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Review

2016: A 'Mitochondria' Odyssey

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The integration of the many roles of mitochondria in cellular function and the contribution of mitochondrial dysfunction to disease are major areas of research. Within this realm, the roles of mitochondria in immune defense, epigenetics, and stem cell (SC) development have recently come into the spotlight. With new understanding, mitochondria may bring together these seemingly unrelated fields, a crucial process in treatment and prevention for various diseases. In this review we describe novel findings in these three arenas, discussing the significance of the interplay between mitochondria and the cell nucleus in response to environmental cues. While we optimistically anticipate that further research in these areas can have a profound impact on disease management, we also bring forth some of the key questions and challenges that remain.

'Thus Spoke Mitochondria'

Mitochondria are cellular organelles with important roles in signaling and bioenergetics. They are surrounded by two membranes, the inner mitochondrial membrane (IMM) and the outer mitochondrial membrane (OMM). In most cell types, mitochondria are not isolated organelles; they radiate from the cell nucleus in a reticular network, displaying high levels of interconnectivity and plasticity facilitating their functional roles within the cell [1].

The field of biology has come a long way in understanding mitochondria since their discovery over a century ago [2]. In 2015, the UK made changes to legislation allowing the use of mitochondrial replacement therapies to help prevent the development of mitochondrial diseases [3]. Despite rapid progress in mitochondrial biology, little emphasis has been placed on mitochondrial involvement in epigenetics, SC biology, or immune defense. These three areas are intricately linked by the functional roles of mitochondria. Consequently, by appreciating this link we may also improve our understanding of the environmental signals that control gene function and influence mitochondrial dysfunction and disease.

This review aims to tie together the recent steps forward in these three underrepresented fields of mitochondrial biology. In addition, to facilitate the development of strategic approaches to answer complex questions in these fields, we discuss rapidly evolving technologies and experimental tools to study mitochondria in great detail. Of clinical relevance, we provide examples of treatments using mitochondria that are either licensed or currently in development aiming to treat various pathologies.

Immunity, SC Biology, and Epigenetics

Mitochondria in Immunity

Mitochondria play a significant role in the human immune system. Pattern recognition receptors (PRRs) recognize pathogen-associated molecular pathogens (PAMPs) and activate signaling cascades that promote inflammatory responses [4]. On viral infection, these inflammatory

Trends

Mitochondria play a pivotal role in the immune system by detecting foreign invaders through signaling pathways (e.g., inflammasomes) and generating immune responses. Modulation of this role might open up new therapeutic potential.

Methylation by DNA methyltransferases contributes to the epigenetic modification of mitochondrial DNA. Dysregulation of the mitochondrial epigenome within cells has been implicated in various diseases.

Mitochondria contribute to tissue regeneration and integrity, which are maintained by stem cell renewal and differentiation. Stem cells present exciting medical possibilities in regenerative medicine. Understanding specific mitochondrial biology in stem cells is vital.

Novel techniques are allowing the study of mitochondria in much greater detail than before.

Possible new therapeutic avenues are emerging with increased scientific knowledge linking mitochondria to immunity, epigenetics, and stem cell biology.

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responses are triggered and virally infected cells can be eliminated by mitochondria-driven apoptosis. In these molecular events, protein-signaling complexes that drive the production of interferons (IFNs) form active complexes on mitochondria [5]. When present, viral RNA forms a complex with **Rig-1-like receptors** (see Glossary) and translocates to the mitochondrial antiviral signaling protein (MAVS) in the OMM. MAVS forms aggregates in the OMM that can subsequently activate the key signaling mediators IFN regulatory factor 3 (IRF3) and the transcription factor nuclear factor kappa B (NF-κB) pathway in the cytoplasm (Figure 1A) [6].

It is increasingly recognized that **mitochondrial DNA (mtDNA)** and mitochondrial reactive oxygen species (mtROS) play significant roles in the cellular immune response. mtDNA released during Bcl-2-mediated apoptosis can bind to cGMP–AMP synthase (cGAS) causing the generation of cGAMP, which in turn activates stimulator of IFN genes (STING). This results in the production of IFN (Figure 1B) [5]. Caspase-3, -9, and -7 of the apoptotic caspase cascade

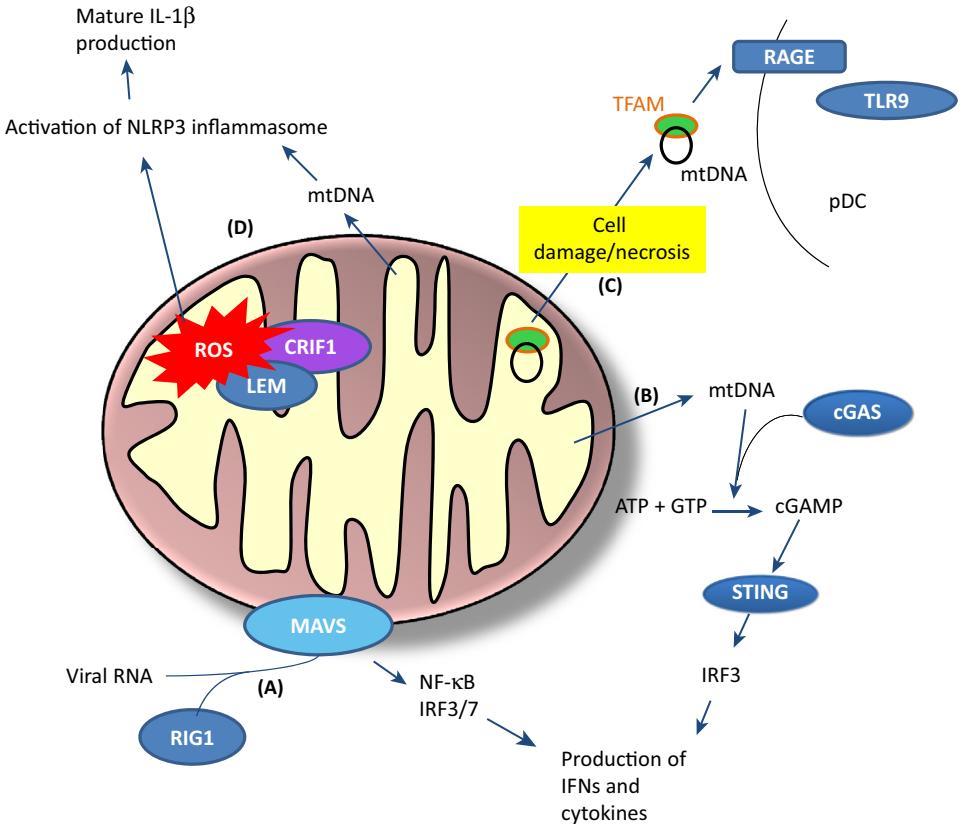

Figure 1. Mitochondria and the Immune System. (A) Viral RNA forms a complex with RIG1 and binds to mitochondrial antiviral signaling protein (MAVS) on the outer mitochondrial membrane (OMM). This then stimulates the nuclear factor kappa B (NF-κB) and interferon (IFN) regulatory factor 3/7 (IRF3/7) pathways resulting in the production of IFNs and cytokines. (B) Mitochondrial DNA (mtDNA) released from the mitochondria is a stress signal and can activate the stimulator of IFN genes (STING) pathway. mtDNA binds to cGMP–AMP synthase (cGAS) generating cGAMP, which activates STING. IRF3 can then induce expression of IFN and other IFN-stimulated genes (ISGs). (C) Transcriptional factor A, mitochondrial (TFAM) is a mtDNA-binding protein. After cell damage/necrosis TFAM acts as a danger signal and enhances the plasmacytoid dendritic cell (pDC) response by binding to the receptor for advanced glycation end products (RAGE) and toll-like receptor 9 (TLR9). (D) CR6-interacting factor (CRIF1) generates reactive oxygen species (ROS) through an interaction with the lymphocyte expansion molecule (LEM). Mitochondrial ROS (mtROS) stimulate the immune system by activating the Nod-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome pathway, which generates downstream mature IL-1β.

Glossary

Acetyl-CoA: metabolic intermediate produced during fatty acid metabolism.
Age-related macular degeneration (AMD): leading cause of vision loss in elderly populations. In the dry form, debris or 'drusen' accumulates. In the wet form, blood vessels grow from the choroid.
Diabetic retinopathy: complication of diabetes affecting the eyes and leading to vision loss.
Genome-scale analysis: analysis of genomic features such as DNA sequence and gene expression over the whole genome. The genome is searched for small variations called SNPs that occur more frequently in people with a particular disease.
Heteroplasmy: the mix of non-mutated and mutated mtDNA that can exist in a cell. The level of heteroplasmy can differ between cells, tissues, and individuals.
Mammosphere: a clump of human mammary gland cells.
Mitochondrial DNA (mtDNA): circular genome inside nucleoids in the inner mitochondrial membrane that encodes for 13 proteins and 24 RNA molecules.
Mitochondrial fission: the process of two mitochondria separating.
Mitochondrial fusion: joining of two more mitochondria to form a network.
***MT-RNR1*:** the mitochondrial gene that encodes 12s RNA.
Nucleoid architecture: pattern by which DNA is compacted, folded, or wrapped.
Oxidative phosphorylation (OXPHOS): metabolic pathway in which mitochondria produce ATP.
Rig-1-like receptor: a PRR in the cytoplasm.
Stemness: common molecular processes underlying the core SC properties of self-renewal and the generation of differentiated progeny.
Superoxide: a compound containing the anion O_2^-.