Mitochondrion xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Review

Mitochondria in biology and medicine — 2012

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ARTICLE INFO

Article history:
Received 5 April 2013
Accepted 21 May 2013
Available online xxxx

Keywords:
Conference
Mitochondria
Mitochondrial disease
Cancer
Aging

ABSTRACT

As the understanding of mitochondria and their importance for the cell and organism is developing, increasing evidence is demonstrating the organelle to be intricately involved in an extensive range of pathologies. This range of pathologies include general signs of premature aging, neuro-muscular dysfunctions, cancer, diabetes, various heart diseases, inflammation and other conditions not previously known to be related to mitochondrial function. A better understanding of mitochondria therefore allows a better understanding of related pathologies. It enables the usage of mitochondrial function as biomarkers for the diseases and most important, it opens the possibility of a treatment or a cure for a disease.

"Mitochondria in Biology and Medicine" was the title of the second annual conference of Society of Mitochondrial Research and Medicine — India. The conference was organized by Rana P. Singh, Keshav Singh and Kumarasamy Thangaraj, and was held at the newly opened School of Life Sciences, Central University of Gujarat (CUG), Gandhinagar, India, during 2–3 November 2012. The conference featured talks from internationally renowned scientists within the field of mitochondrial research and offered both students and fellow researchers a comprehensive update to the newest research within the field. This paper summarizes key outcomes of the presentations.

Contents

1. Mitochondrial regulation of cellular processes

For a long period of time, mitochondria have been known as the organelle responsible for the production of ATP by oxidative phosphorylation, as the primary site for β-oxidation of fatty acids, metabolism of amino acids and lipids and as an organelle with a prominent role in apoptosis initiation. Accumulating evidence is however, also starting to describe mitochondria as the central regulators of many cellular processes. The continued elucidation of the regulatory role of the mitochondria relates the organelle to a range of pathologic conditions including cancer, neurodegeneration, aging and inflammation. Accordingly, *Robert K. Naviaux* of Departments of Medicine, Pediatrics, and Pathology, University of California, San Diego School of Medicine, USA, opened his presentation by challenging the common understanding of the role of mitochondria as the primary supplier of cellular energy and introduced mitochondria as important constituents of cellular danger sensory pathways and activator of cellular defense pathways. Robert K. Naviaux introduced the term of universal cell danger response as a set of ancient metabolic reactions that defends the cell against environmental and genetic neuro-immunotoxicity (Naviaux, 2012). This danger response, involves the mitochondria, as they are able to sense the flow of electrons and metabolites as chemical fluxes. Viruses, intracellular bacteria and fungi all have electrophilic properties. When viral or microbial infection, disease, toxins, or nutritional excess perturbs the concentrations of substrates, mitochondria sense this as a metabolic mismatch between the optimum concentration of those metabolites for a given tissue and the actual concentration (Naviaux, 2012). The metabolic

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http://dx.doi.org/10.1016/j.mito.2013.05.010

mismatch results in the export of ATP to the extracellular compartment *via* connexin and the export functioning as a stress response triggering different systemic responses as inflammation.

The electrophilic properties of viruses, intracellular bacteria and fungi are comparable to those of heavy metals, as well as aromatic and halogenated xenobiotics. Robert K. Naviaux argued that the ever-increasing introduction of xenobiotics, chemicals and additives to the environment results in a variety of environmental diseases mediated through incorrect mitochondrial mediated initiation of cellular defense. This misdirected stress-response can help explain the increase of a range of diseases within the last 50 years, including allergies, development diseases and neurologic diseases.

The topic of the effect of heavy metals on mitochondria and the resulting phenotype was further discussed by *Ilora Ghosh* of Environmental Toxicology and Biochemistry Laboratory, School of Environmental Sciences, Jawaharlal Nehru University, New Delhi, India. Cadmium is an extremely toxic metal pollutant associated with industrial processes. The metal is preferentially accumulated in kidneys and liver of exposed animals and humans. Ilora Ghosh showed a correlation between cadmium exposure and diabetes, involving mitochondria. Cadmium exposure is known to result in decreased mitochondrial mass and a decrease of ATP by oxidative phosphorylation (Takaki et al., 2004). Ilora Ghosh argued that these mitochondrial effects were comparable with those demonstrated in cells from type 2 diabetics and in cells that are insulin resistant. This prompted Ilora Ghosh to investigate if cadmium exposure can induce insulin resistance. He showed that mice treated orally with cadmium for a month were demonstrated to become hyperglycemic and that the resulting liver cells displayed an increased production of reactive oxygen species, low levels of ATP and a decrease of cytochrome *c* activity. Proteomic analysis of mitochondrial protein in liver cells exposed to cadmium was performed, which will serve as the foundation for a better future understanding of the signal pathways involved in cadmium toxicity and insulin resistance.

Dysfunctional mitochondria are frequently detected in human cancers. It is, however, unknown whether dysfunctional mitochondria have a symptomatic or causative relationship with cancer. *Lene Juel Rasmussen* from the Center for Healthy Aging at the University of Copenhagen, Denmark, has demonstrated that human cell lines devoid of mitochondrial DNA have lower levels of cytosolic dNTP than parental cells with functional mitochondria. The lower levels of dNTP are associated with a higher degree of chromosomal instability (Desler et al., 2007). In *Saccharomyces cerevisiae*, DNA lesions that inhibit replication fork progression are met by an up to 10-fold increase in the S-phase specific cellular levels of dNTP (Chabes et al., 2003). Lene Juel Rasmussen has demonstrated that yeast cells with dysfunctional mitochondria are not able induce the dNTP levels after DNA lesion induced replication fork arrest. Increased levels of dNTP are believed to facilitate DNA translesion synthesis (TLS), which allows lesion by-pass and restart of stalled replication forks at the expense of induced mutations. It has been demonstrated the dNTP response is essential for the survival of the yeast cells. This opens the possibility that dNTP levels have a much more regulative role than previously known, and it links the mitochondria to nuclear DNA repair.

Small RNAs (sRNA) are critical regulators of gene expression and are demonstrated to play roles in developmental timing, cell fate, tumor progression and neurogenesis. *Sridipada Lakshmi* of the Department of Cell Biology, School of Biological Sciences and Biotechnology, Indian Institute of Advanced Research, Gandhinagar, India, has generated and characterized a library of sRNAs including miRNA, associated with human mitochondria. The mitochondrial associated miRNAs were characterized as being involved in the regulation of the turnover of mitochondrial mRNA and proteins. Furthermore, miRNA regulating critical cellular processes like RNA turnover, apoptosis, cell cycle and nucleotide metabolism were also found to be associated with mitochondria (Sripada et al., 2012). The miRNAs and target mRNA associated with mitochondria are associated with the outer membrane of the mitochondria. This led Sridipada Lakshmi to the hypothesis that mitochondrial outer membrane may provide a novel platform to assemble the miRNA/RISC complexes to regulate the subcellular site-specific protein levels implicating mitochondria as one of the post-transcriptional destinations of miRNA (Sripada et al., 2012).

2. Mitochondria, tumorigenesis and anticancer therapies

Utilizing the mitochondria to promote apoptosis in cancer cells is a very attractive endpoint when developing cancer therapeutics. In the process of mitochondrial induced apoptosis, mitochondrial cytochrome c is released into the cytosol leading to the activation of the apoptosome which in turn activates caspase-9 resulting in the cleaving of procaspase-3 and procaspase-7 and subsequently the propagation of the apoptotic cascade ending with cell death. The resistance of cancer cells to apoptosis is often due to improper assembly of the apoptosome. *Dhyan Chandra* from the Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, New York, USA, has described the role of nucleotides in the process of regulating of apoptosome formation. Physiological levels of ATP act as critical prosurvival factors by binding to mitochondrial cytochrome c and thereby blocking upstream apoptosome formation. Therefore caspase activation is preceded or accompanied by a decrease of overall levels of nucleotide pools. Interestingly, Dhyan Chandra has found that a severe depletion of the ATP pool also fails to initiate cytochrome c initiated caspase activation (Chandra et al., 2006). His findings indicate that in the absence of ATP, procaspase-9 is directly associated with Apaf-1, a subunit of the apoptosome, and this association inhibits the oligomerization of the apoptosome and therefore inhibits the ensuing apoptotic cascade (Zhang et al., 2011). He argues that this mechanism may be utilized by cancer cells to avoid apoptosis and that anticancer agents that prevent stable association of caspase-9 with the apoptosome, therefore may provide a new approach for cancer therapy.

Silibinin is a dietary agent found in artichoke and milk thistle. It is a molecule that has attracted the attention of *Rana P. Singh* of School of Life Sciences at Central University of Gujarat, Ahmadabad, India, due to its anticancer properties and very low toxicity. Mice who had been xenografted with the human bladder cell tumor RT4 cells and feed with silibinin for a period of 12 weeks displayed significant inhibitory effects on tumor growth when compared to mock treated (Singh et al., 2008). The amount of apoptotic events in the tumor tissue was correspondingly 3–4 fold increased in mice fed with silibinin. The silibinin mediated apoptosis was *in vitro* mediated through the activation of p53 and caspase activation. As presented, the p53 activation by silibinin is mediated *via* the ATM-Chk-2 pathway, which in turn activates caspase 2, in part, *via* the JNK1/2 kinases and initiates a caspase-cascade activation for mitochondrial apoptosis.

The *RECQL4* gene encodes the ATP dependent DNA helicase Q4 (RECQL4). RECQL4 is required for the initiation of DNA replication; the N-terminal domain of the protein is responsible for the binding of DNA polα to chromatin. Mutations of *RECQL4* are associated with the rare autosomal recessive disorder Rothmund Thomson Syndrome (RTS), a condition associated with increased sensitivity to DNA damaging agents and predisposition to the development of especially osteosarcomas and lymphomas. *Sagar Sengupta* from the National Institute of Immunology, New Delhi, India, has demonstrated that the sensitivity of RTS cells, correlates with a nuclear accumulation of transcriptionally active p53 in contrast to untreated normal human cells, where p53, instead colocalize to mitochondria (De et al., 2012). Sagar Sengupta demonstrated that RECQL4 and p53 bind together resulting in a masking of the nuclear localization signal of p53. Upon stress the interaction is disrupted and p53 translocates from the mitochondria to the nucleus. In untreated normal cells RECQL4 optimizes the *de novo* replication of mtDNA, which is consequently decreased in fibroblasts from RTS patients. The results presented by Sagar Sengupta are important for the understanding of RTS, but also for the role of RECQL4 in mitochondria

Please cite this article as: Desler, C., Rasmussen, L.J., Mitochondria in biology and medicine — 2012, Mitochondrion (2013), http://dx.doi.org/10.1016/j.mito.2013.05.010