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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 mitochondria [1]. 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 responses[2]. 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 stressors[1]. 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 dynamics[2].

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 machinery[3]. 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 ($\Delta\Psi m$) and proton motive force that drive multiple mitochondrial functions[3]. nDNA mutations may directly alter other mitochondrial functions, including their dynamics[4].

Deprivation of mitochondrial fuel substrates or oversupply of nutrients, including glucose and fatty acids, are also mitochondrial stressors[4]. Disturbances of intracellular iron[5] 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 injury[8]. 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 proteins[8].

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 production[9]. Alcohol is metabolized in the mitochondria to give rise to toxic products[10]. Staurosporine targets apoptosis-related proteins located at or translocated to mitochondria, including BAX and BAK[11]. Pro-apoptotic chemicals are commonly used research reagents, whereas inhibitors of anti-apoptotic BCL-2 family proteins have been developed for anti-tumor therapy[11]. 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 signaling[12]. 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 biogenesis[13], and recycling via mitochondrial derived vesicles (MDVs) or mitophagy, in which mitochondria are selectively targeted to autophagosomes for degradation[14]. 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 reviews[2], 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 birth[15].

Mitochondrial reshaping mechanisms and responses to stressors

Mitochondrial Motility

Mitochondrial trafficking and localization throughout the cytoplasm depends on interactions with the cytoskeleton and molecular motors[16]. MIRO1/2 are OMM-localized small GTPase-like proteins[17] that anchor mitochondria to either kinesin or dynein (Figure 2A), motors for anterograde or retrograde displacement along microtubules, respectively, via TRAK1/2 adaptors[16]. Myosin motors can also facilitate mitochondrial positioning[18] and short-distance movement along actin filaments[19]. Stable mitochondrial localization in axons is supported by syntaphilin, an OMM protein directly linking mitochondria to microtubules[20].

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 Ca^{2+} buffering[25]. Mitochondrial movements also support fusion-fission[26] and organelle recycling[27]. Impairment of axonal mitochondrial transport is linked to neurological phenotypes in mouse models targeting MIRO[23, 28, 29] or MFN2[30, 31] (Table1).

Mitochondrial motility is controlled by cytoplasmic $[Ca^{2+}]$ ($[Ca^{2+}]_c$)[25]. Physiological $[Ca^{2+}]_c$ transients suppress mitochondrial movements through MIRO1/2 EF-hand Ca^{2+} sensing domains[32] and may involve other Ca^{2+} sensors[23]. The dynamic interplay between

Ca^{2+} release, mitochondrial motility and mitochondrial Ca^{2+} uptake forms the basis for a homeostatic mechanism in mitochondrial distribution and calcium signaling[25, 33]. ROS also suppress mitochondrial motility in Ca^{2+}-dependent and independent manners[34, 35]. Furthermore, extracellular glucose elevation leads to mitochondrial motility inhibition by activating *O*-GlcNAc transferase to target TRAK[36].

Whereas Ca^{2+} 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]. Ca^{2+} and ROS mutually strengthen each other and can generate cycles impairing motility[35, 37]. In skeletal myoblasts, H_2O_2 inhibits mitochondrial motility and prompts fragmentation[38]. In neurons and other cell types, ROS induces Ca^{2+} 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 contacts[39]. In injured axon zones, mitochondrial density increases to support axon regeneration by local energy production[40], highlighting an adaptive response to acute injury. Mitochondrial density might increase because mitochondria are retained by stabilized syntaphilin[41]. 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 lysosomes[42]. In cancer cells, hypoxia and ROS target alternatively spliced syntaphilin, enhancing mitochondrial trafficking associated with tumor cell migration and invasion[43].

Mitochondrial transport in axons is suppressed by deletion or expression of disease mutants of the fusion protein mitofusin 2 (MFN2) that interacts with MIRO[30]. The mitochondrial motility machinery is also targeted by degradative pathways upon stress. Dissipation of $\Delta\Psi m$ leads to PINK1 stabilization, inducing Parkin to mark MIRO for proteasome degradation and halting mitochondrial movement, possibly to prevent spreading of dysfunctional organelles along neurons[44]. In cortical neurons, mitochondrial damage triggers PINK1/Parkin to induce MIRO1 ubiquitination on Lys27, arresting mitochondria for degradation[45]. Oxidative stress activates the OMM-associated PGAM5-KEAP1-Nrf2 pathway leading to MIRO2 proteasomal degradation, causing mitochondrial retrograde trafficking and perinuclear localisation[46]. Perinuclear mitochondrial clustering creates an oxidant-rich nuclear domain required for hypoxia-induced transcription[47]. Oxidative stress and starvation are also sensed by Myo19, an actin-linked motor that retains mitochondria in areas of low ATP/ADP ratio[48]. Upon mechanical injury to neurons, axon regeneration depends on ARMCX1 expression localized to mitochondria, which enhances mitochondrial transport[49]. Mitochondrial stress responses involve the mitochondrial motility machinery, allowing mitochondrial redistribution to areas where bioenergetic needs are increased, or by recycling damaged organelles[25].

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 MFF[52] mediated by MID49/51[53]. Transient actin polymerization at the OMM constriction site[54] and cytoplasmic Dynamin 2 facilitate fission completion[55]. Mitochondria fission can also be facilitated by motors of opposing directions[26] (Figure 2A).

Fusion-mediated mitochondrial component sharing supports multiple elements of mitochondrial biology: mtDNA integrity[56], mitochondrial respiration[57], $\Delta\Psi m$ equilibration[58], apoptosis[51] and signaling events such as $[Ca^{2+}]_c$ oscillations[59]. Fission can facilitate motility and is required for segregation of damaged mitochondria for mitophagy[58], mtDNA replication[60] and mitochondrial redistribution during cell division[61]. 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, 78–8283] (Table 1).

Mitochondrial fusion-fission balance is regulated transcriptionally and post-transcriptionally. MFN2 expression is enhanced by PGC-1α (peroxisome proliferator gamma coactivator 1 alpha)[84]. MFN1/2 and OPA1 levels and activity are affected by phosphorylation[85], redox modifications[86], acetylation[87] and ubiquitination[88, 89]. OPA1 is proteolytically processed by the AAA proteases OMA1 and YME1L, which are regulated by $\Delta\Psi m$[90] and OXPHOS activity[91], respectively. OPA1 function is regulated by cardiolipin in the IMM to prompt fusion[92]. DRP1 recruitment to the OMM and fission are controlled by Ca^{2+}-and cAMP-stimulated phosphoregulatory events[93].

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 hours[35] (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 YMEL1 proteases, which control OPA1 fusogenic activity[94]. Increased OXPHOS activity in cells

grown on ketogenic carbon sources promotes YME1L-mediated OPA1 processing, increasing fusion[91]. Mitochondrial poisons causing oxidative stress and ATP depletion suppress YME1L activity via degradation[94]. 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, SLP2[95]. SLP2 restricts OMA1-mediated OPA1 processing to support hyperfusion[96]. 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 expression[97]. Pathological cardiac stress leads to mitochondrial fusion inhibition through OPA1 hyperacetylation, normally prevented by the mitochondrial matrix deacetylase, SIRT3[87]. Conversely, pressure overload challenge in the heart activates TNFα receptor type 2, OPA1 expression and fusion dependent on STAT3 and NFkB activation[98].

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-cells[100]. Similarly, high glucose exposure of cardiac cells leads to elevated ROS and mitochondrial fission[101], whereas acute intracellular ROS elevation leads to DRP1-mediated mitochondrial fission[102]. ETC inhibition by rotenone or antimycin A recruits DRP1, promoting fission to support autophagic removal of damaged organelles via AMPK activation mediated by MFF phosphorylation[103]. 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 survival[104]. Mitochondrial depolarization combined with sustained $[Ca^{2+}]_c$ elevation activates the cytoplasmic phosphatase calcineurin that dephosphorylates DRP1 Ser637 to stimulate mitochondrial fission[105]. In skeletal muscle, metabolic oversupply during sustained contractile inactivity also causes DRP1 Ser616 phosphorylation associated with mitochondrial fragmentation[106]. Conversely, upon high fat diet, calcineurin inhibition prevents DRP1 Ser637 dephosphorylation leading to hyperelongated mitochondria and improved metabolic performance in skeletal muscle[107]. Mechanical stress induced by bacterial infection also leads to mitochondrial fission[108]. DRP1 activation has been linked to apoptosis mediated by BCL-2 family proteins[2]. 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 migration[109] and effector T cell activation[110].

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 mitochondria[111]. In H9c2 cells, this is preceded by matrix expansion dependent on PTP or K^+ channel opening and ensuing partial detachment from the microtubular track[111]. Donut formation is a stress response and may protect against swelling-induced structural damage[111].

Nanotunnels

Even when physically separated by several microns, mitochondria can form connections through 60–200 nm wide double membrane tubules called mitochondrial nanotunnels[112]. Nanotunnels have been observed in cardiac[113] and skeletal muscle[59], and can be generated in a cell-free system by kinesin (Kif5b) in a microtubule-and ATP-dependent manner[114]. Protein exchange along nanotunnels[115] suggests that mitochondrial nanotunnels may serve functional but possibly not genetic complementation between non-adjacent mitochondria, in tissues with restricted mitochondrial motility[112]. In mice carrying a ryanodine receptor (RyR) 2 mutation (A4860G) associated with human catecholaminergic polymorphic ventricular tachycardia due to aberrant Ca^{2+} homeostasis, mitochondria display increased nanotunnel communication[116]. Mitochondrial nanotunnels are frequent in skeletal muscle of mitochondrial myopathy patients carrying mtDNA deletions or mutations, suggesting that nanotunnels support mitochondrial adaptation to genetic stressors[117].

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 cristae[118]. 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 contraction[119], and decreased energetic demand during inactivity[106], increase and decrease IMJ number, respectively. MitoNEET, an OMM iron-sulphur cluster forming protein, functions in IMJs and has been linked to H_2O_2-induced mitochondrial fragmentation[120].

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 needs[123] and are supported by physical protein-based tethers[124]. Over 60 proteins have been implicated in tethering and many support specific functions[122]. MFN2 can cause diverse contact phenotypes in different paradigms, which may be determined by other tethering proteins[122]. These contacts function in phospholipid biosynthesis, Ca^{2+} 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 $[Ca^{2+}]$[121]. The ER may stop other organelles in their vicinity by emitting Ca^{2+} signals favoring contact formation[25]. 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

manner[126], whereas cardiac ischemia/reperfusion causes tighter contacts via PTPIP51[127]. Virus infections including CMV[128], chronic hepatitis C or acute RNA virus[129] 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 distribution[130] and a shift to a hypoxic/reducing environment influences ERO1α to leave ER-mitochondrial contacts[131]. Stressors affect Ca^{2+} and ROS signaling pathways at the ER-mitochondrial interface via several mechanisms. The IP_3 receptor (IP3R), which mediates local Ca^{2+} transfer in the ER, and the RYR in the sarcoplasmic reticulum, are targets of redox regulation[132, 133]. Moreover, alteration of ER-mitochondrial Ca^{2+} communication affects other aspects of mitochondrial dynamics including fragmentation[134] and autophagy[135].

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 death[138]. 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 starvation[139].

Intra-mitochondrial dynamics to shape cristae and adjust matrix volume

A distinctive feature of mitochondrial ultrastructure is IMM folding into cristae[12] that allows ETC component organization into supercomplexes to enhance bioenergetic efficiency[140]. Mitochondrial cristae display dynamic changes with different metabolic states[141]. Cristae shape is supported by F_1F_0 ATPase localization at the IMM bending regions[142]. 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 formation[145], interacts with OPA1[84]. Oligomeric OPA1 is needed to keep cristae junctions closed[146].

As a physiological adaptation to increased metabolic demands, cristae remodeling with increased density occurs in exercised skeletal muscle[147]. During starvation, OPA1 oligomerization is enhanced to keep cristae narrow, which is required to promote F_1F_0 ATPase assembly and maintain ATP-linked respiration. Mutant OPA1(Q297V) that undergoes oligomerization but is defective in fusion can support survival during starvation[148]. 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 release[150].

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 instability[3].

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 stressors[3]. The accumulation of stressors, such as secondary mtDNA mutations, may overwhelm the system and cause disease once the biochemical threshold is reached[151]. 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 load[151].

As in animal models (Table 1), autosomal mutations particularly in the fusion machinery (MFN2[152], OPA1[63]), but also in fission factors (DRP1[153], MFF[154]) and a motor adaptor (TRAK1[155]) 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, Ca^{2+} signaling or mitophagy[160].

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 aIso increases ROS to mediate fission, and fission further augments ROS emission[162]. 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 cardiomyocytes[167].

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 life[168]. The metabolic oversupply of diabetes increases fission with concurrent accumulation of mtDNA defects in various tissues[168]. Obesity is associated with reorganization of ER-mitochondrial contacts resulting in mitochondrial Ca^{2+} overload, compromised mitochondrial oxidative capacity and augmented oxidative stress[169]. 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 diseases[170]. Chronic alcohol exposure leads to mitochondrial fusion inhibition in cardiac myocytes[115] and in skeletal muscle by targeting MFN1 protein levels[59]. 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 Ca^{2+} dysregulation, often documented in neurodegenerative diseases, can interfere with various aspects of mitochondrial dynamics and can be part of cycles that drive disease progression[34].

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 tracked[16], but may not represent *in vivo* behavior[176]. 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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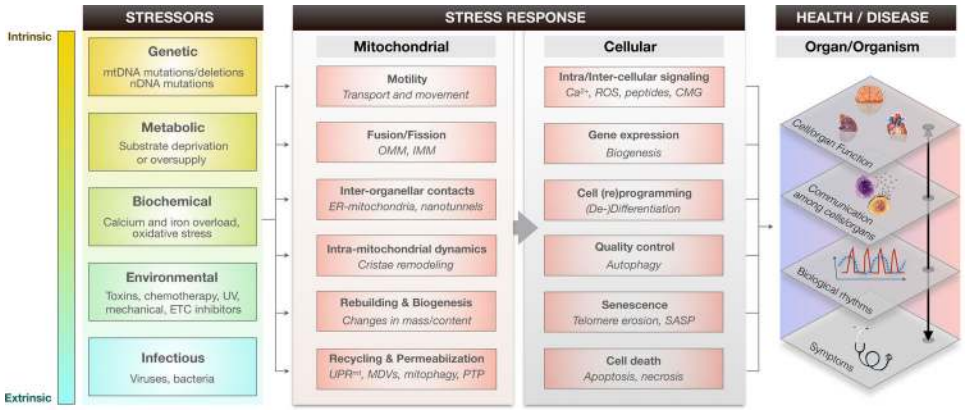

Figure 1. Framework outlining elements of the overall mitochondrial stress response and the link to disease, with a focus on mitochondrial dynamics.

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, ophtalmoplegia), 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.*

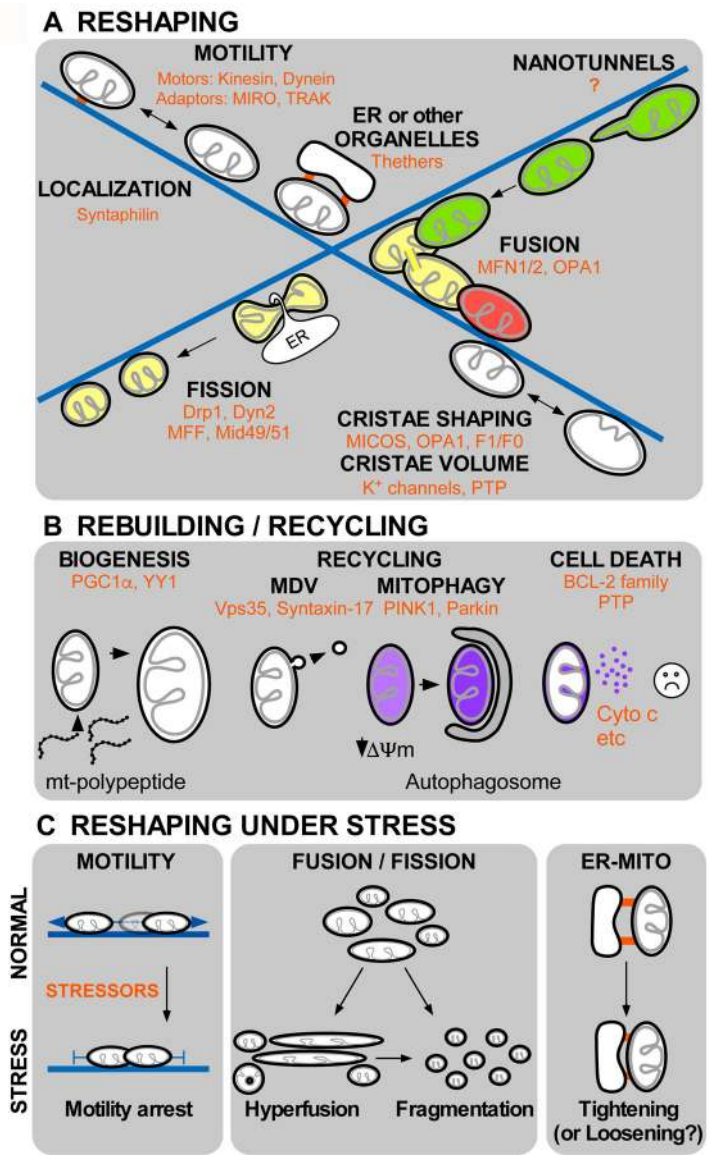

Figure 2. Components of mitochondrial dynamics and their response to stress:

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.

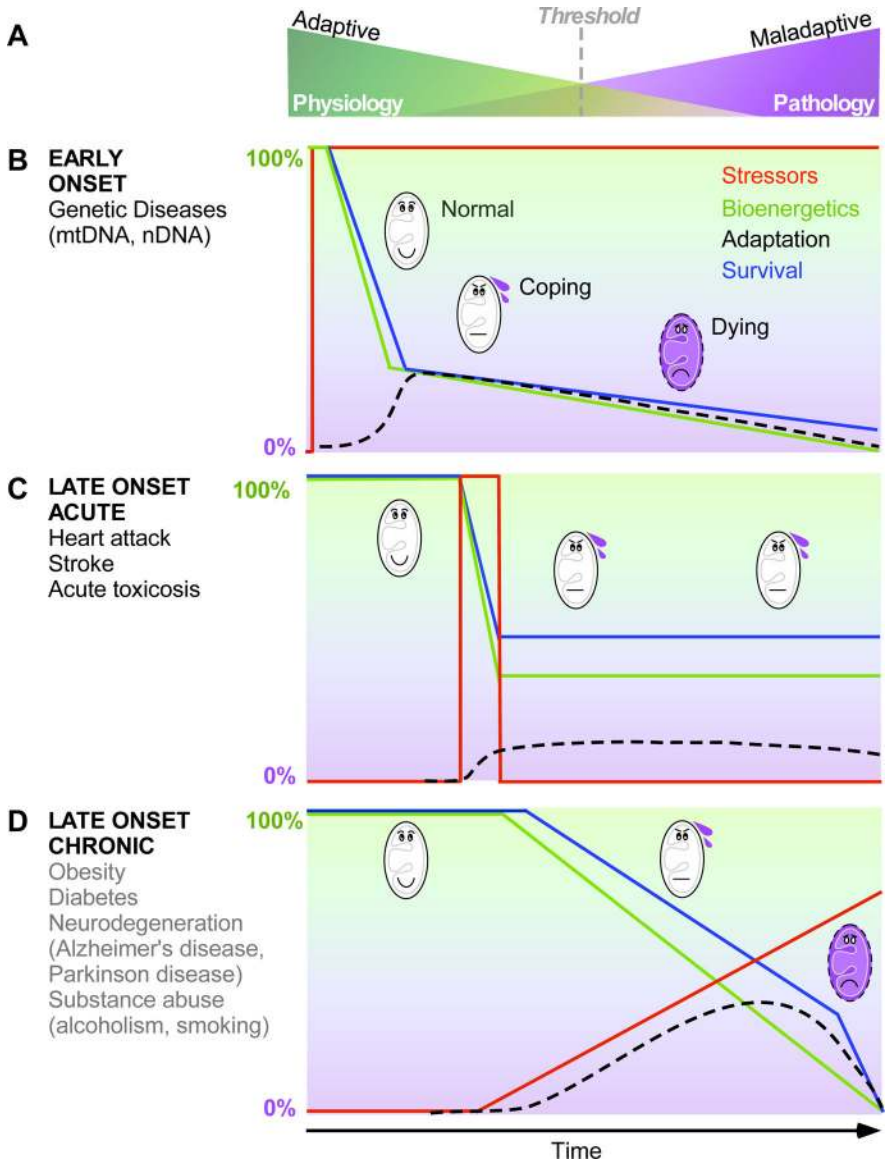

Figure 3. Influence of stressor types on mitochondrial stress responses that progress to disease.

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 $\Delta\Psi m$ 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.

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 & ΔΨm	Not known	Development delay, Lethal E12.5	Not known	62
Mfn2−/−	Fragmentation, ↓ fusion &ΔΨm	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