Abstract

BACKGROUND: Mitochondrial dysfunction known to be associated with most of human inherited disorders and diseases, including neurodegenerative disorders, cardiomyopathies, metabolic syndrome, muscle weakness, cancer, also obesity.

CONTENT: Mitochondria charges for multiple anabolic and catabolic circuitries, as the main provider for adenosine triphosphate (ATP). Mitochondria also responsible for cell-wide stress responses and control non-apoptotic cell death routines, such as autophagy and regulated necrosis. In other words, mitochondria play an extended role in regulating cellular functions, both vital and lethal, from physiological metabolism to stress responses and death to maintain adult tissue homeostasis. Furthermore, mitochondria are crucial for both embryonic and postembryonic development. Therefore, any defect or alteration in mitochondria signaling pathways will lead to a large number of diseases in human, including premature aging, neurodegenerative disorders, muscle weakness, cardiovascular disorders, and cancer.

SUMMARY: Mitochondria perform a dynamic, integrated interconnected network, to maintain tissue homeostasis, beyond the cell boundaries and regulating cells and tissues communication. Certainly any mitochondrial dysfunction could direct to neurodegenerative diseases and metabolic disorders.

KEYWORDS: mitochondria, UPR, mitochondrial quality control, proteostasis, mitohormesis, mitochondrial diseases

Introduction

Mitochondria are known as the powerhouses of the cell. They are crucial in producing cellular energy adenosine triphosphate (ATP) production, regulating cellular activities, such as apoptosis, Calcium (Ca\(^{2+}\)) signaling, redox homeostasis, etc.(1) Since last decade, cell biology researchers found the regulated events of membrane fusion and fission of mitochondria, termed as mitochondrial dynamics, bring forth this organelle as their main interest, together with the mitochondrial network remodeling architecture within the cytoplasm.(2-4) Notably, any abnormality in mitochondrial dynamics could cause bioenergetic defects (5), induce embryonic lethality in transgenic animal models (6), also a different group of human diseases (7), confirming the crucial role of this event in physiopathology (8-10). Many studies demonstrated that mitochondria play a role in the essential cellular signaling pathways and mitochondrial dynamics are involved in regulating cellular activity.(4,11,12) Thus, any perturbation in mitochondrial function will affect human pathologies such as type-2 diabetes, cardiovascular, and neurodegenerative diseases.

Mitochondria have their own DNA, named mtDNA, and maternally inherited, not transmitted through nuclear DNA (nDNA). In human, mtDNA is circular, double-stranded circular molecule of 16.5 kb, encoding 13 subunits of the RC
Mitochondrial diseases can present at any age on any organs, affect one in 2,000 individuals. Most mitochondrial diseases occurred due to the genetic mutations that disrupt mitochondrial gene expression (mtDNA replication and transcription, and mitochondria mRNA translation) (14-16), affect to mitochondrial oxidative phosphorylation because the assembly of the respiratory chain enzyme complexes and ATP synthase in the mitochondrial inner membrane folds called cristae was failed. This assembling need nutrient-derived reducing equivalents to generate an electrochemical potential across the inner membrane and is essential for organelle functions.(17) This might be explained how a dysfunction in mitochondria could lead to many cell-specific stress responses and will induce a range of human diseases, but the exact mechanism remains poorly understood.(18)

Mitochondrial Biogenesis and Functions

Mitochondria employ a series of biochemical activities for providing oxidative ATP production in eukaryotic cells. (19) Mitochondria has an inner impermeable membrane, and an outer permeable membrane up to approximately 5 kd molecular mass, to separate it from the cytoplasm. Acetyl-CoA oxidation will derive nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH) as the electron donors. This electron was needed for electron transport chain of the mitochondrial inner membrane, in order to establish an electrochemical proton gradient across the membrane. When the proton transferred a voltage potential and a pH gradient is produced, and used by the membrane bound ATP synthase to drive the synthesis of ATP by uncoupling proteins to generate heat.

(20) The discovery of peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC)-1α and family (PGC-1β and PGC-1-related coactivator (PRC)) as key players in the regulation of energy metabolism open a major finding of how transcription factors controlling mitochondrial biogenesis by regulating overlapping gene expression programs.(21,22)

Mitochondrial biogenesis is an orchestrated process tightly regulated by the activity of both mitochondrial and nuclear factors. Ninety percent of mitochondrial proteins are nuclear-encoded, except the respiratory chain complexes formation which encode by both nucleus and mitochondria. The two genes had to be synchronous for transcription and translating the protein needed for new organelles generation. Any imbalance will lead to proteotoxic stress and subsequent activation of mitochondrial turnover mechanisms.(23-25) After transcription and translation process, nuclear-encoded proteins are folded through some process coupled to the translocase of the outer membrane (TOM)-mediated import (26), then due to their prerequisite directed to particular mitochondrial subcompartments: the outer mitochondrial membrane (OMM), the intermembrane space (IMS), the gel-like structure called inner mitochondrial membrane (IMM), or the matrix (27). These steps are regulated by the AMP-activated protein kinase (AMPK), the mechanistic target of rapamycin (mTOR), and insulin-like signaling (ILS) pathways, together with the signaling cascades triggered by calcium and nitric oxide.(28-32)

The key components for mitochondrial biogenesis are nuclear respiratory factors (NRF)1 and NRF2.(25) NRF1 transcriptional activity is methylation-dependent.(33) NRF2, or also known as GA-binding protein transcription factor (GABP), controls the expression of mitochondrial transcription factors (TFAM, TFB1M, TFB2M) and components of the respiratory chain (COXIV sub-units).(34) In mice, sirtuin (SIRT)7 deacetylates GABP-β1 and trigger its binding to GABP-α thus increasing its transcriptional activity.(35) AMPK as an additional regulator of mitochondrial homeostasis, in response to nutrient depletion, inhibit mTOR to promote mitophagy and activate Unc-51 like autophagy activating kinase 1 (ULK1). Otherwise, in rat hepatocytes, AMPK-mediated phosphorylation of SIRT1 results in the PGC1-α deacetylation and subsequent activation, apparently as adaptive compensation response for enhanced mitochondrial turnover.(36) Aside from energy production as their main role, mitochondria also involved in major cellular processes, including ion homeostasis, lipid metabolism, and initiation of apoptotic cell death.
Mitochondria as Regulators of Reactive oxygen species (ROS) and Calcium Signaling

Previously, ROS viewed as a toxic by-product of mitochondrial respiration, and by its name we can advise that it is more chemically reactive than O2, then ROS accused of being cellular damaging agents towards lipids, proteins and DNA. Recent studies suggested its appreciation as a mediator in numbers of cellular signaling pathways (37-40), including growth factor signaling, hypoxic signal transduction, autophagy, immune responses, and stem cell proliferation and differentiation. These propose the perspective of ROS from unwanted product of an imperfect system into a nature specific selection for their signaling, evolving our knowledge about the cellular antioxidant defense system. Many oxidant species gain advantages from ROS specificity of signaling, either in chemical reactivity, stability, and lipid diffusion capabilities. O2−, one of ROS species, is generated when O2 go through one electron reduction by cytosolic nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) or n mitochondrial electron transport chain (ETC) complexes I, II, and III (Figure 1). O2− generated by the mitochondrial ETC is released into the matrix and with help of superoxide dismutase 1 (SOD1), cytosolic O2− is rapidly converted to H2O2. O2− also release complex III into the intermembrane space which can cross over through voltage-dependent anion channels into the cytosol and be converted into H2O2 by SOD1. Moreover, H2O2 also produced as a by-product of protein oxidation in the endoplasmic reticulum (ER), as the end product in many peroxisomal oxidation pathways such as in the β-oxidation of very long-chain fatty acids, and by a wide range of enzymes including cytochrome P450. (46) Important thing to note is that ROS specific target at proximal location to these oxidant-generating systems. By this paradigm shifting towards ROS, we need to elucidate the molecular mechanism of ROS signaling in facilitating oxidation, and the possibilities of its potential for providing new therapeutic avenues for a myriad of diseases linked with excessive ROS. (37)

Ca2+ signaling has become the star for coordinating various extracellular stimuli and triggers the cellular function during the past century. (47, 48) Recently mitochondrial Ca2+ uptake take over the stage as the controller for intracellular Ca2+ signaling, cell metabolism, cell survival and other cell-type specific functions as it effectively buffering cytosolic Ca2+ levels and regulating the effectors. Mitochondrial Ca2+ transporters reveals recently, draw the attention for investigation and molecular intervention. (49) Accumulation of Ca2+ in mitochondria regulates the organelle metabolism, including its main task to produce ATP by oxidative phosphorylation. Three matrix dehydrogenases of mitochondria were activated by low concentration of Ca2+: pyruvate dehydrogenase is regulated by a Ca2+-dependent phosphatase, and α-ketoglutarate- and isocitrate-dehydrogenases are regulated by direct binding of Ca2+ to these enzymes. (50-52) When Ca2+-sensitive dehydrogenases stimulated, NADH availability increased and the electrons flow down the respiratory chain, proposed increased ATP synthesis adjust to the cells need. (53) Some genetic disorders affect mitochondrial function due to the defect in respiratory chain thus reduce the driving force for Ca2+ transfer, therefore the ATP production also reduced. (54, 55)

Ca2+ accumulated in mitochondrial matrix through IMM across the steep electrochemical gradient via an electrogenic pathway with help of Ca2+ uniporter (MCU). MCU has a Vmax of >1400 nmol Ca2+ per mg of protein per min and can be inhibited by Ruthenium red1 and lanthanides. (56-58) Na+/Ca2+ exchangers (mNCX) and mitochondrial H+/Ca2+ exchangers (mHCX) counteract the MCU-Ca2+ accumulation, and insensitive to ruthenium red but can be inhibited by benzothiazepine analogues, such as diltiazem, clonazepam and CGP-37157. (59-61)

Besides its property as Ca2+-binding proteins, mitochondria in other side may act as fixed buffer of Ca2+ large elevation from a subcellular domain. This will influence cellular Ca2+ signals, and hence cell function.
(49) Mitochondrial Ca\textsuperscript{2+} performs two manner during physiological variations of workload (Figure 2). Uptake via the mitochondrial Ca\textsuperscript{2+} uniporter is required to meet the energy supply demand, while keeping the antioxidative capacity in a reduces state so ROS emission won’t be disproportionate.\cite{62} The architecture of mitochondrial calcium uniporter is shown in Figure 3.

**Quality Control of Mitochondrial Proteostasis**

In a cell, mitochondria best known as essential organelles, and the powerhouse in generating large amount of energy from food into ATP by an electrochemical proton gradient across the inner membrane activate the ATP synthases. Mitochondria manage the central functions for amino acids and lipids metabolism, as well as iron-sulfur clusters and heme biosynthesis.\cite{66-69} Mitoproteases is a highly regulated proteolytic reactions performed in mitochondria, including protein synthesis, quality control, mitochondrial biogenesis and dynamics, mitophagy and apoptosis. Any impaired or dysregulation function of this degradative function of mitochondria is associated with aging-related diseases such as neurodegenerative disorders, metabolic syndromes and cancer.\cite{70}

Current proteomics and bioinformatics approaches make it possible to define a comprehensive inventory of mitochondrial proteins that role in maintaining mitochondrial healthy function.\cite{71,72} Encoding by two different genomes, mammalian mitochondria harbor their own genome, encoding for 13 polypeptides aside from those synthesized by nuclear genes. The mitochondrial-encoded proteins compose the core components of the respiratory chain complexes, assemble with imported of nuclear-encoded proteins to achieve efficient respiratory chain complex of mitochondria. Discordination of this process may result in unpartnered proteins, which are prone to misfolding or aggregation. ROS, as an inevitable byproduct of the generation of ATP through oxidative phosphorylation, also become another challenge imposed upon mitochondria. When reacting with proteins, DNA or lipids, ROS could result in accumulation of oxidatively damaged products, making them more prone to oxidative damage, and lead to depolarization of the mitochondrial inner membrane. This could propose the outer membrane permeabilization,

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**Figure 2. Role of mitochondrial Ca\textsuperscript{2+} uptake for ATP production and ROS elimination.\cite{62} (Adapted with permission from American Heart Association).**
make it possible for pro-apoptotic proteins to release from intermembrane space into the cytosol, and initiating the apoptotic cascade. Mitochondria has developed its own mechanism for quality control involving damaged protein or organelles removal to keep the homeostasis of its functional network. Blunted quality control will affect in defense pathways for cellular homeostasis and survival and of course the overall cell health, correlated to aging, prevalent neurological disorders like Parkinson's disease and spinocerebellar ataxia. Mitoproteases together with the cytosolic ubiquitin-proteasome system (UPS) form the first line of cellular defense by facilitating the removal of damaged, oxidized or misfolded mitochondrial proteins. Figure 4 explain the mechanisms of mitochondrial quality control briefly.

The first line of mitochondria, from bacteria to higher eukaryotes defense mechanism action in the molecular level, involves the conservation of intraorganellar protein quality control machinery, including chaperon and various proteolytic enzymes. UPS and a mitochondrion-specific unfolded protein response (UPR) also influence mitochondrial protein quality control, by constricting the increasing of misfolded proteins in the organelle. The second line for quality control emerge due to the dynamic nature of mitochondria itself. The organelles naturally tend to constantly fusing and dividing mediated by dynamin-like GTPases in the OMM and IMS. By fusion, a damaged mitochondrion, means it’s defect in certain components, will fuse with a healthy neighbor and replenish its stores. The third stage of these quality controls gate occurs on a cellular level, where the mitochondrial damage were more extensive that the entire cell need to be totally turnover through apoptosis.

On contrary, mitochondria fissions aim to increase the organelles numbers within the cells prior biogenesis, and separate the defect organelles for autophagic degradation, and then by fusion these components will be mix and distribute evenly. Thus, by fusion and fission mitochondrial biogenesis, distribution of mtDNA, and proteome could be facilitated. Practically, chaperones and proteases protect mitochondria protein-folding environment from inevitable errors in expression and assembly as well as prevent the prevent accumulation of unfolded and orphaned subunits. Recent comprehensive knowledge in mitochondrial genetics improve the diagnosis to prevent severe mitochondrial disease, and had a major impact on patient care as well as rise new challenges for therapies in mitochondrial disorders.
Mitochondrial and Nucleus Communication

Mitochondria import more than 1,000 different proteins from the cytosol to perform the bioenergetics, metabolism, and apoptosis function. The protein import machinery was assumed to be constitutively active and not depend on any exact regulation. After all, recent studies found a multiple levels of mitochondrial protein import regulation which were connected to cellular metabolism, signaling, stress, and pathogenesis of diseases. Mitochondrial fitness can be monitored by this activity and also represent the biogenesis regulation, composition, and turnover of the organelle.(69) Nucleus-encoded mitochondrial precursor proteins possess targeting signals which are recognized by receptors on the mitochondrial surface, and direct the precursors to their functional destination in the mitochondrial sub-compartments. These targeting signals can be distinguished into two main groups.(63,64) The first group is the amino-terminal extensions of precursors. This is the classical mitochondrion-targeting signals. Their presequences removed after import into mitochondria by a proteolysis. The second one are some precursor proteins with no particularly cleavable extensions but contain internal targeting signals that remain part of the mature protein including different types of precursor proteins and targeting signals (Figure 5).(67)

Many researches focus on excavating these structural analyses of mitochondrial import components, besides of single-particle electron microscopic analysis of purified translocase complexes (90-93), receptor domains, mitochondrial chaperones and the processing peptidase MPP (94-100). High resolution structures of the membrane-integrated translocation channels, were also important to dig the molecular mechanisms of membrane translocation including that of preproteins in transit.

Mitochondrial function was controlled by nuclear transcription, including the organelle function and capacity coordination, in response to intrinsic and extrinsic signals either alterations to the cell's redox state, nutrient deprivation, and (in muscle) exercise.(101-103) These will increase in mitochondria biogenesis, boost the mitochondrial mass and bioenergetic capacity. An array of transcription factors (TFs) together with co-activators activate and coordinate nuclear and mitochondrial genes expression.(104,105) NRF-1 and NRF-2 are the principal TFs for biogenesis, by controlling the expression of key mitochondrial components involved in oxidative phosphorylation (OXPHOS), haem biosynthesis, the function and regulation of mtDNA, and antioxidant defences.(106) The oestrogen related receptor (ERR)-α, the cAMP response element (CREB), and the Ying Yang 1 (YY-1) transcription factor also role as TF in the regulation of mitochondrial genes. Other TFs such as ERR-α regulates oxidative metabolism through its control of β-oxidation related genes (106), and CREB and YY-1 are involved in the expression of ETC protein components.(107,108) All of them with transcriptional co-activators in the nucleus integrates into the program of biogenesis.(109)

Retrograde (RTG) signaling occurred as a respond to altered mitochondrial bioenergetic state, the expression of

Figure 5. Biogenesis pathways of mitochondrial proteins.(67) (Adapted with permission from Springer Nature).
Mitochondria quality and cellular health. We could conclude that mismatch between the nuclear and mitochondrial genomes, the nuclear and mitochondrial affect in promoting the development of some other clinical phenotypes. Lactic acidosis, and stroke-like episodes (MELAS), and also to be associated with mitochondrial encephalomyopathy, the gene encoding mitochondrial tRNALeu (115), is known to be correlated with mtDNA pathogenic mutations known to be correlated with respiratory function. There are large groups of human mitochondrial dysfunction. There were not enough studies in mammalian cells about this, but some researches in yeast have provided interesting observations that perturbations to mitochondria such as the loss of mtDNA (i.e., petite or rho0 cells) lead to the activation of TF by RTG1, RTG2, and RTG3 (RTG1-3) proteins. RTG signaling in yeast induce the activation of the glyoxylate cycle and the upregulation of fatty acid β-oxidation thus proposed the alter in the metabolic function, involving abundant variety of carbon sources, such as acetate, and compensating for a reduction in capacity or lack of OXPHOS. Involvement of TOR signaling in the RTG signaling pathway open a possibility of such system in higher eukaryotes, since TOR signaling also found from yeast to humans although its sphere of activity may be slightly changed between species.

Mitochondrial genome can communicate and function synergistically with nuclear expression regulate by specific sequence alterations that categorize mtDNA in haplogroups as mtDNA haplotypes, besides being useful to trace maternal phylogenetic lineages. mtDNA variations are specifically associated with disease phenotypes related to specific sequence alterations in mitochondrial components, and can be measured through the bioenergetic and other mitochondrial functional aspects, such as a decrease in respiratory function. There are large groups of human mtDNA pathogenic mutations known to be correlated with clinical phenotypes, such as the A3243G mutation in the gene encoding mitochondrial tRNALeu, is known to be associated with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and also promote the development of some other clinical phenotypes. We could conclude that mismatch between the two genomes, the nuclear and mitochondrial affect in mitochondria quality and cellular health.

Mitophagy

One of the cellular components catabolism process including cytosol, organelles and protein aggregates, is autophagy, over their encapsulation by a double-membrane structure known as the autophagosome. Autophagy will recycle intracellular components to compensate for nutrient deprivation and also selectively eliminates organelles in order to maintain their number and quality control.

Autophagy selectively eliminate mitochondria, in conjunction with mitochondrial biogenesis, to maintain the steady-state mitochondrial number that are needed to meet metabolic demand. Mitophagy through some distinct steps selectively removed any defective or superfluous mitochondria and target them to autophagosomes to maintain quality control. ‘Mitochondrial quality control’ involving the coordination of mitochondrial dynamics, mitophagy, and biogenesis to keep up a healthy pool of mitochondria. Mitochondrial dynamics refer to its constantly modified morphology by fission and fusion events, all while they are being shuttled throughout the cell. This way, fission and fusion allow damaged mitochondria to complement each other. PTEN-induced kinase 1 (PINK1)/parkin pathway affecting fission and fusion, but it is not known how this could cause dopamine neuron degeneration. Under stressful conditions, such as nutritional deprivation, two damaged mitochondria with mutations in different genes can fusion and allow functional complementation by RNA and protein components diffusion result in a newly-formed mitochondria and rescuing its function. The lack of mitochondrial function rescuing ability will render cells to become more vulnerable to mitochondrial deficits. In reverse, by fission mitochondria break into smaller pieces to facilitate transport and autophagic degradation of damaged mitochondria. Surprisingly, fission often leads to dissociation the damaged components from resulting mitochondria, resulting in one highly functional mitochondrion and another damaged mitochondrion with reduced membrane potential. So, impaired fission could risk to the ability of mitophagy in recognizing the dysfunctional mitochondria and even to transport them to and from neurites, which is essential in long and energetically demanding cells, such as neurons.

Therefore, mitochondria quality controls include fission and fusion, mitophagy, transport, and biogenesis. Recent studies on Parkinson’s disease (PD), a progressive neurodegenerative disease that causes a debilitating movement disorder, implicated s defect in parkin and PINK1 related to each axis of mitochondrial quality control. Mutation in autosomal recessive PD at two genes encode OMM kinase PINK1 (122) and the cytosolic E3 ubiquitin ligase parkin (123), two proteins involved in suppressing mitochondrial damage in flies (124-126). Impaired in these will lead to loss of flight muscle and dopaminergic neurons, also affecting to male sterility that is ameliorated by promotion of mitochondrial fission.
In autosomal recessive PD, parkin gene mutation is the most common cause. The gene encodes a 465-amino acid E3 ubiquitin ligase capable of mediating mono- or poly-ubiquitination using different ubiquitin linkages via lysine 27, 29, 48, and 63 of ubiquitin. Investigation from mouse model and postmortem PD brain samples showed that parkin is inactivated by post-translational modifications, including oxidation, nitrosylation, addition of dopamine, and phosphorylation by c-Abl, which is important for stress-activated nonreceptor tyrosine kinase and is activated in sporadic PD brains and in animal models of PD.(121)

Autophagy and apoptosis manage the turnover of organelles and proteins within cells, and of cells within organisms, respectively. Many stress pathways sequentially bring up autophagy and apoptosis within the same cell. Commonly, autophagy and apoptosis blocking and shuts off each other, for exceptional in some special cases autophagy or autophagy-relevant proteins will induce apoptosis or necrosis, where autophagy degrade the cytoplasm excessively, leading to ‘autophagic cell death’. Communication between autophagy and cell death pathways influences the normal clearance of dying cells, as well as immune recognition of dead cell antigens. Thus, the relationship between autophagy and apoptosis has an essential affect in pathophysiological consequences. (130,131)

Mitochondrial UPR and Mitohormesis

Mitochondrial function affects a lot of essential cellular and organismal function, therefore many cell’s mechanisms or pathways have evolved to monitor mitochondrial function and provide a fast respond against mitochondrial stress to recover organelle activity, referred as the RTG responses. This pathways upstreaming the initial signals of mitochondria to communicate with cytosol and nucleus and impact gene transcription and protein synthesis in a protective manner.(132) One potential mechanism to asses mitochondrial quality involving the organelle metabolites such as ATP or iron-sulfur clusters (133) and monitoring mitochondrial protein import efficiency (134). In order to function properly, over than 1,000 proteins composing mitochondria, of which ~99% are encoded by nuclear genes and translated on cytosolic ribosomes, then later imported into mitochondria, where they are appropriately folded and assembled. Transit across the mitochondrial inner membrane requires the Tim23 complex and a completed tricarboxylic acid cycle (TCA) cycle and OXPHOS system to keep the membrane potential and the mitochondrial chaperones located within the matrix.(65,135,136) Therefore, the mitochondrial function could be described by the protein import efficiency.
Proteostasis can be briefly determined as protein homeostasis, means all the cellular pathways that govern the production, folding and degradation of proteins, necessary for cellular and organistical functionality and survival. The UPR is a complex pathways of cellular stress response to ensure proteostasis in different subcellular compartments, with finely communicated with the nucleus, have evolved in the cytosol, endoplasmic reticulum and mitochondria. Proteostasis dysfunction was correlated to several age-related diseases due to protein aggregation. (137) Mitochondrial unfolded protein response (UPRmt), just recently discovered, not like endoplasmic reticulum (UPRER) and the cytosolic heat shock response (HSR) that have been first extensively studied (138,139), also role in on the complex relationships between mitochondria and the nucleus (82,140).

Proteostasis in the mitochondria is provided by an elaborate PQC network, composed of two main functional groups of proteins, chaperones and proteases (76,79). Chaperones mtHsp70, Hsp60 and Hsp10 fold and assemble proteins that are imported into the mitochondria and refold damaged mitochondrial proteins. Each mitochondrial compartment has specific ATP-dependent protein quality control (PQC) proteases to digest any excess proteins that are unassisted by chaperones: the ClpXP and Lon proteases in the matrix, the i-AAA (Yme1L1) and m-AAA proteases (Afg3l2 and Spg7), acting in the IMS and matrix, respectively. These PQC chaperones and proteases are induced upon mitochondrial proteotoxic stress as a result of a RTG mitochondria-to-nucleus signaling termed UPRmt, or can be described as a transcriptional response due to mitochondrial dysfunction or the accumulation of unfolded proteins within mitochondria in the cell.

Studies performed to revealed the pathways using mitochondrial chaperones and proteases as UPRmt biomarkers, found many conditions to trigger UPRmt, most of which interfere with the mitochondrial proteostasis, including disturbing the PQC system or by increasing the load of damaged, unfolded or unassembled proteins, with the intention to alleviate proteostatic stress in mitochondria and promote cell survival along with the repair and recovery of defective mitochondria. (141,142) Thus UPRmt maintain the stability of mitochondrial function, metabolic adaptations, as well as an innate immunity. (143)

While impaired protein quality control and accumulation of misfolded and unfolded proteins direct to proteostasis impairment role in age-related decline, increasing the expression of chaperone, limiting translation, or increasing protein turnover otherwise has been implicated in shifting mitochondrial dysfunction into lifespan extension by hermetic mechanism. (142)

UPRmt is induced by manipulating ETC via downregulation or inhibition of single (or groups of) ETC components, either by encoded mtDNA or nDNA (144), resulting a mismatch between mtDNA and nDNA encoded ETC subunits and an orphaned unassembled subunits conceived. This subunit need to stay associated with chaperones, termed as mitonuclear protein imbalance. (144) ETC subunits also downregulated by eco-1 (complex IV) RNA interference (145,146), in isp-1 (complex III) or clk-1 (ubiquinone synthesis) mutant strains (146,147), or by using pharmacological ETC inhibitors, such as antimycin (148,149) and rotenone (148). Therefore, mitochondrial biogenesis activation by resveratrol or rapamycin (144), or NAD+ levels boosting by the NAD+ precursor, nicotinamide riboside (NR), or by inhibiting NAD+ consumption, as seen after treatment with PARP inhibitors (150), trigger UPRmt by similar mechanisms. However, in NAD+ level raising, mitonuclear imbalance created due to specifically increasing of transcription and translation of mtDNA-encoded ETC subunits, thus triggers the UPRmt. (151)

Under stress, mitochondria will activate several lines of defense. Started with temporarily blocking the production and import of new mitochondrial proteins. General control nonferrepressible (GCN)-2, a specific kinase in worm (152), and protein kinase R (PKR) in mammals (147), phosphorylate eIF2a and leads to global translation attenuation. Yme1l1 protease in mammals, selectively degrades the translocation pore component Tim17A and specifically reduce the mitochondrial import and functions, consistent with the reallocation of ATP production to glycolysis in the cytoplasm. (153,154)

In stress condition, both mitochondrial dynamics and mitophagy pathways contribute to reconstitution of cellular homeostasis, by redistribution and eliminate of the irreversibly damaged elements of mitochondrial network. Under strong mitochondrial stress, insufficient levels of mitophagy and UPRmt activation will induce apoptosis and has negative systemic effects on whole organism physiology. (76,79)

Many publications so far have provided useful information about the communication between mitochondria and nucleus, also how its roles including UPRmt pathways in lifespan regulation from simple model organisms to mammals. However, UPRmt is a transcriptional response that affects over 400 genes controlling different aspects of cell physiology, so we are facing a scientific challenge for years to come to find
which one is the most important and the most available to be manipulated in ameliorating the defects associated with mitochondrial dysfunction.(140,143)

In mild stress, mitochondrial rapidly activate a coordinated response in cytosolic signaling pathways that ultimately alter nuclear gene expression, named mitohormesis, and leave the cell less susceptible to subsequent perturbations. A comprehensive understanding of mitohormesis will provide a better insight into our susceptibility for disease and potentially provide a unifying hypothesis for why we age.(135) Hormesis in general can be defined as any cell response that exhibits a biphasic response to exposure to increasing amounts of a substance or condition.(156) Here, we focus on one form of hormesis, termed mitohormesis, briefly defined as a respond to mild mitochondrial stress due to any insults, exhibit a broad and diverse cytosolic and nuclear response. This response could be varied but appears to induce a wide-ranging cytoprotective state generating in long-lasting metabolic and biochemical changes and finally may reduce our susceptibility for disease and expand out lifespan.(155,156) Then we may warp up that mitochondrial stress induce mitohormetic response which provided both short term metabolic benefits and the potential for long term benefits in increased stress resistance and longevity.

### Mitochondrial Diseases

Human mitochondrial disorders are long-term, genetic, often inherited disorders, in consequence of mutations in mitochondrial and/or nuclear DNA that lead to mitochondria fail to produce enough energy for the body to function properly.(15) Currently, mitochondrial diseases are still incurable, so available treatments only help to relieve the symptoms. The diseases can manifest at any age, at any organ or organ system, including in multiple organs that may have no apparent functional links to each other, such as the brain and liver, or pancreatic β-cells and the auditory system, and can be inherited, either from an autosome, the X chromosome, or maternally depending on where the gene defect lies. Children may recover from one phenotype and later develop another ones.(17,18,157) We don’t have a comprehensive understanding about the natural history of mitochondrial disease until recently, but longitudinal cohort studies involving a large population indicating clinical progression in mitochondrial disorders caused by both mtDNA and nuclear gene mutations.(158)

Genes identification for mitochondrial disorders lead to better mechanisms understanding, such as mutations affecting the structural subunits of the mitochondrial respiratory chain (159) was accompanied by the molecular dissection of the assembly apparatus for complexes IV (160), then I, III (161) and finally V (162). Further observation also showed dual functions and multiple functions in several assembly protein or the structural peptide components of complex I.(163) The most interesting finding is that most sophisticated disease mechanisms turn out not to connected directly to oxidative phosphorylation and ATP synthesis, and in adult, the single most important group heading to disorders affecting the maintenance of mtDNA.(164)

Majority abnormalities in mtDNA expression associated with mtDNA depletion due to insufficient and/or unbalanced deoxyribonucleoside triphosphate (dNTP) pools, impact in aberrant mtDNA maintenance and translation then lead to protein stress (resulting from defects in translation or unbalanced translation of respiratory chain components that are encoded by mitochondrial and nuclear genomes), replication and transcription stress as well as stress.(165) A number of credible evidence pointed that mitochondrial disorders mainly triggered by mitochondrial stress responses because of a primary molecular defect in the organelle, and not the defects in oxidative phosphorylation per se.(18)

Mitochondrial stress responses activate the quality control pathways then initiate reverting signals in mitochondria to activate the nuclear genetic programs for organelle maintenance and heighten the quality control. Studies in human, mice and cell lines showed a robust nuclear transcriptional stress response has also ben induced in coping with the defect on mtDNA maintenance and translation (165-169), upregulating the genes that carry a conserved amino acid response element (AARE) in their upstream regulatory region (170). The amino acid response element (AARE) functions as the binding site of activating transcription factors (ATFs), and was found in different isoforms for ER UPR and mtUPR.(171) These, explained the complex molecular mechanisms responsible for defects of oxidative phosphorylation. A large cohort study recently, after last 25 years of intensive studies aimed to explore the genetic causes and the pathogenic mechanisms of mitochondrial diseases, involving more than 3,000 subjects, phenotypic subgroups and the relationship to genotype, driven the “proof of concept” successes and providing rich natural history data sets to be translated and tested on patients. A proof of maturity in mitochondrial medicine, and
Conclusion

Mitochondrial function and behavior become central for human physiology, and therefore “mitochondrial dysfunction” take charge to a wide range of diseases. Fortunately, our body has own system for mitochondrial “quality control”, monitoring the function of mitochondria in various level, and release mitochondrial signals in particular stress condition, thus lead to a dramatic effect on oxidative and biosynthetic pathways in the cell, affect whole-body metabolism. Mitochondrial dysfunction appears to work on a close link with nutrient-sensing pathways and the one-carbon cycle although still poorly understood. Many efforts to improve our understanding of the metabolic remodeling associated to mitochondrial diseases based on biochemical, metabolic and genomic approaches, expected to enable a construction of a complete human mitochondrial network map. The utilization of NGS technology may exploit the whole mitochondrial DNA and the exons encoding the proteome, and will continue to greatly accelerate these advances.

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