring distinct mutations in *OPA1* that developed optic atrophies following EMB treatment (Guillet et al. 2010; Pradhan et al. 2010). Neither patient had visual impairment prior to EMB treatment. In another patient harboring a point mutation in *MFN2*, EMB treatment exacerbated a pre-existing neuropathy, and induced vocal cord paralysis and optic atrophy (Fonkem et al. 2013). These results and the dual neurodegenerative nature of DOA and EMB (DOA results from a loss of retinal ganglion cells (RGCs), and RGCs are a sensitive target of EMB toxicity (Heng et al. 1999)) suggest that *MFN2* or *OPA1* mutations and EMB represent a novel gene-environment interaction. However, EMB treatment is associated with optic neuropathies in 2–6% of patients (Lee et al. 2008; Sadun and Wang 2008); thus, it is unclear if these case reports represent novel gene-environment interactions, or simply coincide with the 2–6% of patients that develop optic atrophies following EMB treatment. Further work is warranted to test any molecular interactions between loss of mitochondrial fusion and EMB toxicity.

Although the aforementioned clinical observations suggest the environment can play a role in the exacerbation of DOA and CMT2A, experimental evidence is lacking (Table 2). However, results from several model organisms are beginning to suggest that genetic deficiencies in fission and fusion may sensitize individuals to toxicants that specifically induce mitochondrial ROS, including the ETC CI inhibitor rotenone, which can induce production of superoxide anion, and the redox cycler paraquat, which is an amphiphilic herbicide that can accumulate in the mitochondria. For example, *drp-1*-, *fzo-1* (*MFN2*

homolog)-, and *eat-3* (*OPA1* homolog)-deficient *C. elegans* are sensitive to rotenone-induced lethality (Fig. 2) and larval growth delay (*fzo-1* & *eat-3* only: (Luz et al. 2017)); rotenone reduces the viability of cortical neurons isolated from heterozygous $OPA1^{+/-}$ rats (Millet et al. 2016); and transfection with $OPA1^{G300E}$, an OPA1 variant carrying a missense mutation in the GTPase domain, sensitizes primary mice neurons to rotenone-induced axonal degeneration (Lassus et al. 2016). Furthermore, mutations in *drp-1* have been reported to mildly sensitize nematodes to paraquat-induced lethality and larval growth delay (Luz et al. 2017; Yang et al. 2011) while fusion-deficient *C. elegans* (*eat-3, fzo-1*) are sensitive to paraquat-induced lethality and larval growth delay, and *D. melanogaster* (*OPA1*-deficient) display reduced survival following paraquat exposure (Kanazawa et al. 2008; Luz et al. 2017; Tang et al. 2009). Interestingly, paraquat and rotenone exposure have been associated with the development of PD in farmworkers (Tanner et al. 2011), and are also used in animal models of PD [reviewed in (Cicchetti et al. 2009)], and MFN2 deficiency can cause dopaminergic neurodegeneration (Pham et al. 2012). Thus, compared to EMB, there is somewhat more experimental support for this gene-environment interaction, but the mechanistic details of these interactions, and the extent to which they can be extended to other toxicants that cause mitochondrial ROS production or other forms of mitochondrial toxicity, remains to be elucidated.

An interesting potential environmental vulnerability in mitochondria results from the fact that mitochondria lack nucleotide excision repair (NER), which is required for removal of many common forms of environmentally-induced DNA damage [(Meyer et al. 2013) and as reviewed by de Souza Pinto and Roubicek (this issue)]. We have previously shown that the processes of fission, fusion, mitophagy, and autophagy are required for the slow removal of irreparable (due to a lack of mitochondrial NER) ultraviolet C-induced photodimers in mtDNA (Bess et al. 2012; Bess et al. 2013). However, UVC-induced mtDNA damage only caused larval growth arrest in fusion (*fzo-1, eat-3*)-deficient nematodes, suggesting that individuals with fusion deficiencies are more susceptible to toxicity induced by irreparable mtDNA damage. In agreement with this, we have also observed sensitivity to the mycotoxin aflatoxin B_1 and the chemotherapeutic cisplatin, both of which can cause irreparable mtDNA damage (González-Hunt et al. 2014; Niranjan et al. 1982; Podratz et al. 2011), in *fzo-1*- and *eat-3*-deficient but not *drp-1 C. elegans* (Luz et al. 2017). Although the precise reason for sensitivity to irreparable mtDNA damage in fusion-deficient *C. elegans* remains unknown, one possibility is the existence of a threshold effect in which >65% of mtDNA must typically be damaged or lost prior to pathogenesis (Taylor and Turnbull 2005). In support of this, *OPA1* regulates mitochondrial cristae structure and mtDNA stability, and mutations in *OPA1* can result in mtDNA depletion and increased frequency of mtDNA deletions [reviewed in (Belenguer and Pellegrini 2013)], while mutations in *MFN2* have been reported to cause mtDNA depletion in CMT2A patients (Rouzier et al. 2011). Thus, in the context of reduced mtDNA content and genetic inability to remove damaged mtDNAs, irreparable mtDNA damage may more easily exceed the pathogenic threshold resulting in mitochondrial dysfunction. However, further mechanistic studies are required to test this hypothesis. Finally, a number of studies have demonstrated the importance of mitochondrial fusion in protecting against accumulation of mtDNA mutations (Chen et al. 2010; Vidoni et al. 2013).

Finally, we have recently demonstrated that fusion (*fzo-1, eat-3*) -deficient nematodes are hypersensitive to arsenite-induced toxicity (Luz et al. 2017). In fusion-deficient nematodes, exposure to arsenite resulted in impaired mitochondrial respiration, lower ATP levels, and reduced pyruvate and isocitrate dehydrogenase activity, suggesting that disruption of pyruvate metabolism and Krebs cycle activity may underlie the observed mitochondrial dysfunction. Although further experimental work in mammalian models as well as human studies are required to determine the human relevance of this gene-environment interaction, this work is warranted, as over 100 million people are chronically exposed to arsenic through consumption of contaminated drinking water (Ravenscroft et al. 2009).

3.3 Effects of fission deficiency

However, although we and others have reported that fission-deficient nematodes are also mildly sensitive to rotenone (Fig. 2), arsenite, and paraquat (Luz et al. 2017; Yang et al. 2011), and a recent report supports a role for mitochondrial fission in the adaptive response to mitochondrial dysfunction (Benard et al. 2013), loss or inhibition of fission is currently more frequently associated with protection in the literature. For example, *DRP1* siRNA reduced cell death in human SH-SY5Y cells exposed to 6-hydroxydopamine (Gomez-Lazaro et al. 2008), reduced cell death in rat astrocytoma C6 cells exposed to manganese (Alaimo et al. 2014), reduced cell death in mouse HT22 neurons exposed to glutamate (Grohm et al. 2012), reduced cell death in lung epithelial cells exposed to cigarette smoke extract (Mizumura et al. 2014), reduced mitochondrial dysfunction in human L02 hepatocytes exposed to cadmium (Xu et al. 2013a), and protected *drp-1*-deficient nematodes from acrolein-induced larval growth delay (Luz et al. 2017). These results suggest hyperfusion caused by mutations in *drp-1* may be protective under certain conditions. This may be due to that fact that fusion promotes functional complementation, which as described above can provide some buffering capacity against mitochondrial damage. However, hyperfused mitochondria, such as those found in *drp-1*-deficient cells, are somewhat recalcitrant to autophagosomal degradation, which allows mitochondrial damage to accumulate due to impaired recycling of mitochondria (Meyer and Bess 2012; Twig et al. 2008b). This raises the interesting possibility that sensitivity to toxicants in fission-deficient individuals may only manifest after chronic exposures or in aging individuals in which mitochondrial damage has had time to accumulate and exceed the buffering capacity of hyperfused mitochondria. This is supported by the fact that aging *drp-1*-deficient nematodes are hypersensitive to arsenite-induced lethality, while larval nematodes are not (Luz et al. 2017). We recommend that future research be designed to confirm or refute this hypothesis.

4. Conclusions and future directions

Mitochondrial fusion and fission are important homeostatic and toxicant response pathways that have strong mechanistic relations to other mitodynamic process including mitobiogenesis, mitochondrial degradation, and mitochondrial transport. Genetic deficiencies or other factors that alter mitochondrial dynamics can alter sensitivity to exposures, which is of significant concern given the relatively common nature of deficiencies in these processes in the population. However, while deficiencies often sensitize to exposure, they sometimes protect or have no effect. This suggests that if we are to develop

an ability to predict the interaction between mitotoxicants and inter-individual differences in mitochondrial dynamics, we will need to pair mechanistic understandings of the toxicants' biological effects with a detailed understanding of the dynamic mitochondrial response (including fusion and fission, but also related changes such as mobility, morphology, degradation, and biogenesis). For example, we might predict that chemicals that cause mitochondrial fusion at low exposure levels, as part of an adaptive response, might be more toxic in an individual with reduced capacity for mitochondrial fusion. Conversely, if a chemical causes cell death by mitochondrial fission-mediated apoptosis, deficiency in fission might be protective in the short term, while potentially deleterious in the long run due to the inability to recycle damaged mitochondrial components. As discussed above, we recommend that studies that examine mitochondrial dynamics in response to environmental toxicants include a range of doses and timepoints, given that fusion and fission are likely to occur at different timepoints and levels of cellular stress.

It will also be important to put toxicants' effects on mitochondrial dynamics in the context of other environmental variables that affect mitochondria, such as diet (Branco et al. 2016; Hepple 2009) and exercise (Bo et al. 2010); as described above, these are currently among the better-described environmental regulators of mitochondrial fusion and fission. Indeed, dietary and exercise variables have been reported to cause "mitohormesis" (Held and Houtkooper 2015; Merry and Ristow 2016), suggesting a possible protective effect. Interestingly, the same has been reported for low levels of some mitotoxicants, such as arsenic (Schmeisser et al. 2013); however, we recently found that concentrations of arsenic that were harmless or even beneficial in wild-type *Caenorhabditis elegans* were instead toxic to fusion-deficient individuals (Luz et al. 2017). On the other hand, some mitochondrial perturbations can have persistent, deleterious consequences (Berthiaume and Wallace 2007a, b; Chan et al. 2007; Ditzel et al. 2015; Divi et al. 2010; Leung et al. 2013; Saben et al. 2016; Wood et al. 2015), and thus may contribute the developmental origins of adult health and disease. Testing this possibility will be an additional, important future direction, especially given the very different mitochondrial morphologies and functions observed in early-stage organisms and undifferentiated cells.

Acknowledgments

This work was supported by the NIH (R01ES017540, P42ES010356, F31ES026859, 1R21ES026743, and T32ES021432).

References

Alaimo A, Gorojod RM, Beauquis J, Munoz MJ, Saravia F, Kotler ML. Deregulation of mitochondria-shaping proteins Opa-1 and Drp-1 in manganese-induced apoptosis. PLoS ONE. 2014; 9:e91848. [PubMed: 24632637]

Amati-Bonneau P, Valentino ML, Reynier P, Gallardo ME, Bornstein B, Boissiere A, Campos Y, Rivera H, de la Aleja JG, 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 MA, Arenas J, Ayuso C, Garesse R, Lenaers G, Bonneau D, Carelli V. OPA1 mutations induce mitochondrial DNA instability and optic atrophy 'plus' phenotypes. Brain. 2008; 131:338–351. [PubMed: 18158317]

Amiri M, Hollenbeck PJ. Mitochondrial biogenesis in the axons of vertebrate peripheral neurons. Developmental neurobiology. 2008; 68:1348–1361. [PubMed: 18666204]

Anichtchik O, Diekmann H, Fleming A, Roach A, Goldsmith P, Rubinsztein DC. Loss of PINK1 function affects development and results in neurodegeneration in zebrafish. Journal of Neuroscience. 2008; 28:8199–8207. [PubMed: 18701682]

Aravamudan B, Kiel A, Freeman M, Delmotte P, Thompson M, Vassallo R, Sieck GC, Pabelick CM, Prakash YS. Cigarette smoke-induced mitochondrial fragmentation and dysfunction in human airway smooth muscle. Am J Physiol Lung Cell Mol Physiol. 2014; 306:L840–854. [PubMed: 24610934]

Archer SL. Mitochondrial dynamics--mitochondrial fission and fusion in human diseases. N Engl J Med. 2013; 369:2236–2251. [PubMed: 24304053]

Ashley N, Poulton J. Anticancer DNA intercalators cause p53-dependent mitochondrial DNA nucleoid re-modelling. Oncogene. 2009; 28:3880–3891. [PubMed: 19684617]

Babbar M, Sheikh MS. Metabolic Stress and Disorders Related to Alterations in Mitochondrial Fission or Fusion. Molecular and cellular pharmacology. 2013; 5:109–133. [PubMed: 24533171]

Barbosa DJ, Serrat R, Mirra S, Quevedo M, de Barreda EG, Avila J, Ferreira LM, Branco PS, Fernandes E, Bastos MD, Capela JP, Soriano E, Carvalho F. The Mixture of “Ecstasy” and Its Metabolites Impairs Mitochondrial Fusion/Fission Equilibrium and Trafficking in Hippocampal Neurons, at In Vivo Relevant Concentrations. Toxicological Sciences. 2014:139. [PubMed: 24361869]

Belenguer P, Pellegrini L. The dynamin GTPase OPA1: more than mitochondria? Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2013; 1833:176–183. [PubMed: 22902477]

Benard G, Bellance N, James D, Parrone P, Fernandez H, Letellier T, Rossignol R. Mitochondrial bioenergetics and structural network organization. J Cell Sci. 2007; 120:838–848. [PubMed: 17298981]

Benard G, Bellance N, Jose C, Melser S, Nouette-Gaulain K, Rossignol R. Multi-site control and regulation of mitochondrial energy production. Biochimica et biophysica acta. 2010; 1797:698–709. [PubMed: 20226160]

Benard G, Trian T, Bellance N, Berger P, Lavie J, Espil-Taris C, Rocher C, Eimer-Bouillot S, Goizet C, Nouette-Gaulain K, Letellier T, Lacombe D, Rossignol R. Adaptative capacity of mitochondrial biogenesis and of mitochondrial dynamics in response to pathogenic respiratory chain dysfunction. Antioxid Redox Signal. 2013; 19:350–365. [PubMed: 22369111]

Berthiaume JM, Wallace KB. Adriamycin-induced oxidative mitochondrial cardiotoxicity. Cell biology and toxicology. 2007a; 23:15–25. [PubMed: 17009097]

Berthiaume JM, Wallace KB. Persistent alterations to the gene expression profile of the heart subsequent to chronic Doxorubicin treatment. Cardiovascular toxicology. 2007b; 7:178–191. [PubMed: 17901561]

Bess AS, Crocker TL, Ryde IT, Meyer JN. Mitochondrial dynamics and autophagy aid in removal of persistent mitochondrial DNA damage in Caenorhabditis elegans. Nucleic Acids Res. 2012

Bess AS, Leung MC, Ryde IT, Rooney JP, Hinton DE, Meyer JN. Effects of mutations in mitochondrial dynamics-related genes on the mitochondrial response to ultraviolet C radiation in developing Caenorhabditis elegans. Worm. 2013; 2:e23763. [PubMed: 24058863]

Bestman JE, Stackley KD, Rahn JJ, Williamson TJ, Chan SS. The cellular and molecular progression of mitochondrial dysfunction induced by 2,4-dinitrophenol in developing zebrafish embryos. Differentiation. 2015; 89:51–69. [PubMed: 25771346]

Bo H, Zhang Y, Ji LL. Redefining the role of mitochondria in exercise: a dynamic remodeling. Annals of the New York Academy of Sciences. 2010; 1201:121–128. [PubMed: 20649548]

Bobylev I, Joshi AR, Barham M, Neiss WF, Lehmann HC. Depletion of Mitofusin-2 Causes Mitochondrial Damage in Cisplatin-Induced Neuropathy. Mol Neurobiol. 2017

Bohovych I, Chan SS, Khalimonchuk O. Mitochondrial protein quality control: the mechanisms guarding mitochondrial health. Antioxid Redox Signal. 2015; 22:977–994. [PubMed: 25546710]

Bonifati V, Rohe CF, Breedveld GJ, Fabrizio E, De Mari M, Tassorelli C, Tavella A, Marconi R, Nicholl DJ, Chien HF, Fincati E, Abbruzzese G, Marini P, De Gaetano A, Horstink MW, Maat-Kievit JA, Sampaio C, Antonini A, Stocchi F, Montagna P, Toni V, Guidi M, Dalla Libera A, Tinazzi M, De Pandis F, Fabbrini G, Goldwurm S, de Klein A, Barbosa E, Lopiano L, Martignoni E, Lamberti P, Vanacore N, Meco G, Oostra BA. Early-onset parkinsonism associated with PINK1

mutations: frequency, genotypes, and phenotypes. Neurology. 2005; 65:87–95. [PubMed: 16009891]

Branco AF, Ferreira A, Simoes RF, Magalhaes-Novais S, Zehowski C, Cope E, Silva AM, Pereira D, Sardao VA, Cunha-Oliveira T. Ketogenic diets: from cancer to mitochondrial diseases and beyond. European journal of clinical investigation. 2016; 46:285–298. [PubMed: 26782788]

Bukowiecki R, Adjaye J, Prigione A. Mitochondrial function in pluripotent stem cells and cellular reprogramming. Gerontology. 2014; 60:174–182. [PubMed: 24281332]

Busch KB, Kowald A, Spelbrink JN. Quality matters: how does mitochondrial network dynamics and quality control impact on mtDNA integrity? Philos Trans R Soc Lond B Biol Sci. 2014; 369:20130442. [PubMed: 24864312]

Cartoni R, Leger B, Hock MB, Praz M, Crettenand A, Pich S, Ziltener JL, Luthi F, Deriaz O, Zorzano A, Gobelet C, Kralli A, Russell AP. Mitofusins 1/2 and ERRalpha expression are increased in human skeletal muscle after physical exercise. The Journal of physiology. 2005; 567:349–358. [PubMed: 15961417]

Cartoni R, Martinou JC. Role of mitofusin 2 mutations in the physiopathology of Charcot-Marie-Tooth disease type 2A. Experimental neurology. 2009; 218:268–273. [PubMed: 19427854]

Chan DC. Fusion and fission: interlinked processes critical for mitochondrial health. Annual review of genetics. 2012; 46:265–287.

Chan SS, Santos JH, Meyer JN, Mandavilli BS, Cook DL Jr, McCash CL, Kissling GE, Nyska A, Foley JF, van Houten B, Copeland WC, Walker VE, Witt KL, Bishop JB. Mitochondrial toxicity in hearts of CD-1 mice following perinatal exposure to AZT, 3TC, or AZT/3TC in combination. Environmental and molecular mutagenesis. 2007; 48:190–200. [PubMed: 16395692]

Chen HC, Vermulst M, Wang YE, Chomyn A, Prolla TA, McCaffery JM, Chan DC. Mitochondrial Fusion Is Required for mtDNA Stability in Skeletal Muscle and Tolerance of mtDNA Mutations. Cell. 2010; 141:280–289. [PubMed: 20403324]

Chen Y, Dorn GW 2nd. PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. Science. 2013; 340:471–475. [PubMed: 23620051]

Choi BO, Nakhro K, Park H, Hyun Y, Lee J, Kanwal S, Jung SC, Chung K. A cohort study of MFN2 mutations and phenotypic spectrums in Charcot–Marie–Tooth disease 2A patients. Clinical genetics. 2015; 87:594–598. [PubMed: 24863639]

Cicchetti F, Drouin-Ouellet J, Gross RE. Environmental toxins and Parkinson's disease: what have we learned from pesticide-induced animal models? Trends in pharmacological sciences. 2009; 30:475–483. [PubMed: 19729209]

Correia-Melo C, Marques FD, Anderson R, Hewitt G, Hewitt R, Cole J, Carroll BM, Miwa S, Birch J, Merz A, Rushton MD, Charles M, Jurk D, Tait SW, Czapiewski R, Greaves L, Nelson G, Bohlooly YM, Rodriguez-Cuenca S, Vidal-Puig A, Mann D, Saretzki G, Quarato G, Green DR, Adams PD, von Zglinicki T, Korolchuk VI, Passos JF. Mitochondria are required for pro-ageing features of the senescent phenotype. EMBO J. 2016; 35:724–742. [PubMed: 26848154]

Correia-Melo C, Passos JF. Mitochondria: Are they causal players in cellular senescence? Biochimica et biophysica acta. 2015; 1847:1373–1379. [PubMed: 26028303]

Costanzo M, Cisterna B, Vella A, Cestari T, Covi V, Tabaracci G, Malatesta M. Low ozone concentrations stimulate cytoskeletal organization, mitochondrial activity and nuclear transcription. European journal of histochemistry: EJH. 2015; 59:2515. [PubMed: 26150162]

Dagda RK, Cherra SJ, Kulich SM, Tandon A, Park D, Chu CT. Loss of PINK1 Function Promotes Mitophagy through Effects on Oxidative Stress and Mitochondrial Fission. Journal of Biological Chemistry. 2009; 284:13843–13855. [PubMed: 19279012]

Dalmasso G, Marin Zapata PA, Brady NR, Hamacher-Brady A. Agent-Based Modeling of Mitochondria Links Sub-Cellular Dynamics to Cellular Homeostasis and Heterogeneity. PLoS ONE. 2017; 12:e0168198. [PubMed: 28060865]

Das S, Paul A, Mumbrekar KD, Rao SB. Harmonization of Mangiferin on methylmercury engendered mitochondrial dysfunction. Environmental toxicology. 2017; 32:630–644. [PubMed: 28071871]

Davis AF, Clayton DA. In situ localization of mitochondrial DNA replication in intact mammalian cells. The Journal of cell biology. 1996; 135:883–893. [PubMed: 8922374]

Davis CH, Kim KY, Bushong EA, Mills EA, Boassa D, Shih T, Kinebuchi M, Phan S, Zhou Y, Bihlmeyer NA, Nguyen JV, Jin Y, Ellisman MH, Marsh-Armstrong N. Transcellular degradation of axonal mitochondria. Proc Natl Acad Sci U S A. 2014; 111:9633–9638. [PubMed: 24979790]

de Brito OM, Scorrano L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature. 2008; 456:605–610. [PubMed: 19052620]

de Quadros T, Schramm H, Zeni EC, Simioni C, Allodi S, Muller YM, Ammar D, Nazari EM. Developmental effects of exposure to ultraviolet B radiation on the freshwater prawn Macrobrachium olfersi: Mitochondria as a target of environmental UVB radiation. Ecotoxicology and environmental safety. 2016; 132:279–287. [PubMed: 27344016]

Dhingra R, Kirshenbaum LA. Regulation of mitochondrial dynamics and cell fate. Circulation journal: official journal of the Japanese Circulation Society. 2014; 78:803–810. [PubMed: 24647412]

Ding H, Jiang N, Liu H, Liu X, Liu D, Zhao F, Wen L, Liu S, Ji LL, Zhang Y. Response of mitochondrial fusion and fission protein gene expression to exercise in rat skeletal muscle. Biochimica et biophysica acta. 2010; 1800:250–256. [PubMed: 19716857]

Ditzel EJ, Nguyen T, Parker P, Camenisch TD. Effects of Arsenite Exposure during Fetal Development on Energy Metabolism and Susceptibility to Diet-Induced Fatty Liver Disease in Male Mice. Environ Health Perspect. 2015

Divi RL, Einem TL, Fletcher SL, Shockley ME, Kuo MM, St Claire MC, Cook A, Nagashima K, Harbaugh SW, Harbaugh JW, Poirier MC. Progressive mitochondrial compromise in brains and livers of primates exposed in utero to nucleoside reverse transcriptase inhibitors (NRTIs). Toxicol Sci. 2010; 118:191–201. [PubMed: 20702595]

Dominy JE, Puigserver P. Mitochondrial biogenesis through activation of nuclear signaling proteins. Cold Spring Harbor perspectives in biology. 2013:5.

Dorn GW, Vega RB, Kelly DP. Mitochondrial biogenesis and dynamics in the developing and diseased heart. Genes & Development. 2015; 29:1981–1991. [PubMed: 26443844]

Duarte A, Poderoso C, Cooke M, Soria G, Maciel FC, Gottifredi V, Podesta EJ. Mitochondrial Fusion Is Essential for Steroid Biosynthesis. PLoS ONE. 2012:7.

Elachouri G, Vidoni S, Zanna C, Pattyn A, Boukhaddaoui H, Gaget K, Yu-Wai-Man P, Gasparre G, Sarzi E, Delettre C, Olichon A, Loiseau D, Reynier P, Chinnery PF, Rotig A, Carelli V, Hamel CP, Rugolo M, Lenaers G. OPA1 links human mitochondrial genome maintenance to mtDNA replication and distribution. Genome Res. 2011; 21:12–20. [PubMed: 20974897]

Fan X, Hussien R, Brooks GA. H2O2-induced mitochondrial fragmentation in C2C12 myocytes. Free Radic Biol Med. 2010; 49:1646–1654. [PubMed: 20801212]

Fonkem E, Skordilis MA, Binkley EM, Raymer DS, Epstein A, Arnold WD, Kissel JT, Lawson VH. Ethambutol toxicity exacerbating the phenotype of CMT2A2. Muscle & nerve. 2013; 48:140–144. [PubMed: 23733358]

Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J, Voeltz GK. ER tubules mark sites of mitochondrial division. Science. 2011; 334:358–362. [PubMed: 21885730]

Garcia D, Shaw RJ. AMPK: Mechanisms of Cellular Energy Sensing and Restoration of Metabolic Balance. Mol Cell. 2017; 66:789–800. [PubMed: 28622524]

Gautier CA, Kitada T, Shen J. Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci U S A. 2008; 105:11364–11369. [PubMed: 18687901]

Gomes LC, Di Benedetto G, Scorrano L. During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. Nature cell biology. 2011; 13:589–598. [PubMed: 21478857]

Gomez-Lazaro M, Bonekamp NA, Galindo MF, Jordan J, Schrader M. 6-Hydroxydopamine (6-OHDA) induces Drp1-dependent mitochondrial fragmentation in SH-SY5Y cells. Free Radic Biol Med. 2008; 44:1960–1969. [PubMed: 18395527]

González-Hunt CP, Leung MC, Bodhicharla RK, McKeever MG, Arrant AE, Margillo KM, Ryde IT, Cyr DD, Kosmaczewski SG, Hammarlund M. Exposure to mitochondrial genotoxins and dopaminergic neurodegeneration in Caenorhabditis elegans. PloS one. 2014; 9:e114459. [PubMed: 25486066]

Grohm J, Kim SW, Mamrak U, Tobaben S, Cassidy-Stone A, Nunnari J, Plesnila N, Culmsee C. Inhibition of Drp1 provides neuroprotection in vitro and in vivo. Cell Death Differ. 2012; 19:1446–1458. [PubMed: 22388349]

Guan MX. Mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity. Mitochondrion. 2011; 11:237–245. [PubMed: 21047563]

Guillet V, Chevrollier A, Cassereau J, Letournel F, Gueguen N, Richard L, Desquiret V, Verny C, Procaccio V, Amati-Bonneau P. Ethambutol-induced optic neuropathy linked to OPA1 mutation and mitochondrial toxicity. Mitochondrion. 2010; 10:115–124. [PubMed: 19900585]

Guo Z, Hong Z, Dong W, Deng C, Zhao R, Xu J, Zhuang G, Zhang R. PM2.5-Induced Oxidative Stress and Mitochondrial Damage in the Nasal Mucosa of Rats. International journal of environmental research and public health. 2017:14.

Head B, Griparic L, Amiri M, Gandre-Babbe S, van der Bliek AM. Inducible proteolytic inactivation of OPA1 mediated by the OMA1 protease in mammalian cells. The Journal of cell biology. 2009; 187:959–966. [PubMed: 20038677]

Held NM, Houtkooper RH. Mitochondrial quality control pathways as determinants of metabolic health. Bioessays. 2015; 37:867–876. [PubMed: 26010263]

Heng JE, Vorwerk CK, Lessell E, Zurakowski D, Levin LA, Dreyer EB. Ethambutol is toxic to retinal ganglion cells via an excitotoxic pathway. Investigative ophthalmology & visual science. 1999; 40:190–196. [PubMed: 9888443]

Hepple RT. Why eating less keeps mitochondria working in aged skeletal muscle. Exercise and sport sciences reviews. 2009; 37:23–28. [PubMed: 19098521]

Hirata N, Yamada S, Asanagi M, Sekino Y, Kanda Y. Nicotine induces mitochondrial fission through mitofusin degradation in human multipotent embryonic carcinoma cells. Biochemical and Biophysical Research Communications. 2016; 470:300–305. [PubMed: 26774337]

Hoffmann RF, Zarrintan S, Brandenburg SM, Kol A, de Bruin HG, Jafari S, Dijk F, Kalicharan D, Kelders M, Gosker HR, Ten Hacken NH, van der Want JJ, van Oosterhout AJ, Heijink IH. Prolonged cigarette smoke exposure alters mitochondrial structure and function in airway epithelial cells. Respiratory research. 2013; 14:97. [PubMed: 24088173]

Hoppins S. The regulation of mitochondrial dynamics. Current opinion in cell biology. 2014; 29:46–52. [PubMed: 24747170]

Huang XH, Sun L, Ji SX, Zhao T, Zhang WR, Xu JJ, Zhang J, Wang YR, Wang XH, Franzini-Armstrong C, Zheng M, Cheng HP. Kissing and nanotunneling mediate intermitochondrial communication in the heart. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110:2846–2851. [PubMed: 23386722]

Ishihara N, Jofuku A, Eura Y, Mihara K. Regulation of mitochondrial morphology by membrane potential, and DRP1-dependent division and FZO1-dependent fusion reaction in mammalian cells. Biochem Biophys Res Commun. 2003; 301:891–898. [PubMed: 12589796]

Jendrach M, Mai S, Pohl S, Voth M, Bereiter-Hahn J. Short- and long-term alterations of mitochondrial morphology, dynamics and mtDNA after transient oxidative stress. Mitochondrion. 2008; 8:293–304. [PubMed: 18602028]

Juge R, Breugnot J, Da Silva C, Bordes S, Closs B, Aouacheria A. Quantification and Characterization of UVB-Induced Mitochondrial Fragmentation in Normal Primary Human Keratinocytes. Sci Rep. 2016; 6:35065. [PubMed: 27731355]

Kanazawa T, Zappaterra MD, Hasegawa A, Wright AP, Newman-Smith ED, Buttle KF, McDonald K, Mannella CA, van der Bliek AM. The C. elegans Opa1 homologue EAT-3 is essential for resistance to free radicals. PLoS genetics. 2008; 4:e1000022. [PubMed: 18454199]

Khan M, Syed GH, Kim SJ, Siddiqui A. Mitochondrial dynamics and viral infections: A close nexus. Biochimica et biophysica acta. 2015; 1853:2822–2833. [PubMed: 25595529]

Kirkman MA, Yu-Wai-Man P, Korsten A, Leonhardt M, Dimitriadis K, De Coo IF, Klopstock T, Chinnery PF. Gene-environment interactions in Leber hereditary optic neuropathy. Brain. 2009; 132:2317–2326. [PubMed: 19525327]

Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harbor perspectives in medicine. 2012; 2:a008888. [PubMed: 22315721]

Kowald A, Kirkwood TB. Evolution of the mitochondrial fusion-fission cycle and its role in aging. Proc Natl Acad Sci U S A. 2011; 108:10237–10242. [PubMed: 21646529]

Kuznetsov AV, Hermann M, Saks V, Hengster P, Margreiter R. The cell-type specificity of mitochondrial dynamics. Int J Biochem Cell Biol. 2009; 41:1928–1939. [PubMed: 19703655]

Lassus B, Magifico S, Pignon S, Belenguer P, Miquel M-C, Peyrin J-M. Alterations of mitochondrial dynamics allow retrograde propagation of locally initiated axonal insults. Scientific reports. 2016:6. [PubMed: 28442741]

Lee EJ, Kim SJ, Choung HK, Kim JH, Yu YS. Incidence and clinical features of ethambutol-induced optic neuropathy in Korea. Journal of Neuro-Ophthalmology. 2008; 28:269–277. [PubMed: 19145123]

Lemasters JJ. Variants of mitochondrial autophagy: Types 1 and 2 mitophagy and micromitophagy (Type 3). Redox biology. 2014; 2:749–754. [PubMed: 25009776]

Lenaers G, Hamel C, Delettre C, Amati-Bonneau P, Procaccio V, Bonneau D, Reynier P, Milea D. Dominant optic atrophy. Orphanet J Rare Dis. 2012:7. [PubMed: 22269211]

Leung MC, Rooney JP, Ryde IT, Bernal AJ, Bess AS, Crocker TL, Ji AQ, Meyer JN. Effects of early life exposure to ultraviolet C radiation on mitochondrial DNA content, transcription, ATP production, and oxygen consumption in developing Caenorhabditis elegans. BMC pharmacology & toxicology. 2013; 14:9. [PubMed: 23374645]

Lin YF, Schulz AM, Pellegrino MW, Lu Y, Shaham S, Haynes CM. Maintenance and propagation of a deleterious mitochondrial genome by the mitochondrial unfolded protein response. Nature. 2016; 533:416–419. [PubMed: 27135930]

Liu S, Sawada T, Lee S, Yu W, Silverio G, Alapatt P, Millan I, Shen A, Saxton W, Kanao T, Takahashi R, Hattori N, Imai Y, Lu B. Parkinson's disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria. PLoS genetics. 2012; 8:e1002537. [PubMed: 22396657]

Liu X, Weaver D, Shirihai O, Hajnoczky G. Mitochondrial 'kiss-and-run': interplay between mitochondrial motility and fusion-fission dynamics. EMBO J. 2009; 28:3074–3089. [PubMed: 19745815]

Lu H, Li G, Liu L, Feng L, Wang X, Jin H. Regulation and function of mitophagy in development and cancer. Autophagy. 2013; 9:1720–1736. [PubMed: 24091872]

Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denefle P, Wood NW, Agid Y, Brice A, Suscep ECG, Stu FPDG. Association between early-onset Parkinson's disease and mutations in the parkin gene. New Engl J Med. 2000; 342:1560–1567. [PubMed: 10824074]

Luz AL, Godebo TR, Smith LL, Leuthner TC, Maurer LL, Meyer JN. Deficiencies in mitochondrial dynamics sensitize Caenorhabditis elegans to arsenite and other mitochondrial toxicants by reducing mitochondrial adaptability. Toxicology. 2017

Lv H, Wang L, Zhang W, Wang Z, Zuo Y, Liu J, Yuan Y. A cohort study of Han Chinese MFN2-related Charcot–Marie–Tooth 2A. Journal of the neurological sciences. 2015; 358:153–157. [PubMed: 26382835]

Manella G, Asher G. The Circadian Nature of Mitochondrial Biology. Front Endocrinol. 2016:7.

Melentijevic I, Toth ML, Arnold ML, Guasp RJ, Harinath G, Nguyen KC, Taub D, Parker JA, Neri C, Gabel CV, Hall DH, Driscoll M. C. elegans neurons jettison protein aggregates and mitochondria under neurotoxic stress. Nature. 2017; 542:367–371. [PubMed: 28178240]

Merry TL, Ristow M. Mitohormesis in exercise training. Free Radical Bio Med. 2016; 98:123–130. [PubMed: 26654757]

Meyer JN, Bess AS. Involvement of autophagy and mitochondrial dynamics in determining the fate and effects of irreparable mitochondrial DNA damage. Autophagy. 2012; 8:1822–1823. [PubMed: 22929123]

Meyer JN, Leung MC, Rooney JP, Sendoel A, Hengartner MO, Kisby GE, Bess AS. Mitochondria as a target of environmental toxicants. Toxicol Sci. 2013; 134:1–17. [PubMed: 23629515]

Millet A, Bertholet AM, Daloyau M, Reynier P, Galinier A, Devin A, Wissinguer B, Belenguer P, Davezac N. Loss of functional OPA1 unbalances redox state: implications in dominant optic

atrophy pathogenesis. Annals of Clinical and Translational Neurology. 2016; 3:408–421. [PubMed: 27547769]

Mishra P, Chan DC. Mitochondrial dynamics and inheritance during cell division, development and disease. Nat Rev Mol Cell Biol. 2014; 15:634–646. [PubMed: 25237825]

Mishra P, Chan DC. Metabolic regulation of mitochondrial dynamics. The Journal of cell biology. 2016; 212:379–387. [PubMed: 26858267]

Mizumura K, Cloonan SM, Nakahira K, Bhashyam AR, Cervo M, Kitada T, Glass K, Owen CA, Mahmood A, Washko GR, Hashimoto S, Ryter SW, Choi AM. Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. J Clin Invest. 2014; 124:3987–4003. [PubMed: 25083992]

Molina AJ, Wikstrom JD, Stiles L, Las G, Mohamed H, Elorza A, Walzer G, Twig G, Katz S, Corkey BE, Shirihai OS. Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. Diabetes. 2009; 58:2303–2315. [PubMed: 19581419]

Mouli PK, Twig G, Shirihai OS. Frequency and selectivity of mitochondrial fusion are key to its quality maintenance function. Biophysical journal. 2009; 96:3509–3518. [PubMed: 19413957]

Mourier A, Motori E, Brandt T, Lagouge M, Atanassov I, Galinier A, Rappl G, Brodesser S, Hultenby K, Dieterich C, Larsson NG. Mitofusin 2 is required to maintain mitochondrial coenzyme Q levels. The Journal of cell biology. 2015a; 208:429–442. [PubMed: 25688136]

Mourier A, Motori E, Brandt T, Lagouge M, Atanassov I, Galinier A, Rappl G, Brodesser S, Hultenby K, Dieterich C, Larsson NG. Mitofusin 2 is required to maintain mitochondrial coenzyme Q levels. Journal of Cell Biology. 2015b; 208:429–442. [PubMed: 25688136]

Nakada K, Inoue K, Ono T, Isobe K, Ogura A, Goto Y, Nonaka I, Hayashi JI. Inter-mitochondrial complementation: Mitochondria-specific system preventing mice from expression of disease phenotypes by mutant mtDNA. Nature Medicine. 2001; 7:934–940.

Narendra D, Walker JE, Youle R. Mitochondrial quality control mediated by PINK1 and Parkin: links to parkinsonism. Cold Spring Harbor perspectives in biology. 2012:4.

Niranjan B, Bhat N, Avadhani N. Preferential attack of mitochondrial DNA by aflatoxin B1 during hepatocarcinogenesis. Science. 1982; 215:73–75. [PubMed: 6797067]

Olichon A, Baricault L, Gas N, Guillou E, Valette A, Belenguer P, Lenaers G. Loss of OPA1 perturbates the mitochondrial inner membrane structure and integrity, leading to cytochrome c release and apoptosis. J Biol Chem. 2003; 278:7743–7746. [PubMed: 12509422]

Palikaras K, Tavernarakis N. Mitochondrial homeostasis: The interplay between mitophagy and mitochondrial biogenesis. Experimental Gerontology. 2014; 56:182–188. [PubMed: 24486129]

Parameyong A, Charngkaew K, Govitrapong P, Chetsawang B. Melatonin attenuates methamphetamine-induced disturbances in mitochondrial dynamics and degeneration in neuroblastoma SH-SY5Y cells. Journal of pineal research. 2013; 55:313–323. [PubMed: 23889188]

Pareyson D, Saveri P, Sagnelli A, Piscosquito G. Mitochondrial dynamics and inherited peripheral nerve diseases. Neurosci Lett. 2015; 596:66–77. [PubMed: 25847151]

Pham AH, Meng S, Chu QN, Chan DC. Loss of Mfn2 results in progressive, retrograde degeneration of dopaminergic neurons in the nigrostriatal circuit. Hum Mol Genet. 2012; 21:4817–4826. [PubMed: 22859504]

Pletjushkina OY, Lyamzaev KG, Popova EN, Nepryakhina OK, Ivanova OY, Domnina LV, Chernyak BV, Skulachev VP. Effect of oxidative stress on dynamics of mitochondrial reticulum. Biochimica et biophysica acta. 2006; 1757:518–524. [PubMed: 16829229]

Ploumi C, Daskalaki I, Tavernarakis N. Mitochondrial biogenesis and clearance: a balancing act. The FEBS journal. 2017; 284:183–195. [PubMed: 27462821]

Podratz JL, Knight AM, Ta LE, Staff NP, Gass JM, Genelin K, Schlattau A, Lathroum L, Windebank AJ. Cisplatin induced mitochondrial DNA damage in dorsal root ganglion neurons. Neurobiology of disease. 2011; 41:661–668. [PubMed: 21145397]

Pradhan M, Sharp D, Best S, Vincent A, Vaphiades M. Drug-induced optic neuropathy-TB or not TB. Surv Ophthalmol. 2010; 55:378–385. [PubMed: 20083290]

Quist EM, Filgo AJ, Cummings CA, Kissling GE, Hoenerhoff MJ, Fenton SE. Hepatic Mitochondrial Alteration in CD-1 Mice Associated with Prenatal Exposures to Low Doses of Perfluorooctanoic Acid (PFOA). Toxicol Pathol. 2015; 43:546–557. [PubMed: 25326589]

Ravenscroft, P., Brammer, H., Richards, K. Arsenic Pollution: A Global Synthesis. John Wiley & Sons; West Sussex, United Kingdom: 2009.

Rehman J, Zhang HJ, Toth PT, Zhang Y, Marsboom G, Hong Z, Salgia R, Husain AN, Wietholt C, Archer SL. Inhibition of mitochondrial fission prevents cell cycle progression in lung cancer. Faseb J. 2012; 26:2175–2186. [PubMed: 22321727]

Roberts RF, Tang MY, Fon EA, Durcan TM. Defending the mitochondria: The pathways of mitophagy and mitochondrial-derived vesicles. Int J Biochem Cell Biol. 2016; 79:427–436. [PubMed: 27443527]

Ron-Harel N, Santos D, Ghergurovich JM, Sage PT, Reddy A, Lovitch SB, Dephoure N, Satterstrom FK, Sheffer M, Spinelli JB, Gygi S, Rabinowitz JD, Sharpe AH, Haigis MC. Mitochondrial Biogenesis and Proteome Remodeling Promote One-Carbon Metabolism for T Cell Activation. Cell Metab. 2016; 24:104–117. [PubMed: 27411012]

Rothfuss O, Fischer H, Hasegawa T, Maisel M, Leitner P, Miesel F, Sharma M, Bornemann A, Berg D, Gasser T, Patenge N. Parkin protects mitochondrial genome integrity and supports mitochondrial DNA repair. Hum Mol Genet. 2009; 18:3832–3850. [PubMed: 19617636]

Rouzier C, Bannwarth S, Chaussenot A, Chevrollier A, Verschueren A, Bonello-Palot N, Fragaki K, Cano A, Pouget J, Pellissier J-F. The MFN2 gene is responsible for mitochondrial DNA instability and optic atrophy 'plus' phenotype. Brain. 2011:awr323.

Rouzier C, Bannwarth S, Chaussenot A, Chevrollier A, Verschueren A, Bonello-Palot N, Fragaki K, Cano A, Pouget J, Pellissier JF, Procaccio V, Chabrol B, Paquis-Flucklinger V. The MFN2 gene is responsible for mitochondrial DNA instability and optic atrophy 'plus' phenotype. Brain. 2012; 135:23–34. [PubMed: 22189565]

Saben JL, Boudoures AL, Asghar Z, Thompson A, Drury A, Zhang W, Chi M, Cusumano A, Scheaffer S, Moley KH. Maternal Metabolic Syndrome Programs Mitochondrial Dysfunction via Germline Changes across Three Generations. Cell Rep. 2016; 16:1–8. [PubMed: 27320925]

Sadun AA, Wang MY. Ethambutol optic neuropathy: how we can prevent 100, 000 new cases of blindness each year. LWW. 2008

Scarpulla RC. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. Bba-Mol Cell Res. 2011; 1813:1269–1278.

Scheibye-Knudsen M, Fang EF, Croteau DL, Wilson DM 3rd, Bohr VA. Protecting the mitochondrial powerhouse. Trends Cell Biol. 2015; 25:158–170. [PubMed: 25499735]

Schmeisser S, Schmeisser K, Weimer S, Groth M, Priebe S, Fazius E, Kuhlow D, Pick D, Einax JW, Guthke R, Platzer M, Zarse K, Ristow M. Mitochondrial hormesis links low-dose arsenite exposure to lifespan extension. Aging cell. 2013; 12:508–517. [PubMed: 23534459]

Schon EA, Gilkerson RW. Functional complementation of mitochondrial DNAs: mobilizing mitochondrial genetics against dysfunction. Biochimica et biophysica acta. 2010; 1800:245–249. [PubMed: 19616602]

Schrepfer E, Scorrano L. Mitofusins, from Mitochondria to Metabolism. Mol Cell. 2016; 61:683–694. [PubMed: 26942673]

Senyilmaz D, Virtue S, Xu X, Tan CY, Griffin JL, Miller AK, Vidal-Puig A, Teleman AA. Regulation of mitochondrial morphology and function by stearoylation of TFR1. Nature. 2015; 525:124–128. [PubMed: 26214738]

Seo AY, Joseph AM, Dutta D, Hwang JCY, Aris JP, Leeuwenburgh C. New insights into the role of mitochondria in aging: mitochondrial dynamics and more. Journal of Cell Science. 2010; 123:2533–2542. [PubMed: 20940129]

Shirihai OS, Song MS, Dorn GW. How Mitochondrial Dynamism Orchestrates Mitophagy. Circulation Research. 2015; 116:1835–1849. [PubMed: 25999423]

Silva M, Aires C, Luis P, Ruiter J, Ijlst L, Duran M, Wanders R, De Almeida IT. Valproic acid metabolism and its effects on mitochondrial fatty acid oxidation: a review. Journal of inherited metabolic disease. 2008; 31:205–216. [PubMed: 18392741]

Sitarz KS, Yu-Wai-Man P, Pyle A, Stewart JD, Rautenstrauss B, Seeman P, Reilly MM, Horvath R, Chinnery PF. MFN2 mutations cause compensatory mitochondrial DNA proliferation. Brain. 2012; 135:e219, 211–213. author reply e220, 211–213.

Song Z, Ghochani M, McCaffery JM, Frey TG, Chan DC. Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion. Mol Biol Cell. 2009; 20:3525–3532. [PubMed: 19477917]

Sugiura A, McLelland GL, Fon EA, McBride HM. A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J. 2014; 33:2142–2156. [PubMed: 25107473]

Tang S, Le PK, Tse S, Wallace DC, Huang T. Heterozygous mutation of Opa1 in Drosophila shortens lifespan mediated through increased reactive oxygen species production. PloS one. 2009; 4:e4492. [PubMed: 19221591]

Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, Marras C, Bhudhikanok GS, Kasten M, Chade AR. Rotenone, paraquat, and Parkinson's disease. Environmental health perspectives. 2011; 119:866. [PubMed: 21269927]

Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. Nat Rev Genet. 2005; 6:389–402. [PubMed: 15861210]

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 DC, Alexander C, Bauer C, Youle R, Langer T, Martinou JC. SLP-2 is required for stress-induced mitochondrial hyperfusion. EMBO J. 2009; 28:1589–1600. [PubMed: 19360003]

Torralba D, Baixauli F, Sanchez-Madrid F. Mitochondria Know No Boundaries: Mechanisms and Functions of Intercellular Mitochondrial Transfer. Front Cell Dev Biol. 2016; 4:107. [PubMed: 27734015]

Toyama EQ, Herzig S, Courchet J, Lewis TL Jr, Loson OC, Hellberg K, Young NP, Chen H, Polleux F, Chan DC, Shaw RJ. Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. Science. 2016; 351:275–281. [PubMed: 26816379]

Truban D, Hou X, Caulfield TR, Fiesel FC, Springer W. PINK1, Parkin, and Mitochondrial Quality Control: What can we Learn about Parkinson's Disease Pathobiology? Journal of Parkinson's disease. 2016

Twig G, Hyde B, Shirihai OS. Mitochondrial fusion, fission and autophagy as a quality control axis: the bioenergetic view. Biochimica et biophysica acta. 2008a; 1777:1092–1097. [PubMed: 18519024]

Twig T, Elorza A, Molina AJA, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G, Alroy J, Wu M, Py BF, Yuan J, Deeney JT, Corkey BE, Shirihai OS. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. The EMBO Journal. 2008b; 27:433–446. [PubMed: 18200046]

van der Bliek AM. Fussy mitochondria fuse in response to stress. EMBO J. 2009; 28:1533–1534. [PubMed: 19494844]

Van der Bliek, AM., Shen, Q., Kawajiri, S. Mechanisms of Mitochondrial Fission and Fusion. In: Wallace, D., Youle, R., editors. Mitochondria. Cold Spring Harbor Laboratory Press; Cold Spring Harbor, New York: 2014. p. 127-142.

Vidoni S, Zanna C, Rugolo M, Sarzi E, Lenaers G. Why mitochondria must fuse to maintain their genome integrity. Antioxid Redox Signal. 2013; 19:379–388. [PubMed: 23350575]

Voigt A, Berlemann LA, Winklhofer KF. The mitochondrial kinase PINK1: functions beyond mitophagy. J Neurochem. 2016; 139(Suppl 1):232–239. [PubMed: 27251035]

Wang W, Lu J, Zhu F, Wei J, Jia C, Zhang Y, Zhou L, Xie H, Zheng S. Pro-apoptotic and anti-proliferative effects of mitofusin-2 via Bax signaling in hepatocellular carcinoma cells. Med Oncol. 2012; 29:70–76. [PubMed: 21190094]

Wei Y, Chiang WC, Sumpter R Jr, Mishra P, Levine B. Prohibitin 2 Is an Inner Mitochondrial Membrane Mitophagy Receptor. Cell. 2017; 168:224–238. e210. [PubMed: 28017329]

Weimer LH, Podwall D. Medication-induced exacerbation of neuropathy in Charcot Marie Tooth disease. Journal of the neurological sciences. 2006; 242:47–54. [PubMed: 16386273]

West AP, Shadel GS. Mitochondrial DNA in innate immune responses and inflammatory pathology. Nat Rev Immunol. 2017; 17:363–375. [PubMed: 28393922]

Westermann B. Bioenergetic role of mitochondrial fusion and fission. Biochimica et biophysica acta. 2012; 1817:1833–1838. [PubMed: 22409868]

Wikstrom JD, Twig G, Shirihai OS. What can mitochondrial heterogeneity tell us about mitochondrial dynamics and autophagy? Int J Biochem Cell Biol. 2009; 41:1914–1927. [PubMed: 19549572]

Willems PH, Rossignol R, Dieteren CE, Murphy MP, Koopman WJ. Redox Homeostasis and Mitochondrial Dynamics. Cell Metab. 2015; 22:207–218. [PubMed: 26166745]

Wood CE, Hester SD, Chorley BN, Carswell G, George MH, Ward W, Vallanat B, Ren HZ, Fisher A, Lake AD, Okerberg CV, Gaillard ET, Moore TM, Deangelo AB. Latent carcinogenicity of early-life exposure to dichloroacetic acid in mice. Carcinogenesis. 2015; 36:782–791. [PubMed: 25913432]

Xu S, Pi H, Chen Y, Zhang N, Guo P, Lu Y, He M, Xie J, Zhong M, Zhang Y, Yu Z, Zhou Z. Cadmium induced Drp1-dependent mitochondrial fragmentation by disturbing calcium homeostasis in its hepatotoxicity. Cell Death Dis. 2013a; 4:e540. [PubMed: 23492771]

Xu S, Pi H, Chen Y, Zhang N, Guo P, Lu Y, He M, Xie J, Zhong M, Zhang Y, Yu Z, Zhou Z. Cadmium induced Drp1-dependent mitochondrial fragmentation by disturbing calcium homeostasis in its hepatotoxicity. Cell Death Dis. 2013b; 4:e540. [PubMed: 23492771]

Yamada S, Kubo Y, Yamazaki D, Sekino Y, Kanda Y. Chlorpyrifos inhibits neural induction via Mfn1-mediated mitochondrial dysfunction in human induced pluripotent stem cells. Sci Rep. 2017; 7:40925. [PubMed: 28112198]

Yan Z, Lira VA, Greene NP. Exercise training-induced regulation of mitochondrial quality. Exercise and sport sciences reviews. 2012; 40:159–164. [PubMed: 22732425]

Yang CC, Chen D, Lee SS, Walter L. The dynamin-related protein DRP-1 and the insulin signaling pathway cooperate to modulate Caenorhabditis elegans longevity. Aging cell. 2011; 10:724–728. [PubMed: 21463460]

Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. Science. 2012; 337:1062–1065. [PubMed: 22936770]

Yu-Wai-Man P, Sitarz KS, Samuels DC, Griffiths PG, Reeve AK, Bindoff LA, Horvath R, Chinnery PF. OPA1 mutations cause cytochrome c oxidase deficiency due to loss of wild-type mtDNA molecules. Hum Mol Genet. 2010; 19:3043–3052. [PubMed: 20484224]

Yun J, Finkel T. Mitohormesis. Cell Metab. 2014; 19:757–766. [PubMed: 24561260]

Zhao J, Zhang J, Yu M, Xie Y, Huang Y, Wolff DW, Abel PW, Tu Y. Mitochondrial dynamics regulates migration and invasion of breast cancer cells. Oncogene. 2013; 32:4814–4824. [PubMed: 23128392]

Zick M, Rabl R, Reichert AS. Cristae formation-linking ultrastructure and function of mitochondria. Biochimica et biophysica acta. 2009; 1793:5–19. [PubMed: 18620004]

Zubovych IO, Straud S, Roth MG. Mitochondrial dysfunction confers resistance to multiple drugs in Caenorhabditis elegans. Mol Biol Cell. 2010; 21:956–969. [PubMed: 20089839]

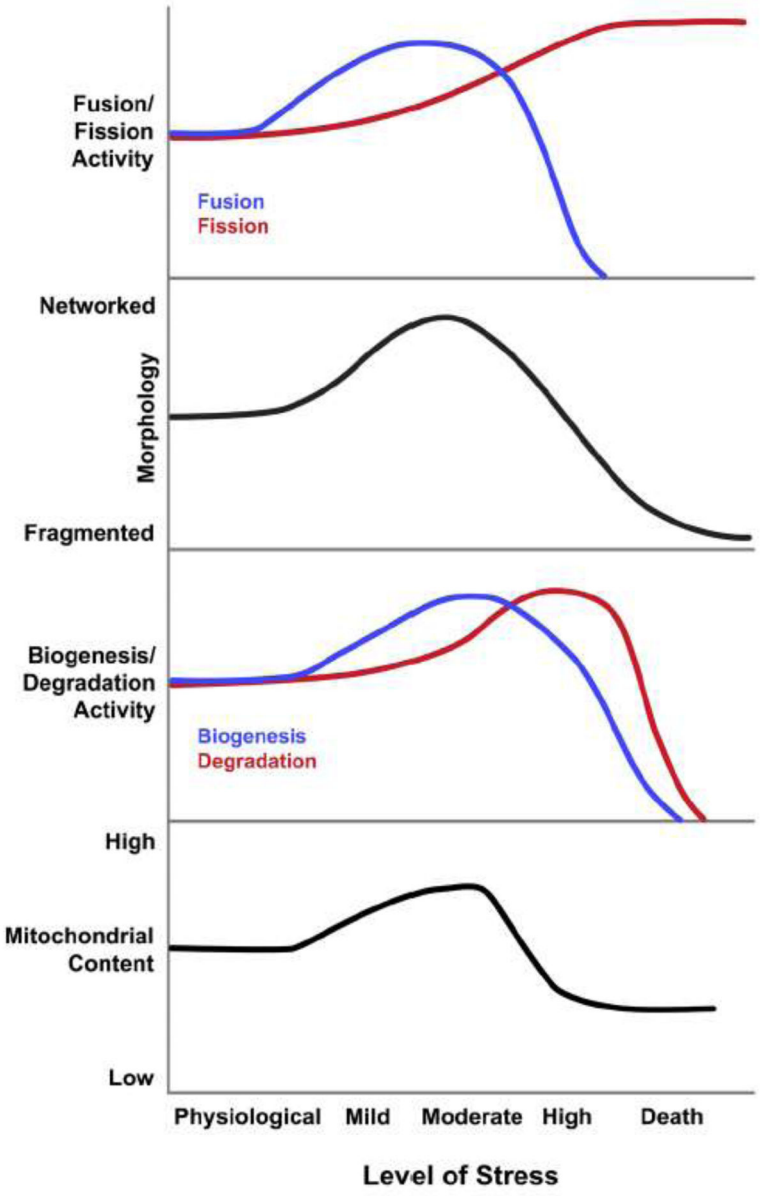

Fig. 1.

Theoretical schematic of the influence of the level of stress on mitochondrial fusion, fission, morphology, biogenesis, and degradation. Note that these patterns would vary by cell type, with length of exposure and time since exposure, and possibly with type of stress (e.g., chemical, dietary, exercise, infection, etc.). For example, starvation results in fusion but not biogenesis. It may be important to consider how these patterns would affect other parameters such as ATP levels, and energy expenditures, ROS production, membrane potential.

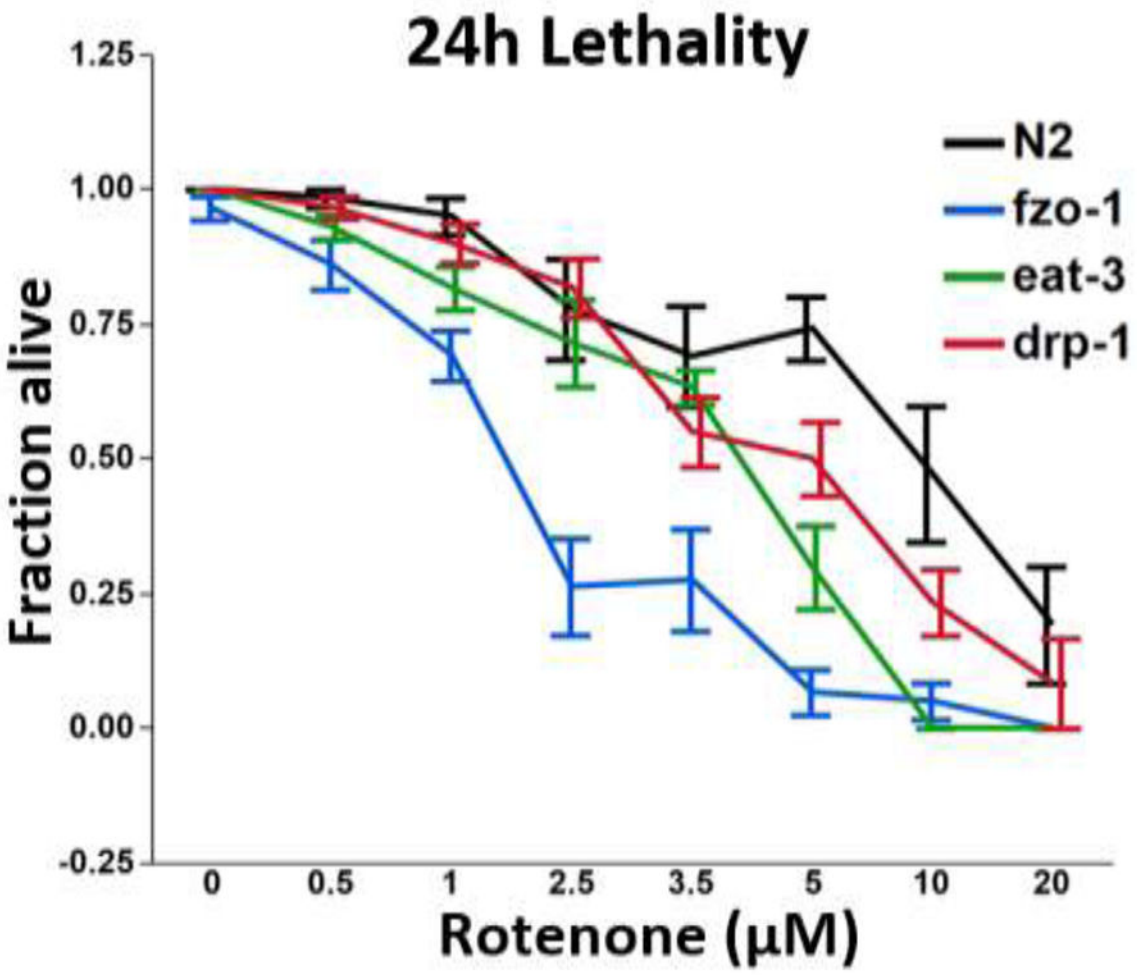

Fig. 2.

Deficiencies in mitochondrial fission (drp-1 (LC50 = 7.5 ± 1.3 µM rotenone)) and fusion (fzo-1 (LC50 = 2.5 ± 0.6 µM), eat-3 (LC50 = 3.8 ± 0.7 µM)) genes sensitize 8-day old nematodes to rotenone-induced lethality.

Table 1

Human disease genes involved in mitochondrial dynamics

Note that this list is not exhaustive, and in particular excludes mitochondrial biogenesis. Incidence values are as cited or estimated: CMT affects 1/2500, but MFN2 deficiency causes type IIA in 20–40% of those cases, so ~1/7,500 (Cartoni and Martinou 2009). Parkinson's Disease currently afflicts ~1/300; of which roughly 10% of cases are early-onset. PARK2 mutations account for as much as 50% (Lucking et al. 2000), and PINK1 ~5% (Bonifati et al. 2005) of early-onset cases, leading to the estimates presented.

Human Gene	Estimated Disease Incidence	Human Disease	Function
MFN2	~1/7500	Charcot-Marie Tooth Neuropathy type 2A	Outer membrane fusion
OPA1	~1/10,000–1/30,000 (Lenaers et al. 2012)	Dominant Optic Atrophy	Inner membrane fusion
DRP1	Very rare (a few known cases) (Mishra and Chan 2016)	Neuro-degeneration and early death	Fission
PARK2	~1/6,000	Parkinson's Disease	Mitophagy
PINK1	~1/60,000	Parkinson's Disease	Mitophagy

Table 2

Literature reports of toxicant exposures that affect mitochondrial fusion, fission, or morphology.

Toxicant class	Toxicant/stressor	Phenotype	Exposure	Model	Reference
Air pollution	Particulate matter ($PM_{2.5}$)	-Increased *Mnf1* and *Opa1* mRNA and protein expression -Decreased *Drp1* and *Fis1* mRNA and protein expression	*In vivo* inhalation to 200, 1000, 3000 μg/m^3 $PM_{2.5}$	Rat nasal mucosal tissues	(Guo et al. 2017)
	Ozone (O_3)	-Decreased cristae length (1 μg O_3/mL) -Increased cristae length and mtHsp70 expression (10 μg O_3/mL)	1 and 10 μg O_3/mL	HeLa cells	(Costanzo et al. 2015)
Cigarette smoke components	Cigarette smoke extract (CSE)	-Decreased mitochondrial branching and branch length -Decrease in *MFN1*, *MFN2*, and *OPA1* expression -Increase in *DRP1* and *FIS1* expression	1% CSE for 48 hrs	Human airway smooth muscle cells	(Aravamudan et al. 2014)
	Nicotine	-Increased fission and reduced MNF1/2 protein	10 mM nicotine	Human embryonal carcinoma cells (NT2/D1)	(Hirata et al. 2016)
Drugs	Cisplatin	-Reduced *Mnf2* expression in proximal nerve segments -Reduced *Mnf2*, *Opa1*, and *Drp1* expression in distal nerve segments -Reduced *Opa1* expression in Schwann cells	IP injection of 3 mg/kg bodyweight twice a week for 2 weeks	Mouse tibial nerves and dorsal root ganglia (L1–L4)	(Bobylev et al. 2017)
	Doxorubicin (DXR)	-Hyperfusion -Increased *MFN1* and *OPA1* expression	7.2 μM DXR for 24 hrs	Human fibroblasts	(Ashley and Poulton 2009)
	MDMA (“ecstasy”)	-Increased fragmentation and decreased mitochondrial trafficking	20 μM MDMA mixture for 24 hrs	Mouse primary hippocampal neurons	(Barbosa et al. 2014)
	Meth[1]	-Increased expression of *FIS1* and *DRP1*	0.5, 1, 2 mM Meth for 24 hrs	Human neuroblastoma SH- SY5Y	(Parameyong et al. 2013)
Industrial compounds	PFOA[2]	-Increased numbers of mitochondria and abnormal mitochondrial morphology	*In utero* exposure (GD 1–17) to 1 mg/kg bodyweight dam	Post-natal day 91 mouse livers	(Quist et al. 2015)
Metals	Cadmium	-Increased fragmentation -Increased *Drp1* expression	*In vitro:* 12uM $CdCl_2$ *In vivo*: 2mg/kg $CdCl_2$	Rat hepatocytes	(Xu et al. 2013b)
	Manganese	-Increased DRP1 protein -Decreased OPA1 protein	Infusion of 1 μM $MnCl_2$	Rat glia	(Alaimo et al. 2014)
	MeHg[3]	-Increased fragmentation	20 μM MeHg	Human HepG2 cells	(Das et al. 2017)
Pesticides	Chlorpyrifos	-Increased fragmentation and decreased mitochondrial membrane potential -Reduced MFN1 protein	30 μM for 24 hrs	Human stem cell-derived neural progenitor cells	(Yamada et al. 2017)
Mitochondrial uncouplers	2,4-DNP[4]	-Increased *opa1* and *peo1* mRNA at 6 hpf	50 μM DNP at 3 hours post fertilization (hpf)	*Danio rerio*	(Bestman et al. 2015)

Toxicant class	Toxicant/stressor	Phenotype	Exposure	Model	Reference
		-Decreased *opa1, peo1,* and *drp1* mRNA at increasing time points			
	CCCP[5]	-Increased fragmentation	20 μM CCCP for 1 to 3 hours	HeLa cells	(Ishihara et al. 2003)
	FCCP[5]	-Increased fragmentation	10 μM FCCP for 48 to 72 hours	HeLa cells	(Pletjushkina et al. 2006)
UV irradiation	UVB	-Increased fragmentation -Accumulation of DRP1 on OMM	100 mJ/cm^2	Normal human epidermal keratinocytes	(Juge et al. 2016)
	UVC	-Increased fusion	60 mJ/cm^2	Mouse embryonic fibroblasts	(Tondera et al. 2009)
	UVB	-Decrease in cristae -Increased fragmentation -Increased *Drp-1* expression (1, 12, 24, and 48h post exposure) -Decreased *Mfn-1* expression (24h post exposure)	558 J/cm^2 UVB for 30 min	Freshwater prawn *Macrobrachium olfersi*	(de Quadros et al. 2016)

[1]Methamphetamine;

[2]Perfluoro-octanoic acid;

[3]Methyl-mercury;

[4]2,4-Dinitrophenol;

[5]Carbonyl cynanide m-chlorophenylhydrazone;

[6]Carbonyl cyanide-p-trifluoromethoxyphenylhydrasone

Table 3

Deficiencies in fission and fusion sensitize to toxicity following drug administration or environmental toxicant exposure

Accumulating evidence from multiple model organisms suggests that genetic deficiencies in mitochondrial fusion (MFN2, OPA1) may sensitize an individual to toxicity following mitochondrial toxicant exposure, whereas deficiencies in mitochondrial fission more frequently provide protection from toxicity.

Function	Gene	Model Organism	Toxicant	Experimental outcome	Reference
OMM Fusion	*fzo-1*[1]	*C. elegans*	Acrolein	Reduced sensitivity to larval growth delay	(Luz et al. 2017)
	fzo-1	*C. elegans*	Cadmium	Reduced sensitivity to larval growth delay	(Luz et al. 2017)
	fzo-1	*C. elegans*	UVC-induced mtDNA damage	Sensitive to larval growth arrest	(Bess et al. 2012)
	fzo-1	*C. elegans*	Aflatoxin B_1	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	fzo-1	*C. elegans*	Cisplatin	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	fzo-1	*C. elegans*	Arsenite	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	fzo-1	*C. elegans*	2,4-DNP	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	fzo-1	*C. elegans*	Rotenone	Sensitive to rotenone-induced lethality & larval growth delay	Figure 2 & (Luz et al. 2017)
	fzo-1	*C. elegans*	Paraquat	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	MFN2	Humans	Ethambutol	Accelerated muscle weakness, optic atrophy, vocal cord paralysis in CMT2A patient	(Fonkem et al. 2013)
IMM Fusion	*eat-3*[2]	*C. elegans*	Hemiasterlin	Increase survival	(Zubovych et al. 2010)
	eat-3[2]	*C. elegans*	Acrolein	Reduced sensitivity to larval growth delay	(Luz et al. 2017)
	eat-3	*C. elegans*	UVC-induced mtDNA damage	Larval growth arrest	(Bess et al. 2012)
	eat-3	*C. elegans*	Aflatoxin B_1	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	eat-3	*C. elegans*	Cisplatin	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	eat-3	*C. elegans*	Arsenite	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	eat-3	*C. elegans*	2,4-DNP	Increased sensitivity to larval growth delay	(Luz et al. 2017)
	OPA1	Humans	Ethambutol	Induced optic atrophy in patients harboring OPA1 mutations with no visual impairment prior to treatment	(Guillet et al. 2010; Pradhan et al. 2010)
	eat-3	*C. elegans*	Paraquat	Reduced survival time & increased sensitivity to larval growth delay	(Kanazawa et al. 2008; Luz et al. 2017)
	OPA1	*Drosophila*	Paraquat	Reduced survival time	(Tang et al. 2009)
	eat-3	*C. elegans*	Rotenone	Sensitive to rotenone-induced lethality & larval growth delay	Figure 2 & (Luz et al. 2017)
	OPA1	P5 Swiss mice	Rotenone	Increased axonal degeneration in isolated primary cerebellar granule neurons	(Lassus et al. 2016)

Function	Gene	Model Organism	Toxicant	Experimental outcome	Reference
	OPA1	Wistar rat cortical neurons	Rotenone	Decreased cell viability in Wistar rat neurons transfected with siOPA1	(Millet et al. 2016)
Fission	*DRP1*	*C. elegans*	Rotenone	Aged nematodes display sensitivity to rotenone-induced lethality, while larval nematodes are insensitive to growth delay	Figure 2 & (Luz et al. 2017)
	DRP1	*C. elegans*	Paraquat	Reduced survival time & mild sensitivity to larval growth delay	(Yang et al. 2011); (Luz et al. 2017)
	DRP1	*C. elegans*	Arsenite	Reduced survival time in aging nematodes & sensitivity to reproductive toxicity	(Luz et al. 2017)
	DRP1	*C. elegans*	Acrolein	Reduced sensitivity to larval growth delay	(Luz et al. 2017)
	DRP1	Human SH-SY5Y cells	6-Hydroxydopamine	*DRP1* siRNA reduced cell death	(Gomez-Lazaro et al. 2008)
	DRP1	Human L02 liver cells	Cadmium	*DRP1* siRNA reduced mitochondrial dysfunction	(Xu et al. 2013a)
	DRP1	Rat astrocytoma C6 cells	Manganese	*DRP1* siRNA reduced cell death	(Alaimo et al. 2014)
	DRP1	Mouse HT22 neurons	Glutamate	*DRP1* siRNA reduced cell death	(Grohm et al. 2012)

[1] *fzo-1* is the *C. elegans* homolog of MFN2.

[2] *eat-3* is the *C. elegans* homolog of OPA1.