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EDITORIAL

CMLS forum reviews: mitochondrial damage control

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Abstract
Mitochondria supply cellular energy through oxidative phosphorylation and fulfill numerous additional functions that are fundamental to cellular homeostasis and stress responses. Mitochondrial malfunction, arising from inherent defects of the organelle itself, aging, or acute or chronic stress, can cause substantial damage to organismal health. For instance, mitochondrial malfunction contributes to inflammation, neurodegeneration, tumorigenesis and cardiovascular diseases. Therefore, various quality control mechanisms exist that support a functional mitochondrial organelle compartment. The CMLS Forum Reviews introduced here present a collection of articles covering select topics on basic mechanisms and pathophysiological contexts of mitochondrial damage control.

Keywords Apoptosis · Autophagy · Mitochondria · Mitophagy · Mitochondrial dynamics · Mitochondrial quality control · Mitochondrial retrograde response · Mitochondrial unfolded protein response · Stress signaling

Introduction

Multiple cellular processes are tasked with the maintenance of a healthy mitochondrial population. Degradative quality control mechanisms at the sub-organelle level include activities of mitochondrial proteases that locally survey the mitochondrial proteome [1]. In addition, compromised mitochondrial components can be delivered to lysosomes via mitochondrial-derived vesicles (MDVs) for degradation [2, 3]. Developmental cues or high degrees of mitochondrial damage can trigger whole organelle degradation via mitophagy [4, 5]. Conversely, the mitochondrial compartment can be replenished and expanded via mitochondrial biogenesis [6], and mitochondria can actively trigger nuclear expression of genes that alleviate dysfunction of the mitochondrial compartment in a process referred to as the mitochondrial retrograde response [7]. Drs. Alba Roca-Portoles and Stephen Tait present an up-to-date, broad overview of current knowledge in the field of mitochondrial quality control, covering aspects in molecular detail as well as at the organelle level.

Aside from their essential functions for cellular survival, mitochondria are important mediators of apoptosis [8]. Apoptosis is a form of regulated cell death with roles ranging from embryonic development, tissue homeostasis and immunity, to disease pathogenesis and therapeutic interventions [9–11]. Central to the transformation of mitochondria into cell death promoting organelles is the process of BAX/BAK-mediated mitochondrial outer membrane permeabilization (MOMP) [12]. Upon MOMP, pro-apoptotic factors that were confined within the mitochondrial intermembrane space are released to the cytosol and there contribute to the activation of proteolytic caspases which dismantle the cell. Anti-apoptotic BCL-2 protein family members safeguard against, while pro-apoptotic BCL-2 proteins promote MOMP. Dr. Ana García-Sáez and colleagues focus in on the current mechanistic and regulatory understanding of MOMP, and offer a detailed, comparative overview on available techniques for studying MOMP at the single-molecule level.

During mitophagy, mitochondria are specifically targeted and enclosed by autophagosomes, and degraded in their entirety upon autophagosomal fusion with lysosomes [4, 5]. Best characterized is the pathway of Parkin-mediated mitophagy, wherein Parkin ubiquitinates outer mitochondrial

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membrane (OMM) proteins that are then recognized and bound by autophagy receptors. These autophagy receptors link mitochondria to autophagososmal membranes by binding to LC3 proteins. Alternatively, mitophagy can be mediated by certain lipids and a growing number of OMM-localized mitophagy receptors. Dr. Kay Macleod and colleague contribute an in-depth summary of currently known mitophagy mechanisms and upstream signaling pathways and discuss the complex roles of mitophagy in tumorigenesis and metastasis.

Accumulating evidence indicates that inter-organelle contacts between mitochondria and various other organelle types is fundamental to mitochondrial function [13, 14]. For instance, membrane contact sites (MCS) between mitochondria and the endoplasmic reticulum (ER) support Ca^{2+} and lipid exchange, and regulate mitochondrial dynamics and apoptosis signaling [15–17]. Also, in addition to their autophagy- and MDVs-mediated connections with the endolysosomal system, mitochondria directly interact with endolysosomal vesicles [18]. Furthermore, recent work has revealed that MCS between mitochondria and the nucleus facilitate the mitochondrial retrograde response [19]. In this context, Dr. Michelangelo Campanella and colleagues postulate an integrated view on mitochondria-to-nuclear signaling, mitochondrial positioning and mitophagy in cancer cells.

The mitochondrial organelle compartment can exhibit a spectrum of morphologies, ranging from small spherical entities to tubular shapes of varying length and branching [20]. Morphological states are achieved through a balance of highly dynamic mitochondrial fusion and fragmentation activities. Mitochondrial morphology phenotypes and extent of mitochondrial interconnectivity are determined in a cell type and tissue-dependent manner, are impacted by the cellular metabolic state and external insults, and influence autophagic targeting and apoptosis signaling [20–22]. Similarly heterogeneous between cell types is the degree of mitochondrial movement throughout the cell, along microtubules [23]. Together, these characteristics are referred to as mitochondrial dynamics. Owing to the reciprocal nature of the relationship between mitochondrial dynamics and cellular homeostasis, its deregulation is implicated in numerous diseases [24]. Here, Dr. David Kashatus and colleague review basic mechanisms of mitochondrial dynamics, their interconnections with oncogenic signaling, and relevance for cancer stem cell biology and therapeutic resistance.

Mitochondrial damage control is particularly relevant also in the long-lived cells of the heart. Cardiac muscle cells are highly energy dependent, with kilogram amounts of ATP produced and utilized in the adult heart each day [25]. ATP production in this cell type can be attributed in its majority to the thousands of densely packed mitochondria that account for approximately 35% of the cytosol [26] and present as predominantly singular spherical-shaped, yet physically and electrically interconnected units [27]. Mitochondrial malfunction is linked to various cardiovascular diseases and tremendous efforts are underway to expand and translate current mechanistic understanding for clinical benefit [28, 29]. Dr. Roberta Gottlieb and colleagues provide an updated discussion of mitochondrial quality control mechanisms, and their clinical relevance, in the heart, ranging from mitochondrial dynamics to mitophagy, and safekeeping of the mitochondrial genome and proteome.

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