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Picturing Molecular Environmental Health from Mitochondria

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Abstract

Environmental factors play an important role in the etiology of various human diseases, such as neurological disorders, cardiovascular diseases, diabetes, obesity and cancer. To design new strategies for disease prevention and therapy, it is crucial to understand the molecular mechanisms underlying the toxic effects of environmental factors to the cell, the building block of human. In the past decade, significant scientific progresses have been made in the biology of mitochondria, a key player in regulating cellular functions. Studies indicate that mitochondria play major roles in environment-caused diseases, and that mitochondria have versatile functions in addition to producing the chemical form of energy, adenosine triphosphate. These newly identified mitochondrial functions include regulating redox-sensitive signaling pathways and mediating innate immune responses, making mitochondria critical for a variety of cellular mechanisms under both physiological and pathological conditions. This essay reviews recent advances in mitochondrial functions and summarizes environmental factors that act on mitochondria for detrimental or protective effects. In addition, the essay provides a unified mitochondrial mechanism that may underlie the molecular interaction between environmental factors and the cell.

Keywords: Environmental health; Mitochondria; Adenosine triphosphate

Introduction

Human diseases are determined by both genetic and environmental risk factors. A recent investigation indicates that environmental factors contribute to about 80% of the 102 diseases and injuries listed by the World Health Organization (WHO) for the year 2002, and account for 24% of the global burden of disease [1]. These data clearly indicate a key role of environmental factors in human health. Modern molecular and cellular studies have revealed a great detail of normal and disease biological processes at the molecular level; however, the molecular mechanisms by which environmental risk factors cause human diseases are still not well understood. An in-depth understanding of these molecular mechanisms is the prerequisite for the design of new strategies of prevention and therapy, and requires intensive investigations in the cutting edge field – Molecular Environmental Health. In this essay, the author uses the organelle mitochondria as an example to connect Molecular Biology and Environmental Health from available literature, to demonstrate the level of clarity of scientific understanding we can achieve by studying environmental health at the molecular and cellular levels.

Recent Advances in Mitochondrial Biology

As an important cellular organelle, mitochondria are known for producing adenosine triphosphate (ATP), buffering calcium and participating apoptosis. Moreover, mitochondria host a variety of metabolic processes, such as the tricarboxylic acid (TCA) cycle, fatty acid beta-oxidation, and synthesis of lipid, steroid, heme and iron-sulfur clusters. In the past decades, several significant progresses have been made which have expanded our conventional understanding of the function and regulation of mitochondria.

One progress is that mitochondria modulate cellular signal pathways by generating reactive oxygen species (ROS). ROS are oxygen-containing, highly chemically reactive molecules, including superoxide anion, hydroxyl radical and hydrogen peroxide. Mitochondria generate superoxide from oxygen at the site of the mitochondrial electron transport chain as an intrinsic product of oxidative phosphorylation. Traditionally, ROS are considered toxic as high level of ROS causes oxidative damage: protein oxidation, lipid peroxidation and DNA mutation. However, numerous studies have demonstrated that moderate or low levels of ROS are an important cellular signaling transducer in cell proliferation, differentiation and migration [2-6]. In fact, mitochondria-generated superoxide is converted to hydrogen peroxide. Hydrogen peroxide is a signaling messenger that can travel for a distance within the cell to oxidize key protein residues such as cysteines, resulting in change of the conformation or activity of kinases, phosphatases or transcription factors in various cellular signaling pathways. These redox-sensitive signaling pathways, such as the mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/Erk), nuclear factor erythroid-derived 2-related factor 2 (Nrf-2), c-Jun NH2-terminal kinase (JNK) and nuclear factor-kappa B (NFκB) pathways, in turn regulate important physiological cellular processes ranging from cell proliferation and death, to stress defense, and to immune response. Furthermore, mitochondrial ROS are required for the activation of the NACHT, LRR and PYD domains-containing protein 3 (NALP3) inflammasome, which is a protein complex that mediates release of interleukin-1β (IL-1β) and IL-18 for inflammation [7,8]. Finally, abnormal production of mitochondrial ROS is found to contribute to disease pathogenesis. For example, oncogenic Kras increases mitochondrial ROS that promote cancer cell growth via the MAPK/ERK pathway and the NFκB pathway [9,10]. Consistently, increased levels of ROS are observed in cancer cells compared to normal cells [11]. Thus, mitochondria-generated ROS serve as an important signaling transducer in both physiological and pathological conditions.

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Except for regulating cellular signaling by releasing ROS, mitochondria are found to directly serve as a platform for protein complex assembly and activation to initiate cytosolic signaling machineries. A typical example is the mitochondrial antiviral signaling protein (MAVS) which mediates the innate immune response against virus [12]. Upon viral infection, viral RNA is recognized by the cytosolic sensors such as retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5), which then bind to mitochondrial surface-localized MAVS. This initial protein interaction is followed by recruitment of multiple cytosolic proteins to the surface of mitochondria to form a MAVS multi-protein complex. The outcome of the propagation of the MAVS anti-viral signaling pathway is the induction of gene expression of type I interferons (IFNs) and pro-inflammatory cytokines, which facilitate clearance of virus. Together, the conventional and newly identified functions of mitochondria are summarized in Figure 1.

Given the crucial role of mitochondria in cellular functionality, how mitochondrial function is regulated becomes pivotal. In this aspect, the discovery of mitochondrial dynamics has established a major regulatory mechanism for mitochondrial function. Instead of being static organelles as perceived in the past, recent studies show that mitochondria are actually highly dynamic organelles that constantly change their morphology, motility and intracellular distribution [13]. This mitochondrial dynamics, broadly defined, is a well-balanced homeostasis of interconnected mitochondrial morphological change, fusion and fission, movement, biogenesis and degradation. For example, mitochondrial movement is driven by motility motors and cooperated by the mechanisms that control mitochondrial morphology and fusion/fission. As a key component of mitochondrial dynamics, the fusion and fission machinery mediates two opposite processes: fusion of two or more mitochondria into one mitochondrion by fusion of the mitochondrial outer and inner membranes, and fission of a mitochondrion into two or more mitochondria by fission of the outer and inner membranes. A balanced fusion and fission is crucial for normal mitochondrial functioning and can be altered under pathophysiological conditions. Collectively, these mitochondrial dynamic machineries distribute mitochondria to appropriate subcellular locations. Failure of proper mitochondrial distribution leads to cellular malfunction. For instance, impairment in the mitochondrial fusion and fission machinery results in loss of mitochondria and mitochondria-generated ATP at the synapses, which lead to defective neurotransmission [14]. Similarly, without mitochondrial movement to the immune synapses, the interface between an antigen-presenting cell or target cell and a lymphocyte such as T cell, the T cell activation is dampened [15].

Importantly, mitochondrial dynamics also regulates mitochondrial functional status. In fact, increased mitochondrial

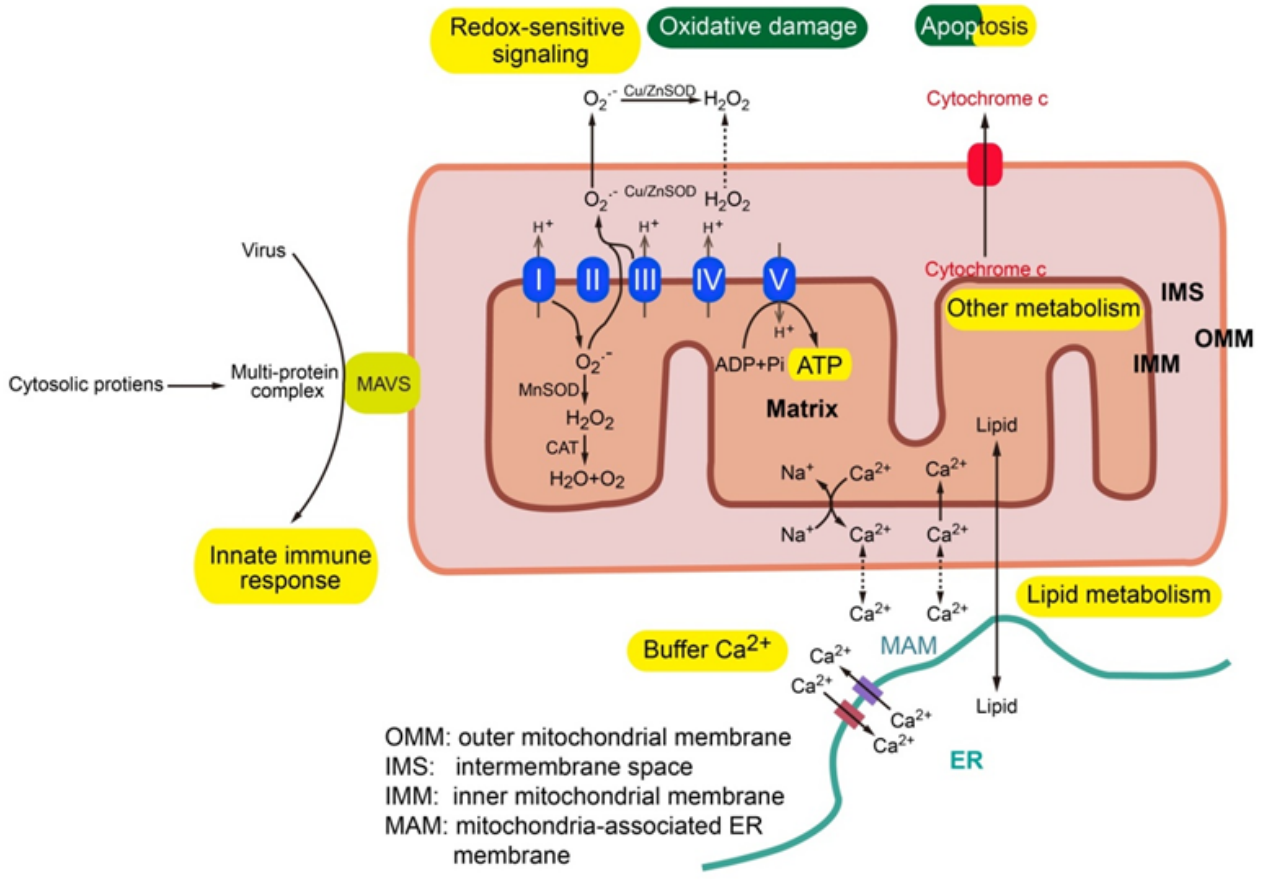


Figure 1: Major mitochondrial functions.Mitochondria are a crucial and versatile cellular organelle that exerts both protective (in yellow color) and detrimental (in green color) effects to the cell. Notably, some of mitochondrial functions, such as mediating redox-sensitive signaling, can also participate in the pathogenesis of human diseases including cancer. In addition, mitochondria-mediated apoptosis, while being a detrimental effect of environmental toxins, is required for maintaining the homeostasis of normal cells and plays other physiological roles such as assisting embryo development.SOD:superoxide dismutase; ER: endoplasmic reticulum.

fission or downregulation of fusion reduces mitochondrial oxidative phosphorylation [16,17]. Mitochondrial fission is also an upstream causal factor for the mitochondrial ROS production induced by high glucose and ionizing radiation, and perturbation of mitochondrial fission reduced such ROS production [18-22]. Accordingly, the treatment that increases mitochondrial fusion in oncogenic K-ras-transformed cells reduces ROS production [23]. How mitochondrial fragmentation affects ROS production is unknown, but evidence suggests that mitochondrial fission results in ultra structure change of the mitochondrial inner membrane where the mitochondrial respiratory chain resides [24]. Interestingly, elevated ROS can also cause mitochondrial fragmentation [25,26], suggesting a vicious cycle of mitochondrial morphology change and ROS production.

Finally, mitochondria biogenesis and degradation machineries ensure an appropriate number of functional mitochondria. Mitochondria cannot be synthesized *de novo*. Instead, a mitochondrion grows in length and divides into two or more daughter mitochondria via the fission process. When mitochondria are impaired, such as having decreased membrane potential, they are separated from health mitochondria and undergo autophagic degradation. Together, mitochondrial dynamics is a highly efficient mechanism that the cell uses to determine where, when and how mitochondria function and to maintain a healthy status and appropriate amount of mitochondria.

Environment Factors that Act on Mitochondria

Coherent to the important roles of mitochondria in cellular function, it becomes clear that mitochondrial impairment is a key component of the pathogenesis of a broad variety of human diseases including neurological disorders, cardiovascular diseases, diabetes, obesity and cancer. At the same time, environmental factors also play a role in the etiology of these diseases. Logically, one would suggest that mitochondria may be a common target of these environmental risk factors. In fact, that is the case; that is, a large number of environmental factors have a deleterious effect on mitochondria.

Multiple metals, such as manganese, arsenic, lead, cadmium and mercury, accumulate in mitochondria and cause decreased mitochondrial membrane potential, increased ROS production and loss of ATP production [27-39]. Polycyclic aromatic hydrocarbons (PAHs) are another type of toxic environmental factor that is mainly produced from incomplete combustion of organic materials in the incidences such as forest fires, combustion of fossil fuels and wood. Structurally, PAHs are hydrocarbon compounds of fused aromatic rings and are highly lipophilic; the latter character makes PAHs enter the cell efficiently and accumulate in mitochondria as mitochondrial membranes have high lipid content [40]. PAHs result in dissipation of mitochondrial membrane potential, decreased ATP production, formation of aberrant mitochondrial morphology, and mitochondria-mediated apoptosis [41,42]. Another combustion-related air pollutant is particulate matter (PM). These tiny pieces of solid or liquid matter are derived from both natural sources such as volcanoes, dust storms and forest fires and human activities such as fossil fuel burning in vehicles and industrial plants. Studies have demonstrated that PMs cause mitochondrial damages, such as increased mitochondrial DNA copy number and structural changes [43-46]. Among environmental pollutants, some are known to directly inhibit the mitochondrial respiratory chain. For example, rotenone is a mitochondrial respiratory chain complex I inhibitor, and carbon monoxide and cyanide are complex IV inhibitors [47-49]. Environmental pollutants also affect mitochondria-mediated cell signaling. For instance, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a polychlorinated dibenzo-p-dioxin and usually formed as a side product in organic synthesis and burning. Studies have shown that TCDD disrupts mitochondrial membrane potential, increases mitochondrial ROS production, and activates mitochondria-mediated signaling pathways including the redox-sensitive NFκB pathway, causing cultured cells to gain invasive behavior and resistance to apoptosis [50].

Different from chemical pollutants, ionizing radiation is another type of environmental hazard that is known to cause nuclear DNA mutagenesis. Radiation also can cause mitochondrial DNA lesions, coherent with the fact that mitochondria are the only organelle containing DNA outside the nucleus [51]. In addition to causing DNA damages, radiation can result in non targeted toxicity, such as defects in survived progeny cells and bystander effects on non-radiated cells [52,53]. Interestingly, radiation-caused late production of mitochondrial ROS has been suggested to be responsible for delayed nuclear DNA mutagenesis [21,54] and such delayed ROS production has been shown as a result of mitochondrial fragmentation [21].

Together, these studies of environmental toxic effects indicate that mitochondrial membrane potential dissipation, ROS production and morphological change are common damages caused by a variety of environmental factors, including those that are not discussed here such as the air pollutant ozone and the carcinogen asbestos [55,56]. Notably, excessive mitochondrial ROS can lead to the mitochondrial permeability transition (MPT) [57]. MPT refers to the opening of the mitochondrial permeability transition pore (mPTP), which is composed of multiple proteins including the mitochondrial matrix protein cyclophilin D, the mitochondrial inner membrane protein adenine nucleotide translocator (ANT) and the outer membrane protein voltage-dependent anion channel (VDAC). MPT results in free trafficking of ions and solutes up to 1.5 kDa into mitochondrial matrix, which in turn causes mitochondrial matrix swelling, loss of the mitochondrial membrane potential, disruption of calcium homeostasis, rupture of the outer membrane and release of cytochrome c, thereby leading to cell necrosis and/or apoptosis [58]. Finally, a large scale of loss of functional mitochondria can create a situation of low energy or even loss of energy of the cell. Hence, solid evidence indicates that mitochondria are a common target of environmental hazards and undergo several key and shared dysfunctions as a result of environmental toxicity, which can lead to cell malfunction or death.

Opposite to the above-mentioned toxins, nature also offers certain environmental factors that are beneficial to human health via modulating mitochondrial functions. One type of these protective environmental factors is natural antioxidant that can alleviate increased mitochondrial ROS production. For example, an active component of the extract of black cumin seeds which has been used as a medicine since ancient times, called thymoquinone, is an antioxidant [59]. When thymoquinone-like derivatives are targeted to mitochondria by conjugating with penetrating cations, they become more effective. This finding highlights the importance of mitochondrial ROS in the pathology of certain diseases and the usefulness of developing natural or naturally derived protective therapeutics to restore normal level of mitochondrial ROS. Another type of protective factors functions by inducing cancer cell death via stimulating mitochondrial ROS production. Many anti-cancer foods belong to this category. For instance, extracted polysaccharides from certain edible mushrooms can cause cancer cell apoptosis *in vitro* by generating high level of

mitochondrial ROS [60]. Other plant-derived environmental factors, such as sanguinarine and herbacetin, also are potent inducers of human cancer cell death via the ROS-mediated mitochondrial apoptotic pathway [61,62]. Finally, some environmental agents that are known to be toxic may also have beneficial effects in the aspect of inhibiting cancer cell growth. For example, danthron is a natural anthraquinone derivative that is considered to be a carcinogen in the U.S. Recently, studies show that danthron can induce mitochondria-mediated apoptosis in rat glioma cells [63].

Interestingly, some environmental factors have dual roles of promoting or inhibiting mitochondria-induced cell death. For instance, polyamines are the organic compounds that have two or more primary amino groups and are common metabolites in both prokaryotic and eukaryotic cells. Studies show that polyamines can either promote or inhibit MPT, dependent on their intracellular concentrations, cell types and cellular metabolic states [64]. Resveratrol, a polyphenol found in grape seed, also has dual effects on mitochondrial function. Studies have demonstrated that intravenous resveratrol treatment can restore mitochondrial dysfunctions, such as the activity of mitochondrial respiratory complexes, and reduce mitochondria-associated cell death in an animal model of cerebral ischemia [65]. Moreover, resveratrol has also been shown to stimulate expression of genes for oxidative phosphorylation and mitochondrial biogenesis, which is accompanied with its protective effects against metabolic disease in animal models [66]. Other studies, on the other hand, show that resveratrol and its derivatives can activate the mitochondrial apoptotic pathway *in vitro* in transformed human cells and *in vivo* in cancer animal models [67-69]. When applied by peritumor injection, resveratrol leads to a decrease of mitochondrial membrane potential in tumor cells [69]. Other natural polyphenolic compounds, such as quercetin, epigallocatechin-3-gallate (EGCG) and kaempferol, are also found either to restore mitochondrial dysfunctions or to result in tumor cell apoptosis via mitochondria-dependent pathways [70-72]. These studies indicate the complexity for natural or naturally derived environmental agents to serve as therapeutics. Further studies are needed to elucidate the mitochondria-involved molecular mechanisms of the therapeutic effects of environmental agents, which may be dose- , application approach-, and/or disease-dependent.

A Mitochondrial Model of the Molecular Interaction between Environmental Factors and the Cell

For molecular environmental health, it is important to elucidate the molecular cascades by which environmental factors cause cell malfunction and by which cells can protect themselves from environmental toxicity. As discussed above, broad environmental toxic factors have mitochondria as a common target and cause similar mitochondrial dysfunction. How do cells cope with such common environmental stress? Here, the author proposes a mitochondrial pathway that may have the potential to interpret the protective mechanisms against environment-caused mitochondrial impairment and the consequences if damaged mitochondria are not able to be repaired or removed. This testable mitochondrial model may be central to the deleterious effects of a variety of environmental factors.

Recent studies have demonstrated that ring-shape mitochondria are a means that the cell repairs damaged mitochondria. Normally, most mitochondria exhibit tubule morphology. Damaged mitochondria, however, undergo morphological transition from tubule-shape to ring-shape and the ring-shape mitochondria can be repaired back to normal tubules [73]. Moreover, studies have demonstrated that ring-shape mitochondria are induced by loss of the mitochondrial membrane potential and increase of mitochondrial ROS that are caused by the uncoupler chemicals carbonil cyanide p-triflouromethoxyphenylhydrazone (FCCP) or carbonyl cyanide m-chlorophenyl hydrazone (CCCP) or the environmental complex I inhibitor rotenone, but not by loss of ATP caused by the ATP synthase inhibitor oligomycin [73-76]. The fact that PAHs, ozone and radiation all can induce formation of ring-shape mitochondria [41,77,78] suggests that ring-shape mitochondria may be a generic form of damaged mitochondria, rather than being specific to one environmental insult. Once ring-shape mitochondria change back to tubule, they recover from the membrane potential dissipation induced by rotenone, whereas those that cannot be recovered undergo further fragmentation to produce more ROS [73]. These findings have established that ring-shape mitochondria are damaged yet recoverable mitochondria as a result of environmental factors-caused mitochondrial membrane potential dissipation and increased ROS production.

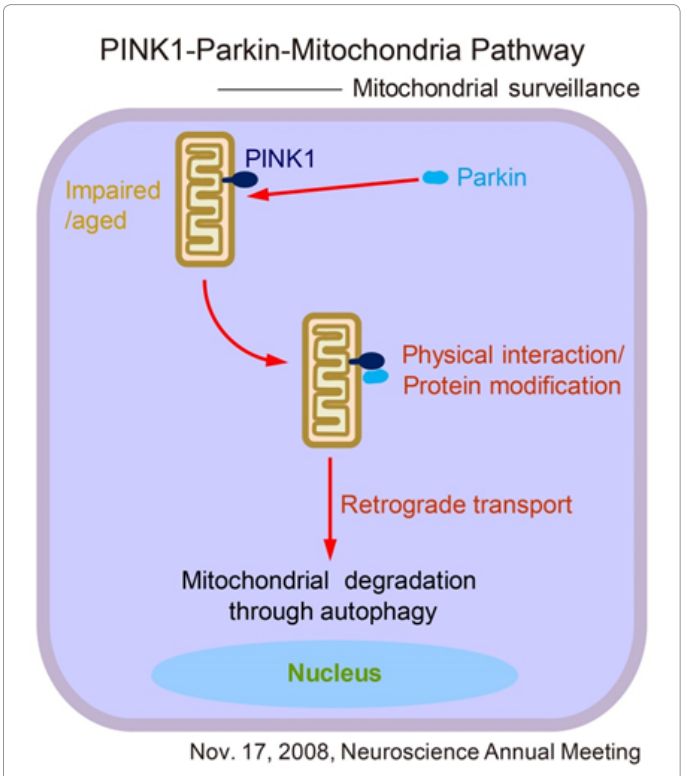
How do mitochondria become ring-shape from tubule-shape? Available evidence points to a potential role of a protein called α-synuclein (α-syn). With a length of 140 amino acids (aa), α-syn is natively unfolded but acquires α-helical structures (either two α-helices or a single extended α-helix) upon binding to lipid membranes *in vitro* [79-82]. The affinity of α-syn to membranes appears due to the interaction between the negatively charged membrane lipids and the positively charged aa in the 11-mer imperfect repeats in the residues 1-95 of α-syn [83,84]. Coherently, studies indicate that α-syn may bind mitochondrial membranes via its N-terminal sequences [85]. Overexpressed α-syn has been known to produce cytotoxicity by forming protein oligomers and aggregates [82,86]. Recent evidence shows that overexpressed α-syn also breaks the tubule structure of mitochondria, a phenomenon known as mitochondrial fission or fragmentation [87]. Interestingly, overexpressed α-syn causes formation of ring-shape mitochondria in the muscle cells of *C. elegans* [88]. Moreover, the mitochondrial toxin1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes formation of ring-shape mitochondria in α-syn transgenic mice of overexpressed α-syn, but not in control mice [89]. Given the intrinsic property of α-syn in generating lipid membrane curvature *in vitro* [90], these converging findings suggest that α-syn may mediate ring-shape mitochondrial formation from tubule mitochondria.

Interestingly, FCCP and CCCP are widely used to create mitochondrial damage in the studies of two proteins: PTEN-induced putative kinase 1 (PINK1) and parkin. PINK1 and parkin are known for initiating mitochondrial autophagy to degrade damaged mitochondria. A major breakthrough in the early molecular events of mitochondrial autophagy in human cells comes from a study that demonstrated that parkin, a cytosolic E3 ubiquitin ligase, is recruited specifically to impaired mitochondria and facilitates their autophagy [91]. At the same time, the author of the present essay proposed a PINK1-Parkin-Mitochondria pathway for mitochondrial surveillance at the 2008 Society for Neuroscience annual meeting (Figure 2). This model indicates that the kinase domain of PINK1, a mitochondrial serine/threonine kinase, interacts with the RING1 domain of parkin at the mitochondrial surface, leading to mitochondrial movement to the perinuclear area for autophagic degradation. The molecular cascades of these early steps of mitochondrial autophagy are further elucidated by major articles [92-95] in which PINK1 and parkin play the crucial

role to "label" damaged mitochondria for degradation [96]. The facts that FCCP and CCCP cause formation of ring-shape mitochondria and activate the PINK1/parkin-mediated mitochondrial autophagy imply that PINK1 and parkin may be responsible for the clearance of severely damaged ring-shape mitochondria. Together, these experimental data in recent years call for a novel unified mitochondrial molecular pathway that may underlie the cellular toxicity caused by a variety of environmental factors (Figure 3). It is worth noting that this model may also be useful for the identification of the environmental factors that are protective against various human diseases in which mitochondria play a role in their pathogenesis.

Perspective

Mitochondria are a key organelle for the physiological function of the cell and play a crucial role in the pathogenesis of a variety of human diseases in which environmental factors are part of the etiology. Research in the past decade has made groundbreaking discoveries of mitochondrial biology that have shifted our understanding of mitochondrial function. Moreover, mounting evidence indicates that mitochondria are a common target of multiple environmental toxic factors. Notably, some environmental agents have potential therapeutic benefits by modulating mitochondrial function. With analysis of the available literature on mitochondria, this review also provides a unified model of a mitochondrial pathway which may shed light to our understanding of the molecular mechanisms responsible for the toxic or beneficial effects of environmental factors. In summary, investigations on the molecular mechanisms through which the environmental toxic and protective factors act on mitochondria are pivotal to our understanding of environmental effects on human health and to the development of new strategies for disease prevention and therapy.



Figue 2: Parkin is recruited to mitochondria via binding to PINK1, resulting in mitochondrial retrograde transport to the perinulcear area for autophagic degradation.

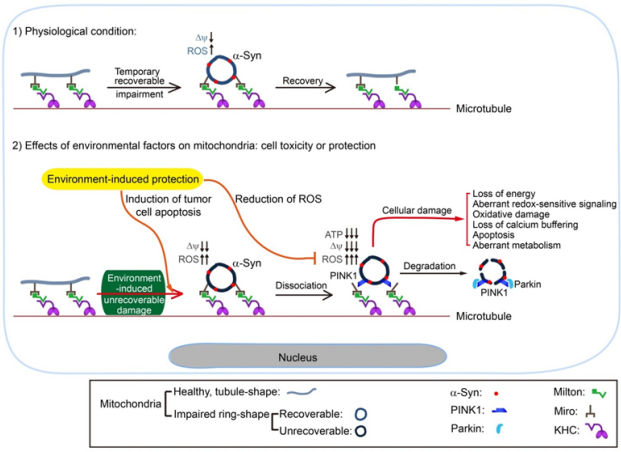


Figure 3: A mitochondrial model of the molecular interaction between environmental factors and the cell. Mitochondria are attached to microtubules via proteins such as Miro, Milton and KHC. Physiologically, mitochondria with suboptimal membrane potential (Δψ) or increased ROS are transformed from tubule to ring-shape, which may be mediated by α-syn. The ring-shape mitochondria are then converted back to tubule with recovered Δψ or reduced ROS levels. Environmental hazards damage Δψ and cause increased ROS, and may affect α-syn's function, resulting in unrecoverable ring-shape mitochondria. PINK1 is stabilized to the damaged ring-shape mitochondria and causes dissociation of the damaged mitochondria from microtubules. Further, PINK1 recruits parkin from the cytosol to the ring-shape mitochondria and parkin mediates ubiquitination of mitochondrial proteins for degradation. Meanwhile, ring-shape mitochondria may be fragmented via Drp1- or α-syn-mediated fission processes. Beneficial environmental agents, on the other hand, protect the cells via modulating mitochondrial function, such as alleviating abnormal mitochondrial ROS production and activating mitochondria-mediated apoptosis.

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