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Mitochondrial dynamics in adaptive and maladaptive cellular stress responses

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Abstract

Mitochondria sense and respond to many stressors and can support either cell survival or death through energy production and signaling pathways. Mitochondrial responses depend on fusion-fission dynamics that dilute and segregate damaged mitochondria. Mitochondrial motility and inter-organellar interactions, including with the endoplasmic reticulum, also function in cellular adaptation to stress. In this Review, we discuss how stressors influence these components, and how they contribute to the complex adaptive and pathological responses that lead to disease.

Cells maintain a dynamic balance of key intracellular parameters, which is constantly perturbed by internal and external “stressors”. The “stress response” is the process elicited by stressors to restore homeostasis. A critical aspect of all molecular and physiological stress response systems is their requirement for energy, in part provided by mitochondria¹. Mitochondria are unique organelles with their own genome, which sustain life via energy transformation and perform several biochemical functions implicated in intracellular signaling and dynamics. Mitochondrial stress responses are central to cell fate, health and disease at the tissue and organismal level (Figure 1)^{2,3}. Mitochondrial dynamics are also critical to stress responses². Understanding the types of mitochondrial stressors, their interplay with mitochondrial dynamics and the mechanisms that orchestrate how cells or organisms respond to them is critical to understanding the transition between health and disease. In the following sections we discuss the mechanisms underlying these facets of mitochondrial biology and their integration with other contributing factors in adaptation and maladaptation of cells, tissues and organisms.

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Mitochondrial stressors and cellular stress responses

Stressors can be chemical or physical, acute or chronic (Figure 1, left). Many stressors target non-mitochondrial cell constituents, but pathways often converge on the mitochondrion, reflecting its key role in energy production and signaling required for surviving and adapting to stressors¹. Mitochondria are integral to programmed cell death required for removal of cells fatally damaged by stressors that exceed the cell's adaptive capacity^{2,3}. Other stressors directly target and interfere with mitochondrial functions, including oxidative phosphorylation, intermediate metabolism, cell death, calcium signaling or cell dynamics².

Among stressors that directly target mitochondria are genetic alterations in mitochondrial and nuclear DNA genes (mtDNA and nDNA genes respectively) that encode >1,000 mitochondrial proteins, including the mtDNA maintenance machinery³. Accumulation of mtDNA mutations or mtDNA depletion interferes with oxidative metabolism and disrupts electron transport chain (ETC) function, which impairs mitochondrial ATP production, one- and two-carbon metabolism, and the transmembrane potential (Ψ_m) and proton motive force that drive multiple mitochondrial functions³. nDNA mutations may directly alter other mitochondrial functions, including their dynamics⁴.

Deprivation of mitochondrial fuel substrates or oversupply of nutrients, including glucose and fatty acids, are also mitochondrial stressors⁴. Disturbances of intracellular iron⁵ and calcium (Ca^{2+}) homeostasis, such as prolonged stimulation by Ca^{2+} -linked agonists, insufficient cytoplasmic Ca^{2+} clearance or decreased mitochondrial Ca^{2+} gatekeeping are also stressors^{6,7}. Various stressors induce increased reactive oxygen species (ROS) production by the respiratory chain, with mitochondria being a prominent source of ROS and subject to ROS-mediated injury⁸. Physiological ETC activity generates ROS that may support signaling mechanisms. However, ETC dysfunction leads to increased ROS production that is commonly pathogenic^{3,8}. Although mitochondrial ROS is an ETC stress response, mitochondria can also be the target of ROS produced by other organelles or of extracellular origin (e.g. generated by ultraviolet (UV) light), in which ROS is a mitochondrial stressor that can elicit changes in mtDNA (e.g. mutations or deletions), mitochondrial lipids and proteins⁸.

Numerous cell permeable toxins also target mitochondria. Rotenone and Antimycin A inhibit complex I and III, respectively, to enhance ROS, whereas the proton ionophores FCCP and DNP depolarize mitochondria to uncouple ETC from ATP production⁹. Alcohol is metabolized in the mitochondria to give rise to toxic products¹⁰. Staurosporine targets apoptosis-related proteins located at or translocated to mitochondria, including BAX and BAK¹¹. Pro-apoptotic chemicals are commonly used research reagents, whereas inhibitors of anti-apoptotic BCL-2 family proteins have been developed for anti-tumor therapy¹¹. Infectious agents such as bacteria and viruses also commonly target mitochondrial function and structure, and elicit immune responses involving mitochondria.

Mitochondrial dynamics

Mitochondrial function and response to stimuli is defined by their complex structure and dynamics. Mitochondria contain outer and inner mitochondrial membranes (OMM and IMM), which border the intermembrane space (IMS) and the matrix. The IMM associates with the OMM at contact points and forms extensive inward folding to form cristae. Each of these compartments has discrete functions in oxidative metabolism, biosynthetic pathways and signaling¹². Mitochondrial dynamics involve reshaping, rebuilding and recycling events that support mitochondrial stability, abundance, distribution and quality and allow compensatory changes when cells are challenged (Figure 2AB).

Reshaping mechanisms do not affect total mitochondrial mass and commonly represent reversible changes at the individual organelle level. By contrast, rebuilding and recycling alter mitochondrial mass and include unidirectional processes such as *de novo* synthesis of mitochondrial building blocks by mitochondrial biogenesis¹³, and recycling via mitochondrial derived vesicles (MDVs) or mitophagy, in which mitochondria are selectively targeted to autophagosomes for degradation¹⁴. Large-scale OMM or IMM permeabilization triggers cells to die, allowing replacement by surviving cells carrying healthy organelles. Whereas recycling has been covered by recent reviews², emerging evidence links stress to reshaping, and is the main subject of this Review. Reshaping, rebuilding and recycling mechanisms are complexly interrelated, for example with respect to metabolic adaptation to changes in substrate availability after birth¹⁵.

Mitochondrial reshaping mechanisms and responses to stressors

Mitochondrial Motility

Mitochondrial trafficking and localization throughout the cytoplasm depends on interactions with the cytoskeleton and molecular motors¹⁶. MIRO1/2 are OMM-localized small GTPase-like proteins¹⁷ that anchor mitochondria to either kinesin or dynein (Figure 2A), motors for anterograde or retrograde displacement along microtubules, respectively, via TRAK1/2 adaptors¹⁶. Myosin motors can also facilitate mitochondrial positioning¹⁸ and short-distance movement along actin filaments¹⁹. Stable mitochondrial localization in axons is supported by syntaphilin, an OMM protein directly linking mitochondria to microtubules²⁰.

Asymmetry and compartmentalization of cellular behavior require mitochondrial transport to different cellular regions. Motility is central to partitioning mitochondria for cell division^{21, 22}. Mitochondrial transport along axons and dendrites and accumulation in the regions of high energy demand are required to maintain neural activity^{23, 24}. Movements of energy-producing organelles may redistribute the spatial pattern of ATP production and Ca²⁺ buffering²⁵. Mitochondrial movements also support fusion-fission²⁶ and organelle recycling²⁷. Impairment of axonal mitochondrial transport is linked to neurological phenotypes in mouse models targeting MIRO^{23, 28, 29} or MFN^{23, 30, 31} (Table1).

Mitochondrial motility is controlled by cytoplasmic [Ca²⁺] ([Ca²⁺]_c)²⁵. Physiological [Ca²⁺]_c transients suppress mitochondrial movements through MIRO1/2 EF-hand Ca²⁺ sensing domains³² and may involve other Ca²⁺ sensors²³. The dynamic interplay between

Ca²⁺ release, mitochondrial motility and mitochondrial Ca²⁺ uptake forms the basis for a homeostatic mechanism in mitochondrial distribution and calcium signaling^{25, 33}. ROS also suppress mitochondrial motility in Ca²⁺-dependent and independent manners^{34, 35}. Furthermore, extracellular glucose elevation leads to mitochondrial motility inhibition by activating *O*-GlcNAc transferase to target TRAK³⁶.

Whereas Ca²⁺ signaling transients, ROS and glucose fluctuations are physiological regulators of mitochondrial motility, larger and more prolonged changes in the same factors can pathologically alter movement dynamics (Figure 2C)^{7, 8}. Ca²⁺ and ROS mutually strengthen each other and can generate cycles impairing motility^{35, 37}. In skeletal myoblasts, H₂O₂ inhibits mitochondrial motility and prompts fragmentation³⁸. In neurons and other cell types, ROS induces Ca²⁺ transients and activates mitogen-activated protein kinases (MAPKs) (JNK, p38) to cause mitochondrial motility inhibition^{35, 37}. Starvation also activates p38 MAPK phosphorylation of ubiquitin ligase Gp78, interfering with mitochondrial motility and disrupting ER-mitochondrial contacts³⁹. In injured axon zones, mitochondrial density increases to support axon regeneration by local energy production⁴⁰, highlighting an adaptive response to acute injury. Mitochondrial density might increase because mitochondria are retained by stabilized syntaphilin⁴¹. Yet, in cortical neurons after mild, reversible mitochondrial stress induced by Antimycin A, mitochondria carrying syntaphilin are recycled by retrograde trafficking and fusion with late endosomes and lysosomes⁴². In cancer cells, hypoxia and ROS target alternatively spliced syntaphilin, enhancing mitochondrial trafficking associated with tumor cell migration and invasion⁴³.

Mitochondrial transport in axons is suppressed by deletion or expression of disease mutants of the fusion protein mitofusin 2 (MFN2) that interacts with MIRO³⁰. The mitochondrial motility machinery is also targeted by degradative pathways upon stress. Dissipation of Ψ_m leads to PINK1 stabilization, inducing Parkin to mark MIRO for proteasome degradation and halting mitochondrial movement, possibly to prevent spreading of dysfunctional organelles along neurons⁴⁴. In cortical neurons, mitochondrial damage triggers PINK1/Parkin to induce MIRO1 ubiquitination on Lys27, arresting mitochondria for degradation⁴⁵. Oxidative stress activates the OMM-associated PGAM5-KEAP1-Nrf2 pathway leading to MIRO2 proteasomal degradation, causing mitochondrial retrograde trafficking and perinuclear localisation⁴⁶. Perinuclear mitochondrial clustering creates an oxidant-rich nuclear domain required for hypoxia-induced transcription⁴⁷. Oxidative stress and starvation are also sensed by Myo19, an actin-linked motor that retains mitochondria in areas of low ATP/ADP ratio⁴⁸. Upon mechanical injury to neurons, axon regeneration depends on ARM CX1 expression localized to mitochondria, which enhances mitochondrial transport⁴⁹. Mitochondrial stress responses involve the mitochondrial motility machinery, allowing mitochondrial redistribution to areas where bioenergetic needs are increased, or by recycling damaged organelles²⁵.

Mitochondrial fusion and fission dynamics

Mitochondrial movements along cellular tracks facilitate encounters between two distant organelles, permitting fusion^{26, 32} involving successive mixing of compartments: i) OMM merging mediated by the mitofusin 1 (MFN1) and MFN2 GTPases, ii) IMS mixing, iii)

IMM fusion mediated by OPA1 GTPase, and iv) matrix complementation^{50, 51}. The fusion product can remain an individual organelle or undergo division upon cytoplasmic DRP1 GTPase recruitment to the OMM by MFN⁵² mediated by MID49/51⁵³. Transient actin polymerization at the OMM constriction site⁵⁴ and cytoplasmic Dynamin 2 facilitate fission completion⁵⁵. Mitochondria fission can also be facilitated by motors of opposing directions²⁶ (Figure 2A).

Fusion-mediated mitochondrial component sharing supports multiple elements of mitochondrial biology: mtDNA integrity⁵⁶, mitochondrial respiration⁵⁷, Ψ_m equilibration⁵⁸, apoptosis⁵¹ and signaling events such as $[Ca^{2+}]_c$ oscillations⁵⁹. Fission can facilitate motility and is required for segregation of damaged mitochondria for mitophagy⁵⁸, mtDNA replication⁶⁰ and mitochondrial redistribution during cell division⁶¹. Thus, mitochondrial fusion/fission dynamics is central to organelle quality control and a variety of cellular functions. To test the physiological relevance of fusion-fission proteins, and the pathophysiology associated with their perturbation, genetic models have been created for MFNs, OPA1 and DRP1 in mouse (Table 1). Whole body knockouts for each interfere with early development and are embryonic lethal^{62–65}. Organ-specific knockouts are either lethal or cause severe dysfunction of the affected organ: as observed in the nervous system^{23, 66–69}, heart^{70–74} and skeletal muscle^{75–77}. Mice expressing human disease-causing mutations of MFN2 or OPA1 display the symptoms of Charcot-Marie-Tooth type 2A disease (CMT2A) or Autosomal Dominant Optical Atrophy (ADOA), respectively^{63, 67, 78–82, 83} (Table 1).

Mitochondrial fusion-fission balance is regulated transcriptionally and post-transcriptionally. MFN2 expression is enhanced by PGC-1 α (peroxisome proliferator gamma coactivator 1 alpha)⁸⁴. MFN1/2 and OPA1 levels and activity are affected by phosphorylation⁸⁵, redox modifications⁸⁶, acetylation⁸⁷ and ubiquitination^{88, 89}. OPA1 is proteolytically processed by the AAA proteases OMA1 and YME1L, which are regulated by Ψ_m ⁹⁰ and OXPHOS activity⁹¹, respectively. OPA1 function is regulated by cardiolipin in the IMM to prompt fusion⁹². DRP1 recruitment to the OMM and fission are controlled by Ca^{2+} - and cAMP-stimulated phosphoregulatory events⁹³.

Through a combination of the mechanisms described above, stressors can cause a hyper-elongated mitochondrial network by stimulation of fusion and/or inhibition of fission; or fragmented mitochondria by stimulation of fission and/or inhibition of fusion. Hyper-elongation and fragmentation can occur sequentially within minutes to hours³⁵ (Figure 2C). A given stressor can induce distinct mitochondrial fusion-fission phenotypes in different cells and tissues, and different stressors can induce opposing phenotypes in the same cell type. Although incompletely understood, specific mitochondrial responses to a given stressor are likely determined by a combination of interacting factors, including fusion-fission factor basal expression, biochemical and metabolic cell state, chronic stressors, and other unknown factors. Thus, a complex relationship exists between stressors and dynamic fusion-fission phenotypes.

In terms of mechanisms affecting fusion, several stressors converge on OMA1 and YME1L proteases, which control OPA1 fusogenic activity⁹⁴. Increased OXPHOS activity in cells

grown on ketogenic carbon sources promotes YME1L-mediated OPA1 processing, increasing fusion⁹¹. Mitochondrial poisons causing oxidative stress and ATP depletion suppress YME1L activity via degradation⁹⁴. Mouse embryonic fibroblasts (MEFs) and cell line exposure to UV-irradiation, serum deprivation or protein synthesis inhibitors leads to mitochondrial hyperfusion, dependent on MFN1 and OPA1 and an IMM scaffold protein, SLP2⁹⁵. SLP2 restricts OMA1-mediated OPA1 processing to support hyperfusion⁹⁶. Downstream of hyperfusion and engagement of the mitochondrial E3 ubiquitin ligase/SUMOylase MULAN/MAPL, NFkB is activated, likely as an adaptive mechanism to promote anti-apoptotic protein expression⁹⁷. Pathological cardiac stress leads to mitochondrial fusion inhibition through OPA1 hyperacetylation, normally prevented by the mitochondrial matrix deacetylase, SIRT3⁸⁷. Conversely, pressure overload challenge in the heart activates TNF α receptor type 2, OPA1 expression and fusion dependent on STAT3 and NFkB activation⁹⁸.

As to fission mechanisms and regulation, starvation induces hyperfused mitochondria by inhibiting fission, protecting the organelle from autophagic degradation^{93, 99}. High glucose causes mitochondrial fission to mediate apoptosis in pancreatic beta-cells¹⁰⁰. Similarly, high glucose exposure of cardiac cells leads to elevated ROS and mitochondrial fission¹⁰¹, whereas acute intracellular ROS elevation leads to DRP1-mediated mitochondrial fission¹⁰². ETC inhibition by rotenone or antimycin A recruits DRP1, promoting fission to support autophagic removal of damaged organelles via AMPK activation mediated by MFF phosphorylation¹⁰³. AMPK likely senses an AMP/ATP ratio increase to phosphorylate MFF but other factors may function in this process, as glucose starvation-related increase in AMP/ATP ratio is associated with inhibited fission. An oxidative stress-response pathway, Keap1-NRF2 is a key regulator of DRP1 levels, leading to hyperelongated mitochondria and cell survival¹⁰⁴. Mitochondrial depolarization combined with sustained $[Ca^{2+}]_c$ elevation activates the cytoplasmic phosphatase calcineurin that dephosphorylates DRP1 Ser637 to stimulate mitochondrial fission¹⁰⁵. In skeletal muscle, metabolic oversupply during sustained contractile inactivity also causes DRP1 Ser616 phosphorylation associated with mitochondrial fragmentation¹⁰⁶. Conversely, upon high fat diet, calcineurin inhibition prevents DRP1 Ser637 dephosphorylation leading to hyperelongated mitochondria and improved metabolic performance in skeletal muscle¹⁰⁷. Mechanical stress induced by bacterial infection also leads to mitochondrial fission¹⁰⁸. DRP1 activation has been linked to apoptosis mediated by BCL-2 family proteins². However, most of the above results suggest that long mitochondria provide protection against stressors. Whereas shorter mitochondria are thought to be maladaptive, this is not always the case, as mitochondrial shortening by fission supports lymphocyte migration¹⁰⁹ and effector T cell activation¹¹⁰.

Fusion-fission perturbation by stressors gives rise to complex mitochondrial shapes. Hypoxia-reoxygenation and other stressors can cause donut-shaped mitochondria via autofusion between the two ends of tubular mitochondria¹¹¹. In H9c2 cells, this is preceded by matrix expansion dependent on PTP or K⁺ channel opening and ensuing partial detachment from the microtubular track¹¹¹. Donut formation is a stress response and may protect against swelling-induced structural damage¹¹¹.

Nanotunnels

Even when physically separated by several microns, mitochondria can form connections through 60–200 nm wide double membrane tubules called mitochondrial nanotunnels¹¹². Nanotunnels have been observed in cardiac¹¹³ and skeletal muscle⁵⁹, and can be generated in a cell-free system by kinesin (Kif5b) in a microtubule- and ATP-dependent manner¹¹⁴. Protein exchange along nanotunnels¹¹⁵ suggests that mitochondrial nanotunnels may serve functional but possibly not genetic complementation between non-adjacent mitochondria, in tissues with restricted mitochondrial motility¹¹². In mice carrying a ryanodine receptor (RyR) 2 mutation (A4860G) associated with human catecholaminergic polymorphic ventricular tachycardia due to aberrant Ca²⁺ homeostasis, mitochondria display increased nanotunnel communication¹¹⁶. Mitochondrial nanotunnels are frequent in skeletal muscle of mitochondrial myopathy patients carrying mtDNA deletions or mutations, suggesting that nanotunnels support mitochondrial adaptation to genetic stressors¹¹⁷.

Homotypic mitochondrial contacts

Mitochondria can exhibit trans-mitochondrial coordination in muscle tissues. When joined by molecularly undefined electron-dense intermitochondrial junctions (IMJs), two adjacent mitochondria can exhibit aligned cristae¹¹⁸. IMJs are molecularly independent from MFNs but are induced within 30 minutes by physically tethering mitochondria through inter-organellar linkers *in vitro*¹¹⁸. Increased energetic demand during muscle contraction¹¹⁹, and decreased energetic demand during inactivity¹⁰⁶, increase and decrease IMJ number, respectively. MitoNEET, an OMM iron-sulphur cluster forming protein, functions in IMJs and has been linked to H₂O₂-induced mitochondrial fragmentation¹²⁰.

Heterotypic inter-organelle communication

Mitochondria dynamically form close contacts with various intracellular organelles (<100nm gap width), which represent a small fraction of the total organellar surface and allow effective local communication without altering the global milieu (Figure 2A)^{121, 122}. The most frequent mitochondrial companion is the endoplasmic reticulum (ER). ER-mitochondrial membrane contacts are reorganized to meet local needs¹²³ and are supported by physical protein-based tethers¹²⁴. Over 60 proteins have been implicated in tethering and many support specific functions¹²². MFN2 can cause diverse contact phenotypes in different paradigms, which may be determined by other tethering proteins¹²². These contacts function in phospholipid biosynthesis, Ca²⁺ transfer between ER and mitochondria, ROS signaling, mitochondrial fission, autophagy and mtDNA synthesis^{121, 122}. Thus, ER-mitochondrial contacts represent a dynamic aspect of mitochondrial behavior impacted by stressors and relevant to other mitochondrial functions.

Contact dynamics are controlled by physical tether formation and destruction. This can be induced by physiological changes in tethering protein abundance, membrane phospholipids and [Ca²⁺]¹²¹. The ER may stop other organelles in their vicinity by emitting Ca²⁺ signals favoring contact formation²⁵. Serum starvation or ER-specific stressors such as tunicamycin cause ER-mitochondrial contact tightening to promote cell death^{124, 125}. Stressors converging on ROS/redox dysregulation have also been linked to changes in ER-mitochondrial contact architecture: hypoxia widens contacts in a Nogo-dependent

manner¹²⁶, whereas cardiac ischemia/reperfusion causes tighter contacts via PTPIP51¹²⁷. Virus infections including CMV¹²⁸, chronic hepatitis C or acute RNA virus¹²⁹ enhance ER-mitochondrial contacts. Thus, a variety of stressors promote closer contacts that might facilitate local communication between interacting organelles (Figure 2C).

Stressors also alter the distribution of specific proteins relative to organelle contacts, influencing contact function. Palmitoylation affects calnexin distribution¹³⁰ and a shift to a hypoxic/reducing environment influences ERO1 α to leave ER-mitochondrial contacts¹³¹. Stressors affect Ca²⁺ and ROS signaling pathways at the ER-mitochondrial interface via several mechanisms. The IP₃ receptor (IP3R), which mediates local Ca²⁺ transfer in the ER, and the RYR in the sarcoplasmic reticulum, are targets of redox regulation^{132, 133}. Moreover, alteration of ER-mitochondrial Ca²⁺ communication affects other aspects of mitochondrial dynamics including fragmentation¹³⁴ and autophagy¹³⁵.

Several signaling pathways of BCL-2 family proteins that reside and exert pro-survival or pro-death functions in the ER and OMM have been linked to the ER-mitochondrial contacts^{136, 137}. Sphingolipid metabolism and ceramide production at ER-mitochondrial contacts is central to Bak/Bax-mediated OMM permeabilization and ensuing cell death¹³⁸. In addition to the ER, mitochondria form dynamic contacts with other organelles, including lysosomes, peroxisomes and lipid droplets, which may function during stress, such as in fatty acid shuttling from lipid droplets to mitochondria during starvation¹³⁹.

Intra-mitochondrial dynamics to shape cristae and adjust matrix volume

A distinctive feature of mitochondrial ultrastructure is IMM folding into cristae¹² that allows ETC component organization into supercomplexes to enhance bioenergetic efficiency¹⁴⁰. Mitochondrial cristae display dynamic changes with different metabolic states¹⁴¹. Cristae shape is supported by F₁F₀ ATPase localization at the IMM bending regions¹⁴². Cristae junctions are secured by the mitochondrial contact site protein complex (MICOS) that helps shape cristae and organize the ETC complexes^{143, 144}. MIC60, a MICOS component critical to IMM bending to support cristae formation¹⁴⁵, interacts with OPA1⁸⁴. Oligomeric OPA1 is needed to keep cristae junctions closed¹⁴⁶.

As a physiological adaptation to increased metabolic demands, cristae remodeling with increased density occurs in exercised skeletal muscle¹⁴⁷. During starvation, OPA1 oligomerization is enhanced to keep cristae narrow, which is required to promote F₁F₀ ATPase assembly and maintain ATP-linked respiration. Mutant OPA1(Q297V) that undergoes oligomerization but is defective in fusion can support survival during starvation¹⁴⁸. Apoptosis-promoting stressors through the BH3-only protein BID interfere with OPA1 oligomerization and trigger cristae junction opening to make cytochrome c available for release^{146, 149}. ROS modulator 1 (ROMO1), regulates OPA1 to control cristae organization and enhance mitochondrial resistance to BID-induced cristae junction opening and cytochrome c release¹⁵⁰.

Mitochondrial dynamics and stress responses leading to disease

The previous section discussed specific mechanisms by which stressors influence different facets of mitochondrial dynamics, promoting cellular adaptation or demise. Below we discuss three stereotypic mitochondrial stress response patterns and how they are translated into disease states. Abnormal mitochondrial dynamics are associated with morphological, genetic, and biochemical mitochondrial recalibrations that trigger cellular stress responses^{2, 3}. These recalibrations engender the production of diffusible signals that influence the organism at multiple levels (Figure 1, *right*), and cause disease in some cases by inducing mtDNA instability³.

Stress responses can have both adaptive and maladaptive effects. Adaptive effects contribute to resilience, whereas maladaptive effects contribute stress pathophysiology and disease state development. As adaptation becomes exhausted and maladaptation becomes dominant, the organism transitions from physiology to pathology (Figure 3A). Based on onset and duration, we distinguish 3 types of stressors which cause different stress response patterns: i) Early onset, chronic; ii) Late onset, acute; and iii) Late onset, chronic (Figure 3B–D).

Early onset chronic stressors

Early onset stressors are generally chronic and produce progressive disease (Figure 3B). Inherited genetic defects in genes of the fusion/fission machineries are stressors that permanently alter mitochondrial dynamics or motility throughout life^{3, 83}. The consequences can be devastating but often the initial defect can be compensated for by increased activity of the quality control provided by mitochondrial dynamics. When the defect impairs a fraction of normal dynamics, these defects can be compensated for, but may be aggravated beyond compensation by the accumulation of subsequent stressors³. The accumulation of stressors, such as secondary mtDNA mutations, may overwhelm the system and cause disease once the biochemical threshold is reached¹⁵¹. In humans, the threshold between physiological adaptation and pathology may vary based on particular mutations, but is estimated to be around 60% of mtDNA mutation load¹⁵¹.

As in animal models (Table 1), autosomal mutations particularly in the fusion machinery (MFN2¹⁵², OPA1⁶³), but also in fission factors (DRP1¹⁵³, MFF¹⁵⁴) and a motor adaptor (TRAK1¹⁵⁵) lead to mitochondrial disorders. The shared clinical symptoms for these neurodegenerative diseases are neurological impairments such as retinal ganglion cell degeneration and neuromuscular symptoms. OPA1, named after its genetic mutation, was shown to be the main cause of ADOA^{156, 157}. MFN2 mutations cause approximately 20% of CMT2A cases, an inherited peripheral neuropathy characterized by abnormal mitochondrial trafficking^{30, 31}. To date, no disease has been associated with mutations in MFN1. In part, the pathogenic mechanism involves the accumulation of mtDNA mutations and deletions that perturb OXPHOS^{75, 158, 159}. However, in many cases, ETC dysfunction is absent, indicating that abnormal fusion activity and motility represent a sufficient stressor to affect cell-level and organ-level function^{153, 154}. The canonical mitochondrial fusion-fission and motility dynamics proteins regulate other aspects of mitochondrial behaviors, and proteins such as MFN2 can cause disease via impairments of ER-mitochondrial communication, Ca²⁺ signaling or mitophagy¹⁶⁰.

Late onset acute stressors

Late onset stressors are generally acquired, can be relatively short-lived, and do not generally affect mitochondrial quality or the ability to produce functional organelles (Figure 3C). Excess of metabolic substrates such as acute hyperglycemia and hyperlipidemia can activate PKA to promote DRP1-dependent fission^{4, 161}. Hyperglycemia also increases ROS to mediate fission, and fission further augments ROS emission¹⁶². Both MFN1 and MFN2 are involved in metabolic sensing and regulation of whole-body energy homeostasis^{163, 164}, illustrating the adaptive cellular role of mitochondrial dynamics in response to acute metabolic stressors. Ischemia-reperfusion injury, such as myocardial infarction or stroke, usually occur late in adult life. The acute drop in oxygen and metabolic substrates followed by rapid reoxygenation causes substantial remodeling of mitochondrial morphology dominated by DRP1-mediated fission^{165, 166}, and the system rarely recovers full function. Some toxic insults cause an acute and permanent tissue injury such as doxorubicin that engages mostly ROS and mtDNA damage the cardiomyocytes¹⁶⁷.

Late onset chronic stressors

Late onset chronic stressors occur mostly in adult life but produce lasting deleterious effects on the system (Figure 3D). Poorly controlled diabetes, which manifests as the chronic elevation of blood glucose and lipids, represents a chronic stressor that generally develops later in life¹⁶⁸. The metabolic oversupply of diabetes increases fission with concurrent accumulation of mtDNA defects in various tissues¹⁶⁸. Obesity is associated with reorganization of ER-mitochondrial contacts resulting in mitochondrial Ca²⁺ overload, compromised mitochondrial oxidative capacity and augmented oxidative stress¹⁶⁹. Repeated environmental and chemical stressors, such as smoking and chronic alcohol abuse, are also late onset chronic stressors that influence mitochondrial dynamics and potentially alter the trajectory of primary mitochondrial diseases¹⁷⁰. Chronic alcohol exposure leads to mitochondrial fusion inhibition in cardiac myocytes¹¹⁵ and in skeletal muscle by targeting MFN1 protein levels⁵⁹. A number of stressors may therefore converge on different facets of mitochondrial dynamics and, when too high in duration and intensity, lead to maladaptive changes which alone or in combination with other stressors, may culminate in disease.

Most neurodegenerative diseases have been linked to primary or secondary changes in mitochondrial dynamics^{171, 172}. In addition to the inherited genetic defects in the proteins assigned to mitochondrial dynamics (see Early Onset Chronic), mutations in other proteins including amyloid precursor protein, presenilins, and α -synuclein, common in neurodegenerative diseases, causes interference with mitochondrial dynamics^{169, 173}. The dynamic structure and function of the ER-mitochondrial contacts seems to be affected in many of these cases^{173, 174}. However, altered ER-mitochondrial contacts and other impairments of mitochondrial dynamics (i.e. fragmentation) are also documented in sporadic cases supporting the view that mitochondrial dynamics is central to the pathogenesis of neurodegeneration^{174, 175}. ROS and Ca²⁺ dysregulation, often documented in neurodegenerative diseases, can interfere with various aspects of mitochondrial dynamics and can be part of cycles that drive disease progression³⁴.

Conclusions and looking forward

Much progress has been made in dissecting the molecular mechanisms that underlie mitochondrial dynamics. Recent *in vitro* and *in vivo* work has begun to map the effects of specific disease-causing stressors on various facets of mitochondrial and cellular responses. A challenge ahead will be to understand how the resulting mitochondrial and cellular recalibrations, both acute and chronic, interact to produce symptoms. Single models with limited readouts do not appear sufficiently precise or inclusive to explain the complex phenotypic variability in symptoms that manifest in animals and individuals with abnormal mitochondrial dynamics. Given the interaction of stressors and responses at the molecular, cellular and organismal levels (see Figure 1, *right*), future efforts may require advances in concurrent measurement of functions across multiple levels of organization, and development of multivariate and biologically meaningful methods and concepts to integrate such multi-level data. This would contribute to understanding the processes that translate stressors into symptoms and disease.

Future work should aim to influence adaptive and maladaptive dynamic physiological responses (see Figure 3) and to restore them towards healthy states. This will require the ability to accurately map dynamic processes at the molecular and organellar levels, and to monitor changes in bioenergetics over considerable time periods. A further challenge is how best to address these questions in physiologically relevant disease models. Most studies highlighting the pathophysiological relevance of mitochondrial motility have been performed in experimentally convenient systems, such as neural axons and dendrites *in vitro* in which mitochondrial trafficking is prominent and easily tracked¹⁶, but may not represent *in vivo* behavior¹⁷⁶. Understanding the physiological role of mitochondrial reshaping, rebuilding and recycling in specialized tissues remains vastly unexplored and an inspiring challenge for the field.

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References

1. Picard M, McEwen BS, Epel ES & Sandi C An energetic view of stress: Focus on mitochondria. *Front Neuroendocrinol* 49, 72–85 (2018). [PubMed: 29339091]
2. Youle RJ & van der Bliek AM Mitochondrial fission, fusion, and stress. *Science* 337, 1062–5 (2012). [PubMed: 22936770]
3. Suomalainen A & Battersby BJ Mitochondrial diseases: the contribution of organelle stress responses to pathology. *Nat Rev Mol Cell Biol* (2017).
4. Liesa M & Shirihai OS Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. *Cell Metab* 17, 491–506 (2013). [PubMed: 23562075]
5. Lemasters JJ Rusty notions of cell injury. *J Hepatol* 40, 696–8 (2004). [PubMed: 15030988]
6. Rizzuto R, De Stefani D, Raffaello A & Mammucari C Mitochondria as sensors and regulators of calcium signalling. *Nat Rev Mol Cell Biol* 13, 566–78 (2012). [PubMed: 22850819]
7. Bagur R & Hajnoczky G Intracellular Ca²⁺ Sensing: Its Role in Calcium Homeostasis and Signaling. *Mol Cell* 66, 780–788 (2017). [PubMed: 28622523]

8. Holmstrom KM & Finkel T Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nat Rev Mol Cell Biol* 15, 411–21 (2014). [PubMed: 24854789]
9. Nicholls DGF, S. J. . (2013).
10. Szabo G et al. RSA 2004: combined basic research satellite symposium - session three: alcohol and mitochondrial metabolism: at the crossroads of life and death. *Alcohol Clin Exp Res* 29, 1749–52 (2005). [PubMed: 16205376]
11. Montero J & Letai A Why do BCL-2 inhibitors work and where should we use them in the clinic? *Cell Death Differ* 25, 56–64 (2018). [PubMed: 29077093]
12. Mannella CA Structure and dynamics of the mitochondrial inner membrane cristae. *Biochim Biophys Acta* 1763, 542–8 (2006). [PubMed: 16730811]
13. Dominy JE & Puigserver P Mitochondrial biogenesis through activation of nuclear signaling proteins. *Cold Spring Harb Perspect Biol* 5 (2013).
14. Youle RJ & Narendra DP Mechanisms of mitophagy. *Nat Rev Mol Cell Biol* 12, 9–14 (2011). [PubMed: 21179058]
15. Gong G et al. Parkin-mediated mitophagy directs perinatal cardiac metabolic maturation in mice. *Science* 350, aad2459 (2015).
16. Schwarz TL Mitochondrial trafficking in neurons. *Cold Spring Harb Perspect Biol* 5 (2013).
17. Fransson A, Ruusala A & Aspenstrom P Atypical Rho GTPases have roles in mitochondrial homeostasis and apoptosis. *J Biol Chem* 278, 6495–502 (2003). [PubMed: 12482879]
18. Pathak D, Sepp KJ & Hollenbeck PJ Evidence that myosin activity opposes microtubule-based axonal transport of mitochondria. *J Neurosci* 30, 8984–92 (2010). [PubMed: 20592219]
19. Quintero OA et al. Human Myo19 is a novel myosin that associates with mitochondria. *Curr Biol* 19, 2008–13 (2009). [PubMed: 19932026]
20. Chen Y & Sheng ZH Kinesin-1-syntrophin coupling mediates activity-dependent regulation of axonal mitochondrial transport. *J Cell Biol* 202, 351–64 (2013). [PubMed: 23857772]
21. Rohn JL et al. Myo19 ensures symmetric partitioning of mitochondria and coupling of mitochondrial segregation to cell division. *Curr Biol* 24, 2598–605 (2014). [PubMed: 25447992]
22. Chung JY, Steen JA & Schwarz TL Phosphorylation-Induced Motor Shedding Is Required at Mitosis for Proper Distribution and Passive Inheritance of Mitochondria. *Cell Rep* 16, 2142–2155 (2016). [PubMed: 27524620]
23. Nguyen TT et al. Loss of Miro1-directed mitochondrial movement results in a novel murine model for neuron disease. *Proc Natl Acad Sci U S A* 111, E3631–40 (2014). [PubMed: 25136135]
24. Vaccaro V, Devine MJ, Higgs NF & Kittler JT Miro1-dependent mitochondrial positioning drives the rescaling of presynaptic Ca²⁺ signals during homeostatic plasticity. *EMBO Rep* 18, 231–240 (2017). [PubMed: 28039205]
25. Yi M, Weaver D & Hajnoczky G Control of mitochondrial motility and distribution by the calcium signal: a homeostatic circuit. *J Cell Biol* 167, 661–72 (2004). [PubMed: 15545319]
26. Liu X, Weaver D, Shirihai O & Hajnoczky G Mitochondrial ‘kiss-and-run’: interplay between mitochondrial motility and fusion-fission dynamics. *EMBO J* 28, 3074–89 (2009). [PubMed: 19745815]
27. Sheng ZH Mitochondrial trafficking and anchoring in neurons: New insight and implications. *J Cell Biol* 204, 1087–98 (2014). [PubMed: 24687278]
28. Lopez-Domenech G et al. Loss of Dendritic Complexity Precedes Neurodegeneration in a Mouse Model with Disrupted Mitochondrial Distribution in Mature Dendrites. *Cell Rep* 17, 317–327 (2016). [PubMed: 27705781]
29. Lopez-Domenech G et al. Miro proteins coordinate microtubule- and actin-dependent mitochondrial transport and distribution. *EMBO J* 37, 321–336 (2018). [PubMed: 29311115]
30. Misko A, Jiang S, Wegorzewska I, Milbrandt J & Baloh RH Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with the Miro/Milton complex. *J Neurosci* 30, 4232–40 (2010). [PubMed: 20335458]
31. Baloh RH Mitochondrial dynamics and peripheral neuropathy. *Neuroscientist* 14, 12–8 (2008). [PubMed: 17911220]

32. Saotome M et al. Bidirectional Ca²⁺-dependent control of mitochondrial dynamics by the Miro GTPase. *Proc Natl Acad Sci U S A* 105, 20728–33 (2008). [PubMed: 19098100]
33. Stephen TL et al. Miro1 Regulates Activity-Driven Positioning of Mitochondria within Astrocytic Processes Apposed to Synapses to Regulate Intracellular Calcium Signaling. *J Neurosci* 35, 15996–6011 (2015). [PubMed: 26631479]
34. Fang C, Bourdette D & Banker G Oxidative stress inhibits axonal transport: implications for neurodegenerative diseases. *Mol Neurodegener* 7, 29 (2012). [PubMed: 22709375]
35. Debattisti V, Gerencser AA, Saotome M, Das S & Hajnoczky G ROS Control Mitochondrial Motility through p38 and the Motor Adaptor Miro/Trak. *Cell Rep* 21, 1667–1680 (2017). [PubMed: 29117569]
36. Pekkurnaz G, Trinidad JC, Wang X, Kong D & Schwarz TL Glucose regulates mitochondrial motility via Milton modification by O-GlcNAc transferase. *Cell* 158, 54–68 (2014). [PubMed: 24995978]
37. Liao PC, Tandarich LC & Hollenbeck PJ ROS regulation of axonal mitochondrial transport is mediated by Ca²⁺ and JNK in *Drosophila*. *PLoS One* 12, e0178105 (2017). [PubMed: 28542430]
38. Iqbal S & Hood DA Oxidative stress-induced mitochondrial fragmentation and movement in skeletal muscle myoblasts. *Am J Physiol Cell Physiol* 306, C1176–83 (2014). [PubMed: 24740540]
39. Li L et al. p38 MAP kinase-dependent phosphorylation of the Gp78 E3 ubiquitin ligase controls ER-mitochondria association and mitochondria motility. *Mol Biol Cell* 26, 3828–40 (2015). [PubMed: 26337390]
40. Han SM, Baig HS & Hammarlund M Mitochondria Localize to Injured Axons to Support Regeneration. *Neuron* 92, 1308–1323 (2016). [PubMed: 28009276]
41. Zhou B et al. Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits. *J Cell Biol* 214, 103–19 (2016). [PubMed: 27268498]
42. Lin MY et al. Releasing Syntaphilin Removes Stressed Mitochondria from Axons Independent of Mitophagy under Pathophysiological Conditions. *Neuron* 94, 595–610.e6 (2017). [PubMed: 28472658]
43. Caino MC et al. Syntaphilin controls a mitochondrial rheostat for proliferation-motility decisions in cancer. *J Clin Invest* 127, 3755–3769 (2017). [PubMed: 28891816]
44. Wang X et al. PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. *Cell* 147, 893–906 (2011). [PubMed: 22078885]
45. Birsa N et al. Lysine 27 ubiquitination of the mitochondrial transport protein Miro is dependent on serine 65 of the Parkin ubiquitin ligase. *J Biol Chem* 289, 14569–82 (2014). [PubMed: 24671417]
46. O’Mealey GB et al. A PGAM5-KEAP1-Nrf2 complex is required for stress-induced mitochondrial retrograde trafficking. *J Cell Sci* 130, 3467–3480 (2017). [PubMed: 28839075]
47. Al-Mehdi AB et al. Perinuclear mitochondrial clustering creates an oxidant-rich nuclear domain required for hypoxia-induced transcription. *Sci Signal* 5, ra47 (2012).
48. Usaj M & Henn A Kinetic adaptation of human Myo19 for active mitochondrial transport to growing filopodia tips. *Sci Rep* 7, 11596 (2017). [PubMed: 28912602]
49. Cartoni R et al. The Mammalian-Specific Protein Armcx1 Regulates Mitochondrial Transport during Axon Regeneration. *Neuron* 92, 1294–1307 (2016). [PubMed: 28009275]
50. Song Z, Ghochani M, McCaffery JM, Frey TG & Chan DC Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion. *Mol Biol Cell* 20, 3525–32 (2009). [PubMed: 19477917]
51. Weaver D et al. Distribution and apoptotic function of outer membrane proteins depend on mitochondrial fusion. *Mol Cell* 54, 870–8 (2014). [PubMed: 24813948]
52. Otera H et al. Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells. *J Cell Biol* 191, 1141–58 (2010). [PubMed: 21149567]
53. Osellame LD et al. Cooperative and independent roles of the Drp1 adaptors Mff, MiD49 and MiD51 in mitochondrial fission. *J Cell Sci* 129, 2170–81 (2016). [PubMed: 27076521]

54. Ji WK, Hatch AL, Merrill RA, Strack S & Higgs HN Actin filaments target the oligomeric maturation of the dynamin GTPase Drp1 to mitochondrial fission sites. *Elife* 4, e11553 (2015). [PubMed: 26609810]
55. Lee JE, Westrate LM, Wu H, Page C & Voeltz GK Multiple dynamin family members collaborate to drive mitochondrial division. *Nature* 540, 139–143 (2016). [PubMed: 27798601]
56. Ono T, Isobe K, Nakada K & Hayashi JI Human cells are protected from mitochondrial dysfunction by complementation of DNA products in fused mitochondria. *Nat Genet* 28, 272–5 (2001). [PubMed: 11431699]
57. Chen H, Chomyn A & Chan DC Disruption of fusion results in mitochondrial heterogeneity and dysfunction. *J Biol Chem* 280, 26185–92 (2005). [PubMed: 15899901]
58. Twig G et al. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *Embo J* 27, 433–46 (2008). [PubMed: 18200046]
59. Eisner V, Lenaers G & Hajnoczky G Mitochondrial fusion is frequent in skeletal muscle and supports excitation-contraction coupling. *J Cell Biol* 205, 179–95 (2014). [PubMed: 24751540]
60. Lewis SC, Uchiyama LF & Nunnari J ER-mitochondria contacts couple mtDNA synthesis with mitochondrial division in human cells. *Science* 353, aaf5549 (2016).
61. Boldogh IR et al. A protein complex containing Mdm10p, Mdm12p, and Mmm1p links mitochondrial membranes and DNA to the cytoskeleton-based segregation machinery. *Mol Biol Cell* 14, 4618–27 (2003). [PubMed: 13679517]
62. Chen H et al. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. *J Cell Biol* 160, 189–200 (2003). [PubMed: 12527753]
63. Davies VJ et al. Opa1 deficiency in a mouse model of autosomal dominant optic atrophy impairs mitochondrial morphology, optic nerve structure and visual function. *Hum Mol Genet* 16, 1307–18 (2007). [PubMed: 17428816]
64. Ishihara N et al. Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. *Nature Cell Biology* 11, 958 (2009). [PubMed: 19578372]
65. Wakabayashi J et al. The dynamin-related GTPase Drp1 is required for embryonic and brain development in mice. *J Cell Biol* 186, 805–16 (2009). [PubMed: 19752021]
66. Chen H, McCaffery JM & Chan DC Mitochondrial fusion protects against neurodegeneration in the cerebellum. *Cell* 130, 548–62 (2007). [PubMed: 17693261]
67. Cartoni R et al. Expression of mitofusin 2(R94Q) in a transgenic mouse leads to Charcot-Marie-Tooth neuropathy type 2A. *Brain* 133, 1460–9 (2010). [PubMed: 20418531]
68. Strickland AV et al. Characterization of the mitofusin 2 R94W mutation in a knock-in mouse model. *J Peripher Nerv Syst* 19, 152–64 (2014). [PubMed: 24862862]
69. Alavi MV et al. A splice site mutation in the murine Opa1 gene features pathology of autosomal dominant optic atrophy. *Brain* 130, 1029–42 (2007). [PubMed: 17314202]
70. Chen Y et al. Mitofusin 2-containing mitochondrial-reticular microdomains direct rapid cardiomyocyte bioenergetic responses via interorganelle Ca(2+) crosstalk. *Circ Res* 111, 863–75 (2012). [PubMed: 22777004]
71. Chen Y, Liu Y & Dorn GW 2nd. Mitochondrial fusion is essential for organelle function and cardiac homeostasis. *Circ Res* 109, 1327–31 (2011). [PubMed: 22052916]
72. Papanicolaou KN et al. Mitofusins 1 and 2 are essential for postnatal metabolic remodeling in heart. *Circ Res* 111, 1012–26 (2012). [PubMed: 22904094]
73. Kasahara A, Cipolat S, Chen Y, Dorn GW & Scorrano L Mitochondrial fusion directs cardiomyocyte differentiation via calcineurin and Notch signaling. *Science* 342, 734–7 (2013). [PubMed: 24091702]
74. Hall AR et al. Hearts deficient in both Mfn1 and Mfn2 are protected against acute myocardial infarction. *Cell Death Dis* 7, e2238 (2016). [PubMed: 27228353]
75. Chen H et al. Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. *Cell* 141, 280–9 (2010). [PubMed: 20403324]
76. Tezze C et al. Age-Associated Loss of OPA1 in Muscle Impacts Muscle Mass, Metabolic Homeostasis, Systemic Inflammation, and Epithelial Senescence. *Cell Metab* 25, 1374–1389.e6 (2017). [PubMed: 28552492]

77. Rodríguez-Nuevo A et al. Mitochondrial DNA and TLR9 drive muscle inflammation upon Opa1 deficiency. *EMBO J* (2018).
78. Detmer SA, Vande Velde C, Cleveland DW & Chan DC Hindlimb gait defects due to motor axon loss and reduced distal muscles in a transgenic mouse model of Charcot-Marie-Tooth type 2A. *Hum Mol Genet* 17, 367–75 (2008). [PubMed: 17959936]
79. Bannerman P, Burns T, Xu J, Miers L & Pleasure D Mice Hemizygous for a Pathogenic Mitofusin-2 Allele Exhibit Hind Limb/Foot Gait Deficits and Phenotypic Perturbations in Nerve and Muscle. *PLoS One* 11, e0167573 (2016). [PubMed: 27907123]
80. Williams PA, Morgan JE & Votruba M Opa1 deficiency in a mouse model of dominant optic atrophy leads to retinal ganglion cell dendropathy. *Brain* 133, 2942–51 (2010). [PubMed: 20817698]
81. Kushnareva Y et al. Mitochondrial dysfunction in an Opa1(Q285STOP) mouse model of dominant optic atrophy results from Opa1 haploinsufficiency. *Cell Death Dis* 7, e2309 (2016). [PubMed: 27468686]
82. Chen L et al. OPA1 mutation and late-onset cardiomyopathy: mitochondrial dysfunction and mtDNA instability. *J Am Heart Assoc* 1, e003012 (2012). [PubMed: 23316298]
83. Sarzi E et al. The human OPA1delTTAG mutation induces premature age-related systemic neurodegeneration in mouse. *Brain* 135, 3599–613 (2012). [PubMed: 23250881]
84. Soriano FX et al. Evidence for a mitochondrial regulatory pathway defined by peroxisome proliferator-activated receptor-gamma coactivator-1 alpha, estrogen-related receptor-alpha, and mitofusin 2. *Diabetes* 55, 1783–91 (2006). [PubMed: 16731843]
85. Chen Y & Dorn GW, 2nd. PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. *Science* 340, 471–5 (2013). [PubMed: 23620051]
86. Shutt T, Geoffrion M, Milne R & McBride HM The intracellular redox state is a core determinant of mitochondrial fusion. *EMBO Rep* 13, 909–15 (2012). [PubMed: 22945481]
87. Samant SA et al. SIRT3 deacetylates and activates OPA1 to regulate mitochondrial dynamics during stress. *Mol Cell Biol* 34, 807–19 (2014). [PubMed: 24344202]
88. Nakamura N, Kimura Y, Tokuda M, Honda S & Hirose S MARCH-V is a novel mitofusin 2- and Drp1-binding protein able to change mitochondrial morphology. *EMBO Rep* 7, 1019–22 (2006). [PubMed: 16936636]
89. Park YY et al. Loss of MARCH5 mitochondrial E3 ubiquitin ligase induces cellular senescence through dynamin-related protein 1 and mitofusin 1. *J Cell Sci* 123, 619–26 (2010). [PubMed: 20103533]
90. Head B, Griparic L, Amiri M, Gandre-Babbe S & van der Blik AM Inducible proteolytic inactivation of OPA1 mediated by the OMA1 protease in mammalian cells. *J Cell Biol* 187, 959–66 (2009). [PubMed: 20038677]
91. Mishra P, Carelli V, Manfredi G & Chan DC Proteolytic cleavage of Opa1 stimulates mitochondrial inner membrane fusion and couples fusion to oxidative phosphorylation. *Cell Metab* 19, 630–41 (2014). [PubMed: 24703695]
92. Ban T et al. Molecular basis of selective mitochondrial fusion by heterotypic action between OPA1 and cardiolipin. *Nat Cell Biol* 19, 856–863 (2017). [PubMed: 28628083]
93. Gomes LC, Di Benedetto G & Scorrano L During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. *Nat Cell Biol* 13, 589–98 (2011). [PubMed: 21478857]
94. Rainbolt TK, Lebeau J, Puchades C & Wiseman RL Reciprocal Degradation of YME1L and OMA1 Adapts Mitochondrial Proteolytic Activity during Stress. *Cell Rep* 14, 2041–2049 (2016). [PubMed: 26923599]
95. Tondera D et al. SLP-2 is required for stress-induced mitochondrial hyperfusion. *EMBO J* 28, 1589–600 (2009). [PubMed: 19360003]
96. Wai T et al. The membrane scaffold SLP2 anchors a proteolytic hub in mitochondria containing PARL and the i-AAA protease YME1L. *EMBO Rep* 17, 1844–1856 (2016). [PubMed: 27737933]
97. Zemirli N et al. Mitochondrial hyperfusion promotes NF- κ B activation via the mitochondrial E3 ligase MULAN. *FEBS J* 281, 3095–112 (2014). [PubMed: 24841215]
98. Nan J et al. TNFR2 Stimulation Promotes Mitochondrial Fusion via Stat3- and NF- κ B-Dependent Activation of OPA1 Expression. *Circ Res* 121, 392–410 (2017). [PubMed: 28637784]

99. Rambold AS, Kostecky B & Lippincott-Schwartz J Together we are stronger: fusion protects mitochondria from autophagosomal degradation. *Autophagy* 7, 1568–9 (2011). [PubMed: 22024745]
100. Molina AJ et al. Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. *Diabetes* 58, 2303–15 (2009). [PubMed: 19581419]
101. Yu T, Sheu SS, Robotham JL & Yoon Y Mitochondrial fission mediates high glucose-induced cell death through elevated production of reactive oxygen species. *Cardiovasc Res* 79, 341–51 (2008). [PubMed: 18440987]
102. Wu S, Zhou F, Zhang Z & Xing D Mitochondrial oxidative stress causes mitochondrial fragmentation via differential modulation of mitochondrial fission-fusion proteins. *FEBS J* 278, 941–54 (2011). [PubMed: 21232014]
103. Toyama EQ et al. Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. *Science* 351, 275–281 (2016). [PubMed: 26816379]
104. Sabouny R et al. The Keap1-Nrf2 Stress Response Pathway Promotes Mitochondrial Hyperfusion Through Degradation of the Mitochondrial Fission Protein Drp1. *Antioxid Redox Signal* (2017).
105. Cereghetti GM et al. Dephosphorylation by calcineurin regulates translocation of Drp1 to mitochondria. *Proc Natl Acad Sci U S A* 105, 15803–8 (2008). [PubMed: 18838687]
106. Picard M et al. Mechanical ventilation triggers abnormal mitochondrial dynamics and morphology in the diaphragm. *J Appl Physiol* (1985) 118, 1161–71 (2015). [PubMed: 25767033]
107. Pfluger PT et al. Calcineurin Links Mitochondrial Elongation with Energy Metabolism. *Cell Metab* 22, 838–50 (2015). [PubMed: 26411342]
108. Helle SCJ et al. Mechanical force induces mitochondrial fission. *Elife* 6 (2017).
109. Campello S et al. Orchestration of lymphocyte chemotaxis by mitochondrial dynamics. *J Exp Med* 203, 2879–86 (2006). [PubMed: 17145957]
110. Buck MD et al. Mitochondrial Dynamics Controls T Cell Fate through Metabolic Programming. *Cell* 166, 63–76 (2016). [PubMed: 27293185]
111. Liu X & Hajnoczky G Altered fusion dynamics underlie unique morphological changes in mitochondria during hypoxia-reoxygenation stress. *Cell Death Differ* 18, 1561–72 (2011). [PubMed: 21372848]
112. Vincent AE, Turnbull DM, Eisner V, Hajnoczky G & Picard M Mitochondrial Nanotunnels. *Trends Cell Biol* 27, 787–799 (2017). [PubMed: 28935166]
113. Huang X et al. Kissing and nanotunneling mediate intermitochondrial communication in the heart. *Proc Natl Acad Sci U S A* 110, 2846–51 (2013). [PubMed: 23386722]
114. Wang C et al. Dynamic tubulation of mitochondria drives mitochondrial network formation. *Cell Res* 25, 1108–20 (2015). [PubMed: 26206315]
115. Eisner V et al. Mitochondrial fusion dynamics is robust in the heart and depends on calcium oscillations and contractile activity. *Proc Natl Acad Sci U S A* 114, E859–E868 (2017). [PubMed: 28096338]
116. Lavorato M et al. Increased mitochondrial nanotunneling activity, induced by calcium imbalance, affects intermitochondrial matrix exchanges. *Proc Natl Acad Sci U S A* 114, E849–E858 (2017). [PubMed: 28096415]
117. Vincent AE et al. The Spectrum of Mitochondrial Ultrastructural Defects in Mitochondrial Myopathy. *Sci Rep* 6, 30610 (2016). [PubMed: 27506553]
118. Picard M et al. Trans-mitochondrial coordination of cristae at regulated membrane junctions. *Nat Commun* 6, 6259 (2015). [PubMed: 25687472]
119. Picard M et al. Acute exercise remodels mitochondrial membrane interactions in mouse skeletal muscle. *J Appl Physiol* (1985) 115, 1562–71 (2013). [PubMed: 23970537]
120. Vernay A et al. MitoNEET-dependent formation of intermitochondrial junctions. *Proc Natl Acad Sci U S A* 114, 8277–8282 (2017). [PubMed: 28716905]
121. Prinz WA Bridging the gap: membrane contact sites in signaling, metabolism, and organelle dynamics. *J Cell Biol* 205, 759–69 (2014). [PubMed: 24958771]
122. Csordas G, Weaver D & Hajnoczky G Endoplasmic Reticular-Mitochondrial Contactology: Structure and Signaling Functions. *Trends Cell Biol* (2018).

123. Yang Z, Zhao X, Xu J, Shang W & Tong C A novel fluorescent reporter detects plastic remodeling of mitochondria-ER contact sites. *J Cell Sci* (2017).
124. Csordas G et al. Structural and functional features and significance of the physical linkage between ER and mitochondria. *J Cell Biol* 174, 915–21 (2006). [PubMed: 16982799]
125. Cieri D et al. SPLICS: a split green fluorescent protein-based contact site sensor for narrow and wide heterotypic organelle juxtaposition. *Cell Death Differ* (2017).
126. Sutendra G et al. The role of Nogo and the mitochondria-endoplasmic reticulum unit in pulmonary hypertension. *Sci Transl Med* 3, 88ra55 (2011).
127. Qiao X et al. PTPIP51 regulates mouse cardiac ischemia/reperfusion through mediating the mitochondria-SR junction. *Sci Rep* 7, 45379 (2017). [PubMed: 28345618]
128. Zhang A et al. Quantitative proteomic analyses of human cytomegalovirus-induced restructuring of endoplasmic reticulum-mitochondrial contacts at late times of infection. *Mol Cell Proteomics* 10, M111 009936 (2011).
129. Horner SM, Wilkins C, Badil S, Iskarpatyoti J & Gale M Jr. Proteomic analysis of mitochondrial-associated ER membranes (MAM) during RNA virus infection reveals dynamic changes in protein and organelle trafficking. *PLoS One* 10, e0117963 (2015). [PubMed: 25734423]
130. Lynes EM et al. Palmitoylation is the switch that assigns calnexin to quality control or ER Ca²⁺ signaling. *J Cell Sci* 126, 3893–903 (2013). [PubMed: 23843619]
131. Gilady SY et al. Ero1alpha requires oxidizing and normoxic conditions to localize to the mitochondria-associated membrane (MAM). *Cell Stress Chaperones* 15, 619–29. [PubMed: 20186508]
132. Joseph SK Role of thiols in the structure and function of inositol trisphosphate receptors. *Curr Top Membr* 66, 299–322 (2010). [PubMed: 22353485]
133. Hidalgo C, Aracena P, Sanchez G & Donoso P Redox regulation of calcium release in skeletal and cardiac muscle. *Biol Res* 35, 183–93 (2002). [PubMed: 12415735]
134. SanMartín CD et al. RyR2-Mediated Ca²⁺ Release and Mitochondrial ROS Generation Partake in the Synaptic Dysfunction Caused by Amyloid β Peptide Oligomers. *Front Mol Neurosci* 10, 115 (2017). [PubMed: 28487634]
135. Khan MT & Joseph SK Role of inositol trisphosphate receptors in autophagy in DT40 cells. *J Biol Chem* 285, 16912–20 (2010). [PubMed: 20308071]
136. Hacki J et al. Apoptotic crosstalk between the endoplasmic reticulum and mitochondria controlled by Bcl-2. *Oncogene* 19, 2286–95 (2000). [PubMed: 10822379]
137. Nutt LK et al. Bax and Bak promote apoptosis by modulating endoplasmic reticular and mitochondrial Ca²⁺ stores. *J Biol Chem* 277, 9219–25 (2002). [PubMed: 11741880]
138. Chipuk JE et al. Sphingolipid metabolism cooperates with BAK and BAX to promote the mitochondrial pathway of apoptosis. *Cell* 148, 988–1000 (2012). [PubMed: 22385963]
139. Rambold AS, Cohen S & Lippincott-Schwartz J Fatty acid trafficking in starved cells: regulation by lipid droplet lipolysis, autophagy, and mitochondrial fusion dynamics. *Dev Cell* 32, 678–92 (2015). [PubMed: 25752962]
140. Lapuente-Brun E et al. Supercomplex assembly determines electron flux in the mitochondrial electron transport chain. *Science* 340, 1567–70 (2013). [PubMed: 23812712]
141. Hackenbrock CR Ultrastructural bases for metabolically linked mechanical activity in mitochondria. I. Reversible ultrastructural changes with change in metabolic steady state in isolated liver mitochondria. *J Cell Biol* 30, 269–97 (1966). [PubMed: 5968972]
142. Strauss M, Hofhaus G, Schröder RR & Kühlbrandt W Dimer ribbons of ATP synthase shape the inner mitochondrial membrane. *EMBO J* 27, 1154–60 (2008). [PubMed: 18323778]
143. Friedman JR, Mourier A, Yamada J, McCaffery JM & Nunnari J MICOS coordinates with respiratory complexes and lipids to establish mitochondrial inner membrane architecture. *Elife* 4 (2015).
144. Harner M et al. The mitochondrial contact site complex, a determinant of mitochondrial architecture. *EMBO J* 30, 4356–70 (2011). [PubMed: 22009199]

145. Tarasenko D et al. The MICOS component Mic60 displays a conserved membrane-bending activity that is necessary for normal cristae morphology. *J Cell Biol* 216, 889–899 (2017). [PubMed: 28254827]
146. Frezza C et al. OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion. *Cell* 126, 177–89 (2006). [PubMed: 16839885]
147. Nielsen J et al. Plasticity in mitochondrial cristae density allows metabolic capacity modulation in human skeletal muscle. *J Physiol* 595, 2839–2847 (2017). [PubMed: 27696420]
148. Patten DA et al. OPA1-dependent cristae modulation is essential for cellular adaptation to metabolic demand. *EMBO J* 33, 2676–91 (2014). [PubMed: 25298396]
149. Yamaguchi R et al. Opa1-mediated cristae opening is Bax/Bak and BH3 dependent, required for apoptosis, and independent of Bak oligomerization. *Mol Cell* 31, 557–69 (2008). [PubMed: 18691924]
150. Norton M et al. ROMO1 is an essential redox-dependent regulator of mitochondrial dynamics. *Sci Signal* 7, ra10 (2014).
151. Rossignol R et al. Mitochondrial threshold effects. *Biochem J* 370, 751–62 (2003). [PubMed: 12467494]
152. Zuchner S et al. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. *Nat Genet* 36, 449–51 (2004). [PubMed: 15064763]
153. Gerber S et al. Mutations in DNMI1, as in OPA1, result in dominant optic atrophy despite opposite effects on mitochondrial fusion and fission. *Brain* 140, 2586–2596 (2017). [PubMed: 28969390]
154. Koch J et al. Disturbed mitochondrial and peroxisomal dynamics due to loss of MFF causes Leigh-like encephalopathy, optic atrophy and peripheral neuropathy. *J Med Genet* 53, 270–8 (2016). [PubMed: 26783368]
155. Barel O et al. Deleterious variants in TRAK1 disrupt mitochondrial movement and cause fatal encephalopathy. *Brain* 140, 568–581 (2017). [PubMed: 28364549]
156. Alexander C et al. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. *Nat Genet* 26, 211–5 (2000). [PubMed: 11017080]
157. Delettre C et al. Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. *Nat Genet* 26, 207–10 (2000). [PubMed: 11017079]
158. Amati-Bonneau P et al. OPA1 mutations induce mitochondrial DNA instability and optic atrophy ‘plus’ phenotypes. *Brain* 131, 338–51 (2008). [PubMed: 18158317]
159. Hudson G et al. Mutation of OPA1 causes dominant optic atrophy with external ophthalmoplegia, ataxia, deafness and multiple mitochondrial DNA deletions: a novel disorder of mtDNA maintenance. *Brain* 131, 329–37 (2008). [PubMed: 18065439]
160. Schrepfer E & Scorrano L Mitofusins, from Mitochondria to Metabolism. *Mol Cell* 61, 683–694 (2016). [PubMed: 26942673]
161. Wikstrom JD et al. Hormone-induced mitochondrial fission is utilized by brown adipocytes as an amplification pathway for energy expenditure. *EMBO J* 33, 418–36 (2014). [PubMed: 24431221]
162. Yu T, Botham JL & Yoon Y Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. *Proc Natl Acad Sci U S A* 103, 2653–8 (2006). [PubMed: 16477035]
163. Schneeberger M et al. Mitofusin 2 in POMC neurons connects ER stress with leptin resistance and energy imbalance. *Cell* 155, 172–87 (2013). [PubMed: 24074867]
164. Ramirez S et al. Mitochondrial Dynamics Mediated by Mitofusin 1 Is Required for POMC Neuron Glucose-Sensing and Insulin Release Control. *Cell Metab* 25, 1390–1399 e6 (2017). [PubMed: 28591639]
165. Kumar R et al. Mitochondrial dynamics following global cerebral ischemia. *Mol Cell Neurosci* 76, 68–75 (2016). [PubMed: 27567688]
166. Tian L et al. Ischemia-induced Drp1 and Fis1-mediated mitochondrial fission and right ventricular dysfunction in pulmonary hypertension. *J Mol Med (Berl)* 95, 381–393 (2017). [PubMed: 28265681]

167. Meyer JN et al. Mitochondria as a target of environmental toxicants. *Toxicol Sci* 134, 1–17 (2013). [PubMed: 23629515]
168. Picard M & Turnbull DM Linking the metabolic state and mitochondrial DNA in chronic disease, health, and aging. *Diabetes* 62, 672–8 (2013). [PubMed: 23431006]
169. Arruda AP et al. Chronic enrichment of hepatic endoplasmic reticulum-mitochondria contact leads to mitochondrial dysfunction in obesity. *Nat Med* 20, 1427–35 (2014). [PubMed: 25419710]
170. Kirkman MA et al. Gene-environment interactions in Leber hereditary optic neuropathy. *Brain* 132, 2317–26 (2009). [PubMed: 19525327]
171. Schon EA & Przedborski S Mitochondria: the next (neurode)generation. *Neuron* 70, 1033–53 (2011). [PubMed: 21689593]
172. Smith EF, Shaw PJ & De Vos KJ The role of mitochondria in amyotrophic lateral sclerosis. *Neurosci Lett* (2017).
173. Guardia-Laguarta C, Area-Gomez E, Schon EA & Przedborski S A new role for alpha-synuclein in Parkinson's disease: Alteration of ER-mitochondrial communication. *Mov Disord* 30, 1026–33 (2015). [PubMed: 25952565]
174. Area-Gomez E & Schon EA On the Pathogenesis of Alzheimer's Disease: The MAM Hypothesis. *FASEB J* 31, 864–867 (2017). [PubMed: 28246299]
175. Hedskog L et al. Modulation of the endoplasmic reticulum-mitochondria interface in Alzheimer's disease and related models. *Proc Natl Acad Sci U S A* 110, 7916–21 (2013). [PubMed: 23620518]
176. Lewis TL Jr., Turi GF, Kwon SK, Losonczy A & Polleux F Progressive Decrease of Mitochondrial Motility during Maturation of Cortical Axons In Vitro and In Vivo. *Curr Biol* 26, 2602–2608 (2016). [PubMed: 27641765]
177. Song M, Franco A, Fleischer JA, Zhang L & Dorn GW Abrogating Mitochondrial Dynamics in Mouse Hearts Accelerates Mitochondrial Senescence. *Cell Metab* 26, 872–883.e5 (2017). [PubMed: 29107503]
178. Le Page S et al. Increase in Cardiac Ischemia-Reperfusion Injuries in Opa1+/- Mouse Model. *PLoS One* 11, e0164066 (2016). [PubMed: 27723783]
179. Zhang Z et al. The dynamin-related GTPase Opa1 is required for glucose-stimulated ATP production in pancreatic beta cells. *Mol Biol Cell* 22, 2235–45 (2011). [PubMed: 21551073]

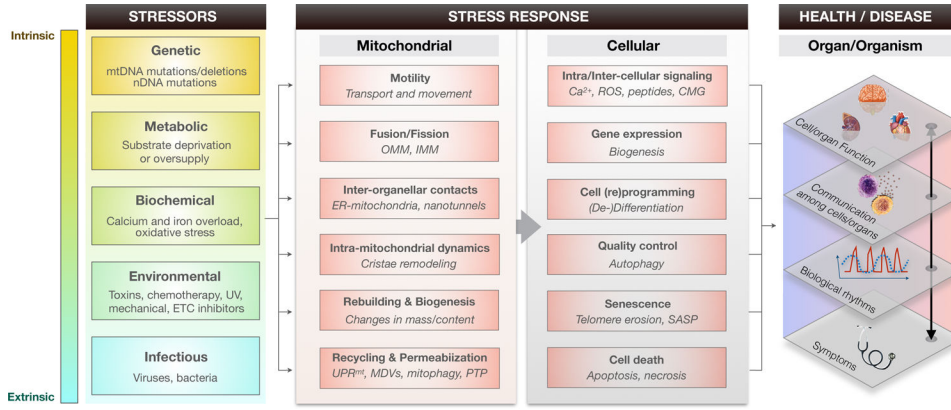


Figure 1. Framework outlining elements of the overall mitochondrial stress response and the link to disease, with a focus on mitochondrial dynamics.

Stressors affecting mitochondria vary in nature and origin (left). Intrinsic stressors are those that arise from the molecular and biological components of the organism itself, such as DNA mutations and the product of chemical reactions. Stressors induce specific stress responses involving multiple facets of mitochondrial dynamics and key cellular processes (center). Components of the mitochondrial and cellular stress responses are not mutually exclusive, and also interact and influence each other (not depicted in the figure). Collectively, stress responses affect health and disease trajectories in a multi-level way by influencing inter-related domains of organ and organism function (right). Physiology and pathology can therefore manifest at each level, clinically at the level of symptoms and disorders (e.g., fatigue, ataxia, opthalmoplegia), and sub-clinically in the disruption of biological rhythms (e.g., circadian oscillations, mitochondrial membrane potential oscillations), of cell-cell communication (e.g., production of mitochondria-derived metabolites, pro-inflammatory molecules and cytokines), or of organ systems (e.g., brain and cognitive function, cardiac contractility, hormone biosynthesis). Levels of function are interconnected. *Abbreviations: mtDNA, mitochondrial DNA; nDNA, nuclear DNA; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; ER, endoplasmic reticulum; UPR^{mt}, mitochondrial unfolded protein response; MDVs, mitochondria-derived vesicles; PTP, permeability transition pore; ROS, reactive oxygen species; CMG, circulating mitochondrial genome (also ccf-mtDNA); SASP, senescence-associated secretory profile; ETC, electron transport chain.*

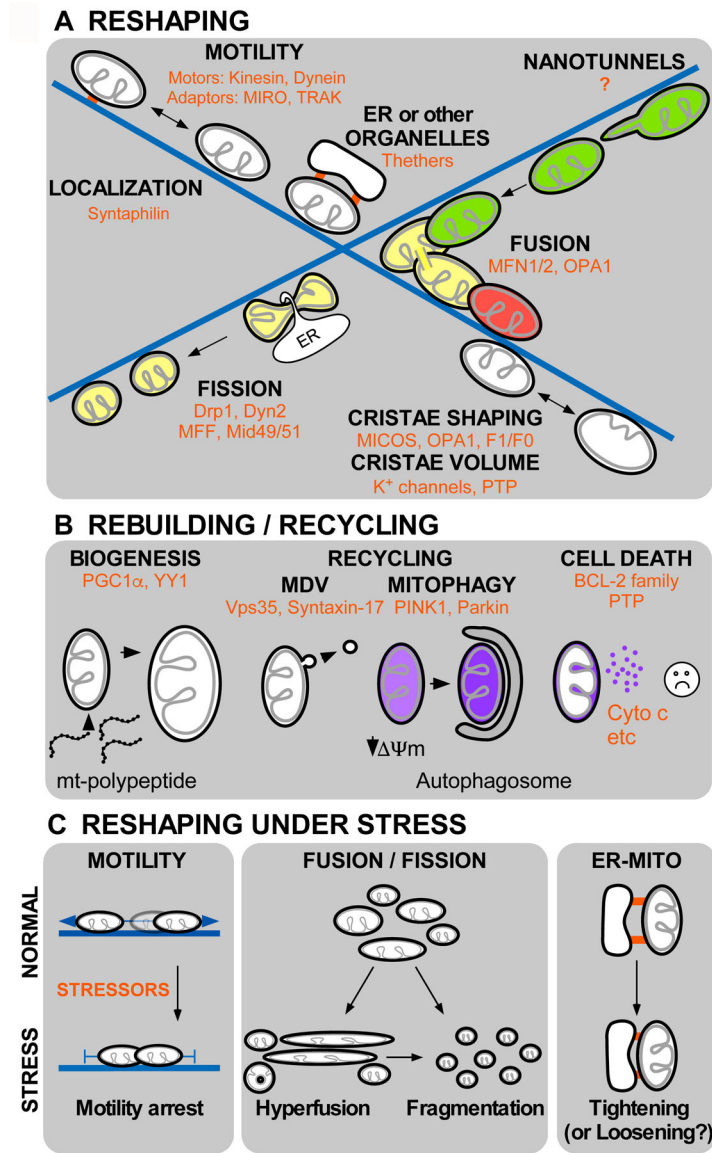


Figure 2. Components of mitochondrial dynamics and their response to stress:
A. Reshaping, localization and motility of mitochondria (depicted by black OMM and gray IMM) along the microtubules (blue) supported by molecular motors (Kinesin and Dynein) and adaptors (MIRO and TRAK) facilitates the inter-organelle communication and physical tethering with the ER or other organelles. Mitochondrial fusion (green and red organelles merge to result yellow post-fusion content) occurs in association to microtubules and mediated by GTPase proteins located at the OMM (MFN1/2) and IMM (OPA1). Fission of mitochondria is also supported by association with the ER, and triggered by DRP1 and Dynamin2 GTPases. Recently described dynamic processes are mitochondrial nanotunnel formation that also depends on interaction with microtubules, intra-mitochondrial dynamics directed by MICOS (mitochondrial contact site and cristae organizing system), OPA1 and F1/F0 (ATP synthase) and matrix volume changes, depending on IMM K⁺ channels and the Permeability Transition Pore (PTP). **B. Rebuilding and recycling processes**, mitochondrial

biogenesis involves expression of organelle-targeted proteins upon activation of transcriptional factors PGC1- α and YY1, and phospholipids biosynthesis. Recycling of mitochondria can be mediated by mitochondria derived vesicles (MDVs) regulated by Vps35, Syntaxin-17, and mitophagy, driven by PINK1 and Parkin. Mitochondria host cell death signaling pathways that control cytochrome c release to decide on cell survival or removal **C. Mitochondrial reshaping under stress.** Diverse stressors (red) trigger adaptive responses in mitochondrial reshaping processes. Stressors commonly cause mitochondrial motility arrest, hyperelongation and donut formation or total fragmentation. Under stress, ER-mitochondria contacts usually become tighter but loosening has also been documented.

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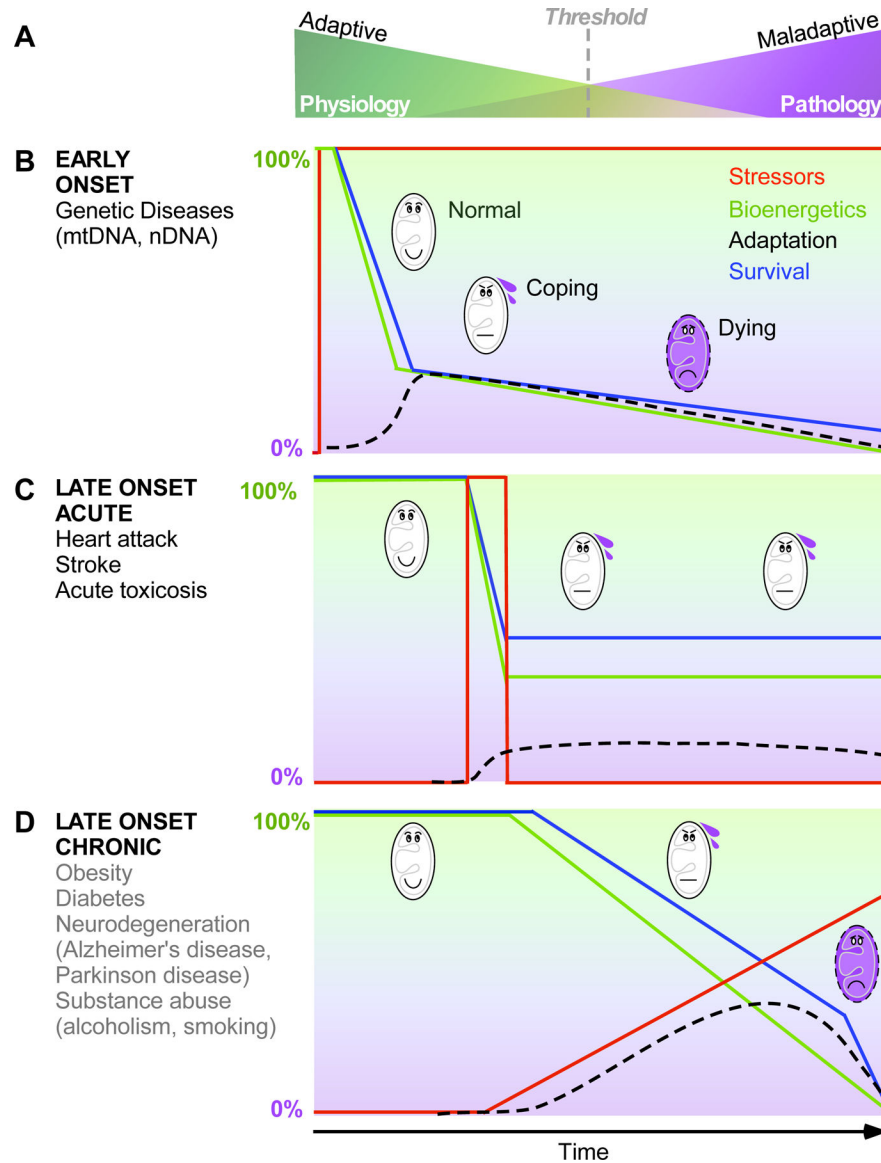


Figure 3. Influence of stressor types on mitochondrial stress responses that progress to disease. **A.** Biological systems stand in balance between adaptative and maladaptative states that determine physiological and pathological outcomes. The threshold between these states can vary between individuals, and over time. **B-D.** Three main types of stressors can be identified based on their onset and duration. *Stressors* refer to a singular perturbation with a time of onset and specific duration; *Bioenergetics* is the capacity to use OXPHOS to transform energetic substrates and oxygen into Ψm to generate ATP and perform work (e.g., Ca^{2+} uptake), illustrated here as the transition from green to purple; *Adaptation* reflects the activation of secondary processes (e.g., gene expression, mitochondrial biogenesis, increased contractility) that act to compensate for bioenergetic defects. *Survival* indicates the ability of cells and organs to sustain viability and normal functions. **B.** EARLY ONSET stressors are generally chronic in nature, such as inherited mtDNA and nDNA mutations that alter key components of mitochondrial dynamics and bioenergetics. Early onset chronic

stressors may cause a substantial initial loss in bioenergetic capacity (i.e., fitness) and lead to progressive decline in survival. **C. LATE ONSET ACUTE** stressors are punctual, arising from chemical exposure, ischemia, or other reversible event. Late onset acute stressors generally induce a rapid and substantial loss of bioenergetic capacity and survival associated with an induction of compensatory adaptive processes that may remain elevated beyond the duration of the stressor, enabling the maintenance of sub-maximal but sufficient functional capacity. **D. LATE ONSET CHRONIC** stressors are those that also arise punctually later in life but remain active and often progress in intensity, such as metabolic dysregulation in diabetes, neurodegenerative processes, and toxic compound exposure from substance abuse. Late onset chronic stressors generally lead to progressive decline in bioenergetics and survival, the progression of which is reduced by compensatory adaptive mechanisms.

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Table 1:
Mouse models for mitochondrial reshaping proteins

A summary of defects observed for reshaping proteins at the level of mitochondrial dynamics and bioenergetics, targeted organs, systemic consequences and response upon stressor exposure. *MEF=Mouse Embryonic Fibroblasts; SM= Skeletal muscle, CM=Cardiomyocytes, ETC= Electron transport chain activity.*

Genetic stressor	Mitochondrial dynamics & bioenergetics defects	Affected organs	Pathology & Symptoms	Interaction with other stressors	Ref.
Mfn1 ^{-/-}	Fragmentation, ↓ fusion & Ψ _m	Not known	Development delay, Lethal E12.5	Not known	62
Mfn2 ^{-/-}	Fragmentation, ↓ fusion & Ψ _m	Placenta	Lethal E11.5	Not known	62
Cerebellum, conditional ⁶⁶	Fragmentation, altered distribution & cristae, ↓ COX & SOD & nucleoid	Cerebellum	Locomotion defects	Not known	66
Heart, inducible ⁷⁰	↑ Area, ↓ [Ca ²⁺] _{mt} uptake & SR-mito tethering	Heart	Not known	Isoproterenol: Ca ²⁺ and ETC, dysregulation	70
T105M ^{+/+} ⁷⁸ T105M ^{+/-} neuroectoderm ⁷⁹	Altered distribution, ↓ abundance in peripheral nerves	Hindlimbs, SM	CMT2A-like	Not known	7879
Mfn2 R94W ^{+/+} Mfn2 R94W ^{+/-}	Fragmentation, ↓ ATP	Brain, pan-neuronal	Lethal @ P1 CMT2A-like	Not known	68
Mfn2 R94Q, neuro	↑ number in motoneurons	Neurons	CMT2A-like	Not known	67
Mfn1/2 SM, conditional	↑ Area, cristae defects, ↓ mtDNA, ↑ deletions, ↓ COX	SM	Low body weight, SM atrophy	Exercise: ↑ lactate	75
Mfn1/2 Heart, conditional ⁷¹⁻⁷³ Heart, inducible adult ^{71, 74}	Fragmentation, cristae defects ^{72, 73} , ↓ mtDNA, ↓ biogenesis, ↓ COX ⁷² Fragmentation, ↓ OCR ^{71, 74} ↓ ER-mito tethering ⁷⁴	Heart	Lethal E9.5 ⁷¹ , E15 ⁷³ . ↓ cardiac function (P7) & death <3wks, heart failure ⁷² , ↓ cardiac development ⁷³ Dilated cardiomyopathy ⁷¹	Ischemia/ Reperfusion: Protection ⁷⁴	71-74
Mfn1/2 & Drp1 KO, Inducible	Clustering, ↓ OXPHOS & impaired mitophagy	Heart	Cardiac hypertrophy Heart failure	Not known	177
Opa1 ^{-/-}	Not known	Not known	Developmental delay, lethal E13.5	Not known	63
Opa1 ^{-/+} Q285STOP	Fragmentation ^{63, 81} , ↓ OCR & Complex IV ⁸¹ , Heart: cristae defects, ↓ mtDNA, OCR, ATP & ETC ⁸²	Retina, brain, spleen, liver, heart	ADOA-like ⁶³ , Dendro-pathy ⁸⁰ , Late-onset cardiomyopathy ⁸²	ER-stress-induced apoptosis: resistance ⁸¹ Ischemia/ Reperfusion: ↓ viability ⁸²	63, 80-82
Opa1 ^{-/+} (c.1065 + 5G→A)	Cristae defects in optic nerve	Optic Nerve	(+/+): Lethal <E12 (+/-): ADOA-like, ↓ retinal ganglion cells	Not known	69
Opa1delTTAG ^{-/+} ^{83, 178}	Fragmentation, ↑ cristae area ⁸³ , ↓ Ca ²⁺ uptake in CM ¹⁷⁸	Optic nerve, SNS, SM	(+/+): Lethal E10.5 ADOA-like, deafness, locomotion defects ⁸³	Ischemia/ Reperfusion: ↑ infarct area ¹⁷⁸	83, 178
Opa1 ^{-/-} , SM, conditional ⁷⁶ and inducible ^{76, 77}	↓ mass, mosaic topology, cristae, ↓ ETC & supercomplex ⁷⁶ , ↓ mtDNA, nucleoid # & OCR	SM, adipose tissue, liver, epithelium	Lethal P9, hypoglycemia, SM atrophy ⁷⁶ , weakness, atrophy, inflammation, early aging ⁷⁶ , myopathy ⁷⁷	Aging: ↓ Opa1 Diet-induced obesity: Normal glucose level (28607005)	76, 77
Opa1 ^{-/-} , β-Cells ¹⁷⁹	Fragmentation, altered cristae & Complex IV	Pancreas	Hyperglycemia Glucose intolerance	Not known	179

Genetic stressor	Mitochondrial dynamics & bioenergetics defects	Affected organs	Pathology & Symptoms	Interaction with other stressors	Ref.
Drp1 ^{-/-}	Aggregation, hyperelongation	Placenta, brain, heart, vessels	Lethal E11.5–12.5, Brain hypoplasia	Bax-and Ca ²⁺ -linked apoptosis inducers: resistance	64, 65
Miro1 ^{-/-}	↓retrograde ²³ & anterograde ²⁸ transport.	Brainstem	Lethal P0, brainstem motor-neuron loss, short neurite.	Not known	23, 28
Miro2 ^{-/-}	Normal shape & transport		No animal phenotype	Not known	28
Miro1 ^{-/-} -neuronal	Lack of mitochondria in spinal cord axons	Brainstem, lumbar spinal cord	Upper motoneuron disease, Death P35	Not known	23
Miro1/2 ^{-/-}	Short and rounded, perinuclear gathering.	Placenta	Lethal E10.5, lack of vascularization	Not known	29

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