RESEARCH

Targeting Mitochondria for Health and Disease

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ABSTRACT

Mitochondria are an integral part of the cell, and play a crucial role in the regulation of energy metabolism, cell differentiation, signaling, and cell death. Mitochondrial dysfunction leads to several pathological conditions and are bewildering in their variety and complexity. The crosstalk between the nuclear and mitochondrial genes adds to the complexity of the field, and has led to a better understanding of mitochondrial functions and their pathogenesis, which is important for the diagnosis and prognosis of mitochondrial diseases. The 7th annual conference of the Society for Mitochondria Research and Medicine (SMRM)- India titled "Targeting Mitochondria for Health and Disease" was held at the CSIR-Central Drug Research Institute in Lucknow, India during 28 - 30 November 2018. The purpose of this meeting was to discuss about the recent developments in the field of mitochondrial biology and medicine. The conference featured talks from scientists of international repute; from India, USA, Denmark, and Taiwan. This review summarizes the major outcomes of the deliberations.

KEYWORDS: Mitochondria, genetics, disease, metabolism, stem cells.

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1. Introduction

The seventh annual conference of the Society for Mitochondrial Research and Medicine (SMRM) entitled "Targeting Mitochondria for Health and Disease" was organized by Durga Prasad Mishra, Bhupendra N. Singh and Srikanth Rath at the CSIR-Central Drug Research Institute in Lucknow, India. Several national and international researchers, working in the field of mitochondrial biology, participated in the conference and presented their recent findings. This review summarizes the major outcomes of the presentations.

2. Award presentation: Targeting mitochondria in lung disease

Mitochondria play a critical role in energy production *via* oxidative phosphorylation (OXPHOS), and are essential for nutrient and oxygen sensing, and regulation of cellular processes including apoptosis and inflammation (Cloonan and Choi, 2016). Several studies have shown that mitochondrial dysfunction can lead to lung pathogenesis (Simoes et al., 2012, Heinzmann et al., 2003, Jones et al., 2004). The first session of the conference was "Dr. Lalji Singh memorial lecture award presentation". Anurag Agarwal from the CSIR-Institute of Genomics and Integrated Biology, New Delhi, India presented the award lecture. He narrated his research journey, highlighting the critical role of mitochondrial dysfunction in the pathogenesis of asthma and how mesenchymal stem cells donate mitochondria to dysfunctional airway epithelium. His findings suggest that Miro1 regulates intercellular mitochondrial transport from mesenchymal stem cells (MSC) to epithelial cells (EC) (Ahmed et al., 2014). MSCs of different tissue origin have intrinsic differences in the mitochondrial respiration, donation capacity and therapeutic efficacy. He explained the benefits of MSCs and thus, open up a new avenue for stem cell therapeutics (Paliwal et al., 2018).

3. Mitochondria in cell biology and model organisms

Many human disorders are categorized by either primary or secondary mitochondrial dysfunction. Both cell and animal models are being used to understand mitochondrial dysfunctions in disease pathogenesis with the ultimate aim of identifying therapeutic strategies. Keshav K. Singh from Center for Aging and UAB Comprehensive Cancer Center, University of Alabama at Birmingham, USA, presented his discovery of reversing the phenotype of wrinkled skin and loss of hair in mice by restoring mitochondrial function (Singh et al., 2018). Mitochondrial DNA (mtDNA) depletion impairs mitochondrial function that leads to mtDNA depletion syndromes (MDSs). MDSs are a heterogeneous group of disorders, characterized by low mtDNA copy number declines with age, and such changes increase the risk of age-associated diseases (Tuppen et al., 2010). He explained that his group created an inducible mouse (mtDNA-depleter) expressing a dominant-negative mutation in the polymerase domain of *POLG1* to induce depletion of mtDNA in different tissues. The experimental analysis showed that these mice had reduced mtDNA content, alteration in mitochondrial protein expression and reduced stability of mitochondrial OXPHOS complexes. He also demonstrated how ubiquitous depletion of mtDNA in mice had profound and predominant effects on the skin resulting in wrinkles and hair loss. Another interesting aspect of his talk was altered expression levels in mice for ageing-associated markers including IGF1R, KLOTHO, VEGF and MRPS5. His presentation concluded that the restoration of mitochondrial functions lead to reversal of the skin and hair pathology (Singh et al., 2018).

Yau-Huei Wei from Centre for Mitochondrial Medicine and Free Radical Research, Changhua Christian Hospital, Changhua city, Taiwan, elucidated the importance of human stem cells and induced pluripotent cell (iPSCs) in cell therapy

and regenerative medicine. He showed that mitochondrial biogenesis, respiratory function and antioxidant enzymes such as catalase and Mn-superoxide dismutase are upregulated during osteogenic and adipogenic differentiation of human mesenchymal stem cells. He highlighted that iPSC lines generated from the skin fibroblasts of a MERRF (myoclonic epilepsy with ragged red fibers) syndrome patient with m.8344A>G mutation (Wu et al., 2017) showed mitochondrial dysfunction with, reactive oxygen species (ROS) overproduction and imbalanced expression of antioxidant enzymes. His findings support the notion that iPSCs and differentiated lineage-specific cells can serve as a cellular model for studying pathomechanisms and pharmacological screening (Wu et al., 2017) to treat patients with mitochondrial diseases.

Rajesh Singh from the Department of Biochemistry, MS University of Baroda, Vadodara, India discussed the NLRX1, a member of NOD family receptor proteins. He highlighted the emerging role of mitochondria in the regulation of innate immunity, inflammation, and apoptosis (Koopman et al., 2012). It was known that the mitochondrial protein complexes serve as a molecular platform in innate immune signaling (Arnoult et al., 2011). NLRX1 translocates to the mitochondrial matrix and regulates mitochondrial RNA processing, which further modulates mitochondrial complex assembly. He confirmed the role of NLRX1 in altering mitochondrial function and its turnover to regulate cell death and survival response by investigating the presence of TNF-α in human breast cancer cell lines. Furthermore, he highlighted the regulatory mechanism of NLRX1 in preserving the mitochondrial homeostasis during inflammatory stress conditions using breast cancer cell lines (Singh et al., 2018).

Richa Rikhy from Morphogenesis and Differentiation Lab, Indian Institute of Science Education and Research (IISER), Pune, India presented her work on the interaction of mitochondrial fusion and fission pathways with signaling during development, using *Drosophila* oogenesis and embryogenesis as a model system. She presented her findings on depletion of the mitochondrial fission protein, Drp1, that results in loss of Notch-mediated differentiation of the follicle stem cell lineage (Mitra et al., 2012). Fused mitochondria in follicle cells result in the accumulation of phosphorylated ERK, responsible for the abrogation of the Notch pathway. Furthermore, she explained how ERK accumulation increases mitochondrial membrane potential (MMP), infused mitochondria in Drp1 depleted cells and loss of MMP in Drp1 mutant follicle results in reversal of Notch-mediated differentiation (Tomer et al., 2017).

4. Mitochondria in cancer

Dysfunction of mitochondria have been correlated with different types of cancer. Several compounds have been identified that target the mitochondria for the treatment of various diseases, including cancer (He et al., 2015; Peng et al., 2017). Hari K. Bhat from School of Pharmacy, University of Missouri-Kansas City, USA presented that the 4-(E)-{(p-tolylimino)-methylbenzene-1,2-diol} (TIMBD) as a potential chemotherapeutic agent with anticancer and antioxidant properties. His group synthesized a resveratrol analog TIMBD (Siddiqui et al., 2013), and he highlighted that *in vitro* use of compound significantly inhibiting the proliferation of a number of human breast cancer cell lines compared to non-neoplastic human breast epithelial cells, and *in vivo* inhibiting the development of breast tumors in animal models (Ronghe et al., 2016a, b; Chatterjee et al., 2018). He also emphasized the underlying mechanisms of TIMBD and its beneficial effects.

Rana P Singh from Cancer Biology Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India presented his work on the effect of butyric acid on mitochondrial fission and apoptosis in colorectal cancer cells (CRCs). Colorectal cancer is most commonly diagnosed

cancer in the world. Human gastro-intestinal (GI) track carries more than 100 billion microbial cells over 1000 different species and these gut microbiotas have direct correlation with dietary habits and health. Butyric acid (BA) is the byproduct of anaerobic microbial fermentation inside the GI tract and inhibit the growth of various cancers. He described the findings that how the regulation of DRP1-dependent mitochondrial fission mediates the cell proliferation and migration, and emphasized that it could be a novel target to regulate colon cancer growth, progression and metastasis (Tailor et al., 2014, 2015). He concluded that the microbial anaerobic fermentation of dietary fibers in the gut, may relate to the incidence of colorectal cancer.

Archana Singh from All India Institute of Medical Sciences (AIIMS), New Delhi, India summarized her work on assessment of mitochondrial copy number in pediatric acute lymphoblastic leukemia. She showed a significant increase in mtDNA copy number and mitochondrial deletion ratio among patients compared to controls. However, she said that the patient group showed a decreased copy numbers after chemotherapy. She highlighted that the patients with higher copy numbers are with significantly inferior survival rate than the patients with lower copy numbers (Jain et al., 2018). She concluded that the outcome of their study needs to be validated in a larger sample size.

Anil Shanker from Vanderbilt University, USA, presented his work on preventing cancer development and escape: role of lymphocyte interplay and mitochondrial Ca^{2+} dynamics. He explained about his findings on lymphocyte crosstalk following various pre and post-tumor protocols of adoptive transfer in mice. His team noticed that activated $CD8^{+}$T-cells elicit intratumoral NK cell effector functions, and the combined activity of both effectors provide efficient immune-surveillance to prevent tumor development and escape. Intermembranous exchange with significantly increased mitochondrial $[Ca^{2+}]_m$ transport between activated $CD8^{+}$T and NK cells enhances effector signaling in NK cells. Conversely, NK cells restrain IL-2/STAT5 signaling in $CD8^{+}$T-cells, are abrogated by $[Ca^{2+}]_m$ uptake blockers. Interestingly, he has shown that mice deficient in $[Ca^{2+}]_m$ handling-regulatory gene *Fus1* show an increased incidence of spontaneous sarcomas, lymphomas, and leukemia. He concluded his talk with findings that reveals the capacity of $CD8^{+}$T- NK cell antitumor immunosurveillance to completely prevent tumor development and eliminate escape variants by mechanisms dependent on $[Ca^{2+}]_m$ transport and membranous exchange (Uzhachenko and Shanker, 2019).

5. Genomics and signalling

Kapaettu Satyamoorthy from School of Life Sciences, Manipal Academy of Higher Education, Manipal, India, presented multi-genic etiology of MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome). MELAS syndrome is a multi-organ disease with broad manifestations including stroke-like episodes, recurrent headaches, myopathy, short stature, hearing impairment and diabetes (El-Hattab et al., 2015). The m.3243A>G mutation in *MT-TL1* gene was described as the major cause of the MELAS syndrome, which affects $tRNA^{Leu(UUR)}$ aminoacylation and mitochondrial translation of OXPHOS protein subunits (Meseguer et al., 2019). However, recent studies on suspected mitochondrial disorder patients with m.3243A>G mutations have highlighted the vast clinical heterogeneity underpinning the necessity to interrogate the nuclear genome for a better understanding of complex mitochondrial disorders (Pickett et al., 2018). He highlighted that the whole-exome sequencing analysis of MELAS patients revealed pathogenic mutations in nuclear genes that are involved in mtDNA maintenance, dNTP pool, metabolism, and translation. He summarized the utility of Next Generation Sequencing (NGS) technologies for the

identification of nuclear genes that are responsible for MELAS.

Sagar Sengupta from the National Institute of Immunology, New Delhi, India presented his work on how MITOL dependent ubiquitylation regulates the entry of RECQL4 and POLGA into mitochondria. It was known that mutation(s) in *RECQL4* and *POLG*, lead to Rothmund-Thomson syndrome (RTS) and progressive external ophthalmoplegia (PEO), respectively. He provided evidence that both RECQL4 and POLGA are ubiquitylated by MITOL/MARCH5/RNF153 at specific residues via K6-linkage. MITOL-dependent ubiquitylation of RECQL4 and POLGA negatively regulates their binding to Tom20, their mutual interaction, entry into the mitochondrial matrix and finally their functions during mtDNA replication. He has shown that this negative regulatory circuit has both physiological implications and pathological consequences. Hence, in aged animals, levels of RECQL4 and POLGA are diminished due to hyper-ubiquitylation; while in RTS and a subset of PEO patients, the entry of these proteins in the mitochondrial matrix is compromised. However, POLGA in PEO patients can be reactivated by multiple mechanisms that allow these mutant proteins to carry out their functions with similar efficiency as wildtype POLGA. He concluded that manipulation of the ubiquitylation- dependent entry of key proteins involved in mtDNA replication can have beneficial consequences for a subset of mitochondrial disorders.

Amit Singh from the Indian Institute of Science, Bangalore, India delivered a talk on redox signaling coordinates HIV-1 latency and reactivation. Redox signaling plays a crucial role in the pathogenesis of human immunodeficiency virus type-1 (HIV-1) (Bhaskar et al., 2015). He has shown that how his group used a roGFP-based specific bioprobe of glutathione redox potential ($E_{GSH;}$ Grx1-roGFP2) and measured subcellular changes in E_{GSH} during various phases of HIV-1 infection using U1 monocytic cells (latently infected U937 cells with HIV-1). He also showed that U937 and U1 cells demonstrate significantly reduced cytosolic and mitochondrial E_{GSH} (approximately – 310 mV), and active viral replication induces substantial mitochondrial oxidative stress (E_{GSH} more than – 240mV). He found that exposure to a physiologically relevant oxidant, hydrogen peroxide (H_2O_2), induces significant deviations in subcellular E_{GSH} between U937 and U1, which distinctly modulates susceptibility to apoptosis. He demonstrated that, using Grx1-roGFP2, a marginal increase of about 25 mV in E_{GSH} is sufficient to switch HIC-1 from latency to reactivation, raising the possibility of purging HIV-1 by redox modulators without triggering detrimental changes in cellular physiology. Finally, he concluded that the expression analysis of U1 and patient peripheral blood mononuclear cells confirmed a major recalibration of cellular redox homeostatic pathways during persistence and active replication of HIV.

6. Developmental biology and autophagy

Sandhya P. Koushika from Tata Institute of Fundamental Research, Mumbai, India described that the mitochondrial positioning is regulated in non-myelinated neurons *in vivo* and co-relates with basal calcium spikes. Mitochondria are essential both for providing ATP to power nerve cell function and for calcium buffering (Sheng et al., 2014). She described the development of a microfluidic device for long term imaging to assess how mitochondria are added during development to maintain the density. In addition, she also described that the density can be changed through alteration in axonal transport either increasing or decreasing the density that occurs through motors but independently of Miro. Furthermore, she observed that spontaneous calcium sparks correlate with presence of mitochondria. Mutations in genes involved in mitochondrial transport (*ric-7*), L-type Voltage Gated Calcium Channels and blocking Ca^{2+} release

from ER all affect the frequency and amplitude of these sparks. Interestingly, these genes along with optogenetic stimulation of cytosolic calcium also alter mitochondrial distribution. She pointed out that mitochondrial Ca^{2+} uniporter MCU plays a role while the Ca^{2+} binding motor adapter Miro-1 does not play a role in mitochondrial distribution. She explained that the precisely controlled mitochondrial positioning is essential for gentle touch response of the animal. Her talk indicated a potential cell intrinsic mechanism by which mitochondria can read local calcium transients to control mitochondrial positions/distribution and thereby animal behavior.

Ravi Manjithaya from Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India presented selective autophagy that can capture intracellular organelles, such as peroxisomes, mitochondria, aggregated proteins and intracellular pathogens. Mitochondrial dysfunction is associated with various age-related neurodegenerative disorders including Alzheimer's disease (AD). He started his presentation by briefing the link between mitochondrial dysfunction and AD pathologies, and also elaborated on the emerging evidence that mitochondrial quality control (QC) (i.e., mitophagy) is involved in the pathophysiology of AD. Mitophagy plays an important role in the maintaining of neuronal health and function. He highlighted that compromised mitophagy may lead to impairment in autophagosome-lysosome fusion and lysosomal acidification. In addition, restoring mitophagy functions could be used for understanding the AD pathogenesis and therapeutic interventions. He summarized the recent developments in the field of mitophagy and mitochondrial dysfunction in AD (Chakravorty et al., 2019).

Lene Juel Rasmusen from University of Copenhagen, Denmark, presented the insights of Rev1 that contributes to proper mitochondrial function. Nucleic acids are continuously exposed to endogenous and exogenous damaging agents including reactive oxygen species (ROS) and reactive aldehydes (Burcham, 1999). It is challenging to maintain genome stability and integrity over the life of the cell. Unrepaired DNA lesions, such as single- and double-stranded DNA breaks (SSBs and DSBs), and single-stranded gaps can block progression of the DNA replication fork, causing replicative stress and/or cell cycle arrest. Translesion synthesis (TLS) DNA polymerases, such as Rev1, have the ability to bypass the replication fork arrest and minimize replicative stress. She pointed out that Rev1-deficiency in mouse embryo fibroblasts or mouse liver tissue is associated with replicative stress and mitochondrial dysfunction (Fakouri et al., 2017). In addition, she has shown the experimental evidence that Rev1-deficiency is associated with high poly (ADP) ribose polymerase 1 (PARP1) activity, low endogenous NAD^+, low expression of SIRT1 and PGC1α and low adenosine monophosphate (AMP)-activated kinase (AMPK) activity. Her talk concluded that replication stress via Rev1-deficiency contributes to metabolic stress caused by compromised mitochondrial function via the PARP-NAD^+-SIRT1-PGC1α axis (Fakouri et al., 2017).

Linda Hildegard Bergersen, University of Oslo, Norway, explained how lactate benefits the brain. She described that the lactate receptor, hydroxycarboxylic acid receptor 1 (HCAR1 also known as GPR81), is highly expressed in pial fibroblast-like cells that line the vessels supplying blood to the brain, and in pericyte-like cells along with microvessels. Activation of HCAR1 improves cerebral vascular endothelial growth factor A (VEGFA) and cerebral angiogenesis. She described that the high density interval exercise (5 days weekly for 7 weeks), as well as L-lactate subcutaneous injection leads to high blood lactate levels comparable to those after exercise, increases brain VEGFA protein and capillary density in wild-type mice but not in knockout mice lacking HCAR1. Further, she elucidated that the skeletal muscle has no vascular HCAR1 expression and no HCAR1-dependent change in vascularization induced by

exercise or lactate (Morland et al., 2017). She concluded that the lactate receptor HCAR1 may provide a useful nutraceutical target for intervention in persons at risk for dementia, who are unable to exercise sufficiently to achieve optimal HCAR1 stimulation through rises in blood lactate (Bergersen, 2015).

7. Mitochondrial function and disease

The current knowledge on mitochondrial function and its role in disease pathophysiology is emerging exponentially. Mitochondrial functions are linked to a myriad of diseases either the primary or secondary mitochondrial defects (Niyazov et al., 2016). Several studies have shown that mitochondrial dysfunction is a common phenomenon across various diseases, particularly in organs that require high energy for normal function (Govindaraj et al., 2019; Selvaraji et al., 2019; Sonam et al., 2017; Reddy, 2009; Cartoni and Martinou, 2009). Both mtDNA and nuclear DNA mutations are responsible for mitochondrial dysfunction and disease. Periyasamy Govindaraj from the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, explained the genotypic and phenotypic spectrum of mitochondrial disorders. He started his presentation with an overview of mitochondrial disorders and the approaches used in the diagnosis. He presented a large cohort of patients with mitochondrial disorders consisting of both syndromic and non-syndromic groups. He also discussed the conventional histological and ultrastructural diagnosis of mitochondrial myopathies in muscle and the importance of biochemical assessment of respiratory chain enzyme deficiencies. He demonstrated that analysis of complete mitochondrial genome revealed several novel and pathogenic mutations in a cohort of patients (Khan et al., 2017; Sonam et al., 2017). In addition, he discussed the nuclear gene mutations (*POLG1*, *POLG2*, *C10orf2* & *SURF1)* and their clinical phenotypes. Furthermore, he described a case of ethylmalonic encephalopathy with a novel missense variation (c.493G>C; p.D165H) in the *ETHE1* gene (Govindaraj et al., 2020). He concluded his talk by suggesting the need for multidisciplinary approach for precision diagnosis and treatment.

Kumarasamy Thangaraj from the CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India, provided a talk that focused on the nuclear gene defects in mitochondrial disorders. Recent studies have reported that around 90% of mitochondrial disorders are due to mutations in nuclear genes that control mitochondrial functions (Craven et al., 2017). He explained that based on the mtDNA profile, his group analyzed the exons and intron-exon boundaries of common nuclear genes, such as; *POLG*, *C10orf2* and *MPV17*, in more than 300 unrelated patients with mitochondrial disorders and identified several novel and reported pathogenic mutations (Paramasivam et al., 2019; Pyal et al., 2017; Paramasivam et al., 2016). Furthermore, he showed that his group performed exome sequencing of the patients, who did not harbor mtDNA and known nuclear gene mutations, and identified several pathogenic mutations in *NDUFAF5* and *SLC25A46* that are associated with severe phenotypes and early death. In addition, he highlighted the finding of two novel genes that are associated with unique mitochondrial disorder phenotypes. He also showed the functional characterization of novel gene in a Zebrafish model.

In addition to invited talks, there was one session for short oral presentation on the second day of the conference with four presentations on the role of mitochondria in different diseases. Lastly, there are several poster presentations on wide range of topics in mitochondrial biology. The 7th annual conference of SMRM established networks between various groups working in the area of mitochondrial biology within India and several other countries. We are optimistic that this interaction may pave way for establishing collaborative projects, exchange programmes, etc in the field of mitochondrial research.

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Conflict of interest statement

The author declares no competing or conflict of interests. The funders had no role in study design, writing of the manuscript and decision to publish.

Authors' contributions

Periyasamy Govindaraj and Kumarasamy Thangaraj conceptualized and drafted the manuscript.

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