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JSM Environmental Science & Ecology

Editorial

Mitochondria and Environmental Health

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Submitted: 11 August 2013

Accepted: 30 August 2013

Published: 02 Septemb er 2013

ABBREVIATIONS

ERK: Extracellular signal-Regulated Kinases; IRF: Interferon-Regulatory Factors; JNK: c-Jun NH2-terminal Kinase; MAPK: Mitogen-Activated Protein Kinases; NFκB: Nuclear Factor Kappa-light-chain-enhancer of activated B cells; Nrf-2: Nuclear Factor erythroid 2-related factor 2; RIG-1: Retinoic acid-Inducible Gene I; WHO: World Health Organization

INTRODUCTION

Mitochondria are known as the powerhouse of the cell, as they transform energy essentially from the food into the usable chemical form of adenosine triphosphate (ATP). In the past decade, it has become increasingly clear that mitochondrial dysfunction plays an important role in the aging process and a variety of human diseases especially chronic diseases, such as neurological disorders, cardiovascular diseases, diabetes, obesity and cancer. For example, diminished mitochondrial function and increased production of reactive oxygen species (ROS) and mutations of mitochondrial DNA (mtDNA) underlie the aging process [1]. Reduced mitochondrial mass and function have been linked to the pathogenesis of diabetes and obesity [2]. Similarly, mitochondrial defects such as impaired respiration are implicated in the progression of myocardial dysfunction [3]. Furthermore, conversion of ATP production from mitochondrial oxidative phosphorylation to cytosolic glycolysis appears to be an active process for cancer cell growth [4]. These findings indicate the crucial and complex role of mitochondria in human health that is far beyond energy production.

In fact, mitochondria have diverse roles in key cellular processes, making this organelle crucial for most eukaryotic cells to function properly. Mitochondria host important metabolic pathways including the tricarboxylic acid (TCA) cycle, fatty acid beta-oxidation, and synthesis of lipid, steroid, heme and iron-sulfur clusters. These processes span a wide range of important functions of mitochondria in cellular metabolism. More importantly, however, through their metabolic products, mitochondria participate in various cellular signaling pathways, thereby having profound effects on cell function. For instance, during production of ATP by oxidative phosphorylation, the mitochondrial electron transport chain generates superoxide from oxygen. Hydrogen peroxide, a metabolite of superoxide, is a signaling molecule that modulates redox-sensitive cellular pathways, even though it is toxic at excessive levels. This signaling function of hydrogen peroxide is attributed to its ability to travel for a distance within the cell and to directly oxidize protein residues such as cysteine to change the conformation or activity of kinases, phosphatases or transcription factors in various cellular signaling pathways. These redox-sensitive pathways, such as the MAPK/Erk, Nrf-2, JNK and NFκB pathways, regulate a variety of key cellular processes ranging from cell proliferation and death, to stress defense, and to immune response. Another important metabolic product of mitochondria is heme, the iron form of protoporphyrin IX. Heme can be degraded by heme oxygenase into carbon monoxide, biliverdin and free iron. Carbon monoxide is a signaling molecule that inhibits inflammatory response and is involved in neurotransmission [5]. Mitochondria further regulate plasma membrane-initiated cell signaling by modulating calcium homeostasis. In addition to the classic role of mitochondria in buffering calcium during the neurotransmitter release process, a recent paradigm is that mitochondria buffer calcium flux to sustain the receptor-mediated signaling for T cell activation at the immune synapses [6], the cell contact sites between immune cells such as between a T cell and an antigen-presenting cell. Moreover, mitochondria mediate apoptotic signaling by releasing pro-apoptotic molecules such as cytochrome c to drive caspase activation. Finally, mitochondria can serve as a platform for protein complex assembly and activation to initiate protective cellular machineries. A major breakthrough in this aspect is the identification of the mitochondrial antiviral signaling (MAVS) protein which mediates the innate immune response against viruses [7]. In this molecular pathway, the outer mitochondrial membrane (OMM) serves as the platform for the OMM protein MAVS to sense single- or double-stranded RNA of invading viruses via the cytosolic protein RIG-I and then to form an active protein complex with cytosolic proteins, thereby propagating the signaling of IRF and NF-κB to produce pro-inflammatory cytokines.

Equally important to the elucidation of the complex functions of mitochondria in cell metabolism and key signaling pathways is the discovery of mitochondrial dynamics. Instead of being static organelles as perceived in the past, mitochondria are actually highly dynamic organelles that constantly change their morphology, motility and intracellular distribution [8]. Broadly defined, mitochondrial dynamics refers to a well-balanced homeostasis of mitochondrial morphological change, fusion and fission, movement, biogenesis and degradation.

Mitochondrial dynamics distributes mitochondria to proper subcellular locations and regulates mitochondrial function. For example, mitochondrial fission can enhance mitochondrial ROS production [9,10]. Moreover, impairment of the mitochondrial fusion and fission machinery results in loss of mitochondria and mitochondria-generated ATP at synapses, which leads to defective neurotransmission [11]. On the other hand, without mitochondrial movement toward the immune synapses, T cell activation is dampened [6]. Together, these scientific advances in the past decade highlight the key role of mitochondria in cell physiology and the pathophysiology of a variety of human diseases, and provide a solid knowledge on mitochondrial functions and regulatory mechanisms of mitochondrial function. Thus, scientists are now better positioned to decipher the mechanisms of human aging and diseases through research on mitochondria, which has led to newly emerged multidisciplinary research fields, such as mitochondrial endocrinology and mitochondrial pharmacology.

To understand the molecular mechanisms of human aging and diseases, we draw attention to the study of the effects of environmental factors on mitochondria, due to the facts that environmental factors contribute to about 80% of the diseases listed by the WHO and account for 24% of the global burden of disease [12]. Mitochondria have a role in the pathophysiology of major environment-related diseases, such as respiratory diseases, viral infections, neurological disorders, cardiovascular diseases and cancer. Hence, it is not surprising that a large number of environmental factors have a deleterious effect on mitochondria. For example, multiple metals, such as manganese, arsenic and lead, accumulate in mitochondria and cause decreased mitochondrial membrane potential and increased ROS production. Other pollutants, such as polycyclic aromatic hydrocarbons (PAHs), paraquat (complex I inhibitor) and carbon monoxide (complex IV inhibitor) also target mitochondria. The vulnerability of mitochondria to broad environmental toxins may be partially due to the fact that mitochondria have a negative potential and alkaline pH in the matrix, and that mitochondrial membranes have high lipid content, making them accumulate cationic metals, amphiphilic organic chemicals and lipophilic compounds [13]. Adding to the examples of mitochondria-targeting environmental factors are air particulate matter, lipo polysaccharides, cigarette smoke and radiation, among others [13,14].

Here we summarize the main approaches to study the toxic effects of environmental factors on mitochondria. First, mitochondrial functional assays have been significantly improved due to the development of various mitochondrial functional markers. For instance, mitochondrial membrane potential, ROS and ATP levels can be detected *in situ* in cultured cells using specific markers such as tetramethylrhodamine methyl ester (TMRM), mitochondria-targeted reduction-oxidation sensitive green fluorescent protein (mt-roGFP) [15] and the mitochondrial ATP-sensor mitAT1.03 [16], respectively. These signals can be visualized and analyzed by confocal microscopy or by fluorescence-activated cell sorting (FACS) technology. More advanced is the ability of these markers to be used in live cell imaging, which allows a time course observation of the toxic effects of environmental factors in cultured cells. Alternatively, mitochondria can be isolated for analysis of oxygen consumption and enzyme activities by conventional biochemical methods [17]. Second, the mitochondrial proteome is useful to detect the expression and post-translational modification of mitochondrial proteins. Mitochondria have 1000~1500 proteins suitable for proteomic analysis. For example, mitochondrial proteomic approaches have been explored to identify novel mediators of cardioprotection [18], diabetes [19] and cancer [20]. Unlike mitochondrial functional assays, mitochondrial proteomic analyses can potentially identify the cytosolic proteins that form active protein complexes on OMM, thereby offering clues to the effects of environmental factors in cellular signaling. Third, analysis of mtDNA mutations and mitochondrial microRNAs is of importance. Human mitochondria have a circular ~16.5-kb DNA of 37 genes, encoding 13 proteins of respiratory complex I, III, IV and V, and RNAs. MtDNA mutation has been implicated in the aging process and various human diseases [21]. MicroRNA is a type of noncoding RNAs that regulates gene expression. Recently, mitochondria have been shown to possess unique microRNAs that may modulate mtDNA expression and other mitochondrial functions [22,23]. Thus, detection of mtDNA mutations and the profiles of mitochondrial specific microRNAs may facilitate the identification of associations between environmental toxicants and mitochondrial dysfuction. Finally, the influence of environmental factors on mitochondrial dynamics, a main regulatory mechanism for mitochondrial function, needs to be studied using tools such as mitochondria-specific fluorescent markers, which have been used to demonstrate that both arsenic and manganese alter mitochondrial morphology [17,24].

In summary, there is a critical need for interdisciplinary research to address how environmental factors damage mitochondrial function and dynamics, and importantly, how this mitochondrial damage plays a role in the pathophysiology of environment-related diseases. This research will improve our understanding of the etiology of human diseases and aging, and eventually help develop novel prevention and therapeutic strategies.

ACKNOWLEDGEMENTS

The authors thank Dr. Joseph Graziano and Dr. Regina Santella for their valuable advices.

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Cite this article

Zhou C, Guilarte TR (2013) Mitochondria and Environmental Health. JSM Environ Sci Ecol 1(1): 1002.