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Mitochondria: sensors and mediators of innate immune receptor signaling

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By integrating stress signals with inputs from other cellular organelles, eukaryotic mitochondria are dynamic sensing systems that can confer substantial impact on innate immune signaling in both health and disease. This review highlights recently discovered elements of innate immune receptor signaling (TLR, RLR, NLR, and CLR) associated with mitochondrial function and discusses the role of mitochondria in the initiation and/or manifestation of inflammatory diseases and disorders. We also highlight the role of mitochondria as therapeutic targets for inflammatory disease.

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Introduction

Mitochondria are maternally inherited double membrane organelles that possess their own genome, transcriptome, and proteome [1]. Mitochondria form a dynamic interconnected intracellular network, moving through the use of cytoskeletal motors and changing size and shape via processes such as fission and fusion. Mitochondrial fission and fusion facilitates mitochondrial DNA (mtDNA) protection, alteration of cellular energetics, and regulation of cell division [2]. Damaged or defective mitochondria are removed by selective encapsulation into double membraned autophagosomes and delivered to the lysosome for degradation by a process called mitophagy. Each mitochondrion has the ability to carry out oxidative phosphorylation (OXPHOS) using its electron transport chain (ETC), where the metabolic products generated from the Krebs cycle drive the generation of a proton gradient at the inner mitochondrial membrane (IMM), providing the energy needed for ATP generation. As well as being the main intracellular producers of energy (heat and ATP), mitochondria are sensors of oxygen, calcium, and fuel (carbohydrates, fatty acids), manufacturers of metabolites and reactive oxygen species (ROS) and are effective inducers of cell death (apoptosis) [1]. Importantly for the purpose of this review, mitochondria can also sense danger signals and induce inflammation by activating and controlling the innate immune system.

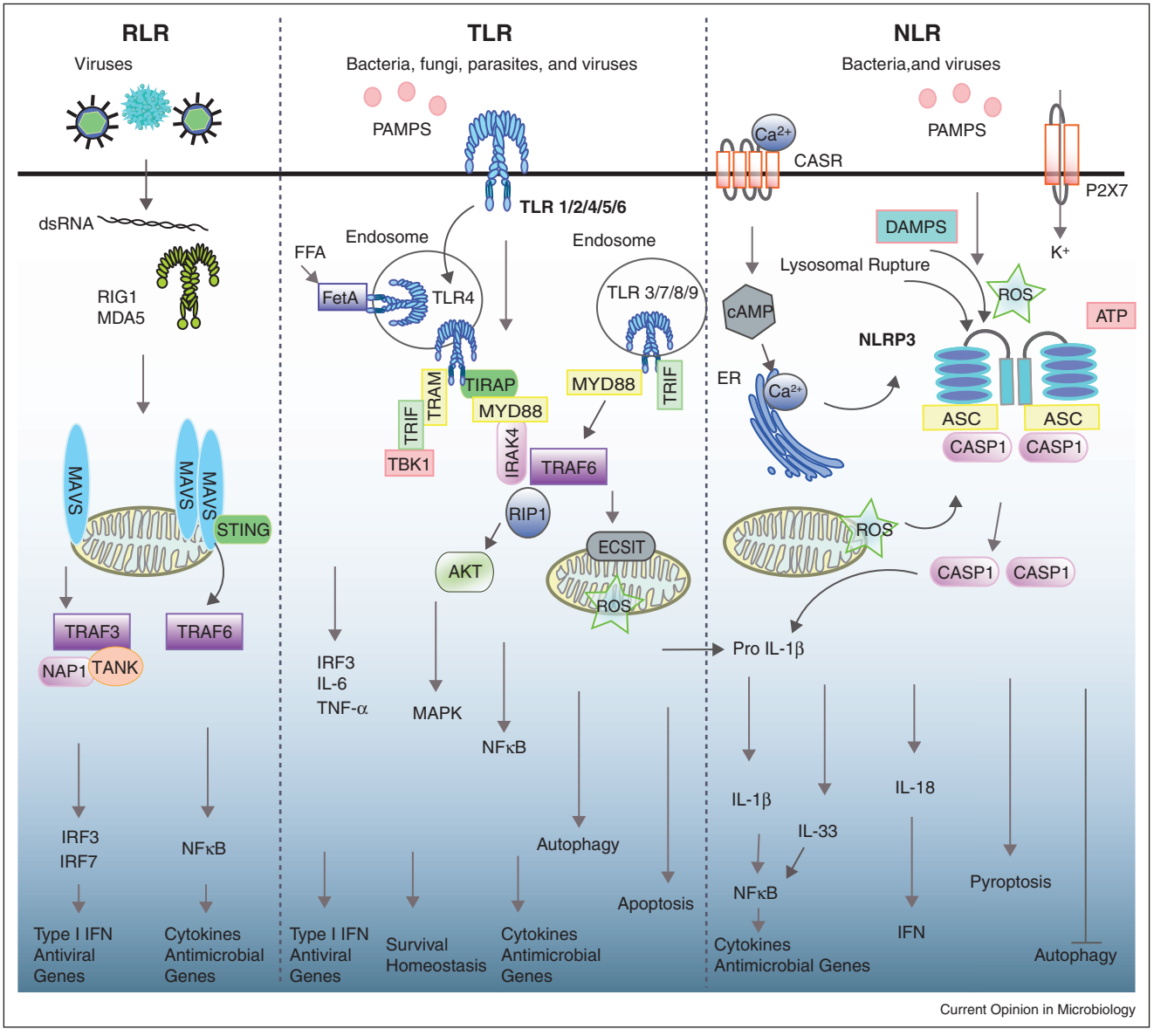
Mitochondria and the innate immune response

The innate immune response relies on pattern recognition receptors (PRRs) for the detection of infectious agents, cellular stresses or tissue damage. PRRs are a series of germline-encoded receptors that recognize conserved sets of molecular targets called pathogen-associated molecular patterns (PAMPs) and include retinoic acid inducible gene (RIG-1)-like receptors (RLRs), C-type lectin receptors (CLRs), Toll-like receptors (TLRs), and nuclear oligomerization domain (NOD)-like receptors (NLRs) [3]. PRRs allow for the rapid induction of inflammatory responses mediated by various cytokines and chemokines facilitating the eradication of pathogens. PRRs can also recognize damage-associated molecular patterns (DAMPs) that arise from endogenous molecules secreted or released from intracellular or extracellular sources as a result of tissue injury [1] (Figure 1 and Table 1). Emerging literature on the role of mitochondria in RLR, NLR and TLR signaling is discussed below. To date, little or no information exists on the role of mitochondria in CLR signaling pathways.

Mitochondria and RIG-1-like receptors

Cytoplasmic double stranded viral RNA is primarily detected by the RLRs, RIG-I and melanoma differentiation-associated gene 5 (MDA-5). These receptors activate nuclear factor B (NF-κB) and interferon regulatory factor 3 (IRF-3), resulting in the production of type I interferons (IFNs) and other proinflammatory cytokines that promote adaptive antiviral immunity [4] (Figure 1). Mitochondria provide an integral platform (termed the mitoxosome) [5] for RLR signaling and are involved in the pathogenesis of numerous RLR-related inflammatory diseases (Table 1). The mitoxosome is composed of the nuclear encoded outer mitochondrial membrane (OMM) protein, termed mitochondrial antiviral signaling protein (MAVS) or IFNβ promoter stimulator 1 (IPS1), CARD adaptor inducing IFNβ (CARDIF) or virus-induced signaling adaptor (VISA). MAVS interacts with RIG-I resulting in the induction of antiviral and inflammatory responses mediated by the interaction with

Figure 1



Innate immune signaling by PRRs. Cytosolic viral RNA is recognized by the RIG I-like receptors that activate MAVS. MAVS interacts with RIG-I via TRAF, resulting in the induction of antiviral and inflammatory responses including NF-κB and IRF signaling pathways. TLRs recognize PAMPS from viruses, bacteria, parasites, and fungi. TLRs are responsible for the recruitment of various adaptor molecules to activate downstream signaling pathways, including NF-κB, leading to the transcription of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. The glycoprotein, Fetuin-A acts as an adaptor between saturated FFAs and TLR4. Members of the cytosolic NLR family act as central components of the multiprotein inflammasome complex. The best-characterized inflammasome is that consisting of NLRP3, ASC, and caspase-1. Inflammasome components assemble, by a yet undefined mechanism in response to a number of physically and chemically diverse triggers including endogenous DAMPS, ATP, lysosomal rupture, and calcium. This in turn promotes the activation of caspase-1 leading to the maturation and secretion of IL-1β, IL-18, and IL-33.

the tumor necrosis factor receptor-associated factor (TRAF) family (Figure 2). MAVS, which is expressed ubiquitously in various cell types, also coordinates apoptotic and metabolic functions by associating with peroxisomes, endoplasmic reticulum (ER) and autophagosomes [6].

RLR signaling relies on intact healthy mitochondria and a functional elongated mitochondrial network. Cells with a dissipated mitochondrial membrane potential ($\Delta\psi_m$) are deficient in MAVS-mediated antiviral signaling [6] and mimicking mitochondrial elongation favors the binding of MAVS to stimulator of interferon genes (STING), an ER