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Mitochondria in autoinflammation: cause, mediator or bystander?

Robert van der Burgh and Marianne Boes

Department of Pediatric Immunology and Infectious Diseases and Laboratory of Translational Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht EA, 3584, The Netherlands

People suffering from autoinflammatory disease (AID) have recurring sterile inflammation due to dysregulated inflammasome activation. Although certain genes have been associated with several AIDs, the molecular underpinnings of seemingly spontaneous inflammation are not well understood. Emerging data now suggest that mitochondrial reactive oxygen species (ROS), mitochondrial DNA (mtDNA), and autophagy might drive key signaling pathways towards activation of the inflammasome. In this review, we discuss recent findings and highlight common features between different AIDs and mitochondrial (dys)function. Although it is still early to identify clear therapeutic targets, the emerging paradigms in inflammation and mitochondrial biology show that mitochondria play an important role in AIDs, and understanding this interplay will be key in the development of new therapies.

Importance of mitochondria in autoinflammatory disease

Mitochondria are best known for their role as the energy producers of the cell. In addition to supplying cellular energy, they play pivotal roles in various cellular processes including cell cycle progression, cellular differentiation and growth, and inflammation. Mitochondria are positioned near the endoplasmic reticulum (ER) [1], where they supply energy for protein production and ROS for disulfide-bond formation [2], and contribute to lipid biosynthesis [3]. They are also master regulators of apoptosis [4], and contribute to the activation of the inflammasome and thereby to directing immune responses [5] (Figure 1). The concept that mitochondria contribute to inflammasome activation is relatively new, with data gathered mostly during the last decade. Unsolicited inflammasome activation is now known to cause sterile inflammation [6]. Indeed, AID involves recurrent sterile inflammation due to inappropriate inflammasome activation [7]. In this review, we focus on the role of mitochondria in initiation and propagation of AID. We examine various aspects of mitochondrial signaling in the activation of the inflammasome and the possible consequences for AID development. Finally, we discuss possible mechanistic links between distinct AID types.

Autoinflammation and AID

The innate immune system is mobilized for activation upon sensing an external agent associated with pathogen infection. In autoinflammation (see Glossary), however, innate immune activation occurs upon perception of not external but internal cues [8]. A beneficial role for autoinflammation lies in responsiveness to injuries, supporting wound healing [9,10], through a process called sterile inflammation [6]. Autoinflammation can also turn pathological, presenting as AID. The signaling routes contributing to AID are not clear, although key molecules in immune activation pathways are deduced by clarification of genes that cause

Glossary

Autoinflammation: refers to the activation of the inflammation pathway without the presence of foreign or pathogenic triggers. The immune response is indistinguishable from a normally triggered response.
Autoinflammatory disease (AID): autoinflammatory disease is characterized by periodic fever and inflammatory symptoms followed by complete resolution of the inflammation. It is mostly caused by monogenetic hereditary mutations.
Inflammasomes: are large intracellular multiprotein complexes that play central role in innate immunity. They contain a cytosolic receptor for molecular patterns and, when triggered, activate caspase-1. Most known inflammasomes contain a member of the NOD-like receptor (NLR) family.
Mitochondria associated membrane (MAM): refers to the interface between mitochondria and the endoplasmic reticulum (ER). MAM are part of the ER and are reversibly tethered to mitochondria. This site is important for the exchange of metabolites, lipid biosynthesis, protein folding and calcium homeostasis.
Mitochondrial fission and fusion: Mitochondria undergo fission and fusion to ensure their proper function. This process is regulated by the master regulator proteins mitofusin 1 and 2 (MFN1 and MFN2), mitochondrial fission protein 1 (FIS1), dynamin-related protein 1 (DRP1), Optic atrophy 1 (OPA1), and the ER.
Reactive oxygen species (ROS): synthesis of ATP in mitochondria occurs through a process called respiration in which oxygen is used, and which simultaneously produces reactive byproducts. A foremost product is the superoxide radical O_2^-, which can cause cellular damage if it is not neutralized. Under normal conditions such radicals are contained and neutralized in the mitochondria. There are other sources of ROS in the cell, but oxygen metabolism is the main contributor.
Mitophagy: mitochondria undergo continuous quality control to ascertain overall health of cellular mitochondria. Damaged mitochondria are, degraded by the cell by a specialized form of autophagy, called mitophagy.
NLR family, pyrin domain containing 3 (NLRP3): also called cryopyrin, is a Pyrin-like protein containing a Pyrin domain, a nucleotide-binding domain (NBD), and a leucine-rich repeat (LRR) motif. NLRP3 functions as cytosolic sensor and is activated by numerous stimuli. When activated it oligomerizes and forms a complex with the adaptor protein ASC and caspase-1. The mature complex is called an inflammasome and processes the inactive pro-forms of IL-1β and IL-18 into their mature bioactive forms.
Sterile inflammation: Inflammation that occurs without the presence of pathogens or foreign material. This can be triggered by endogenous danger signals, such as IL-1β, or by inappropriate activation of inflammasomes, as is the case in AID.

Corresponding author: Boes, M. (m.l.boes@umchtrecht.nl).
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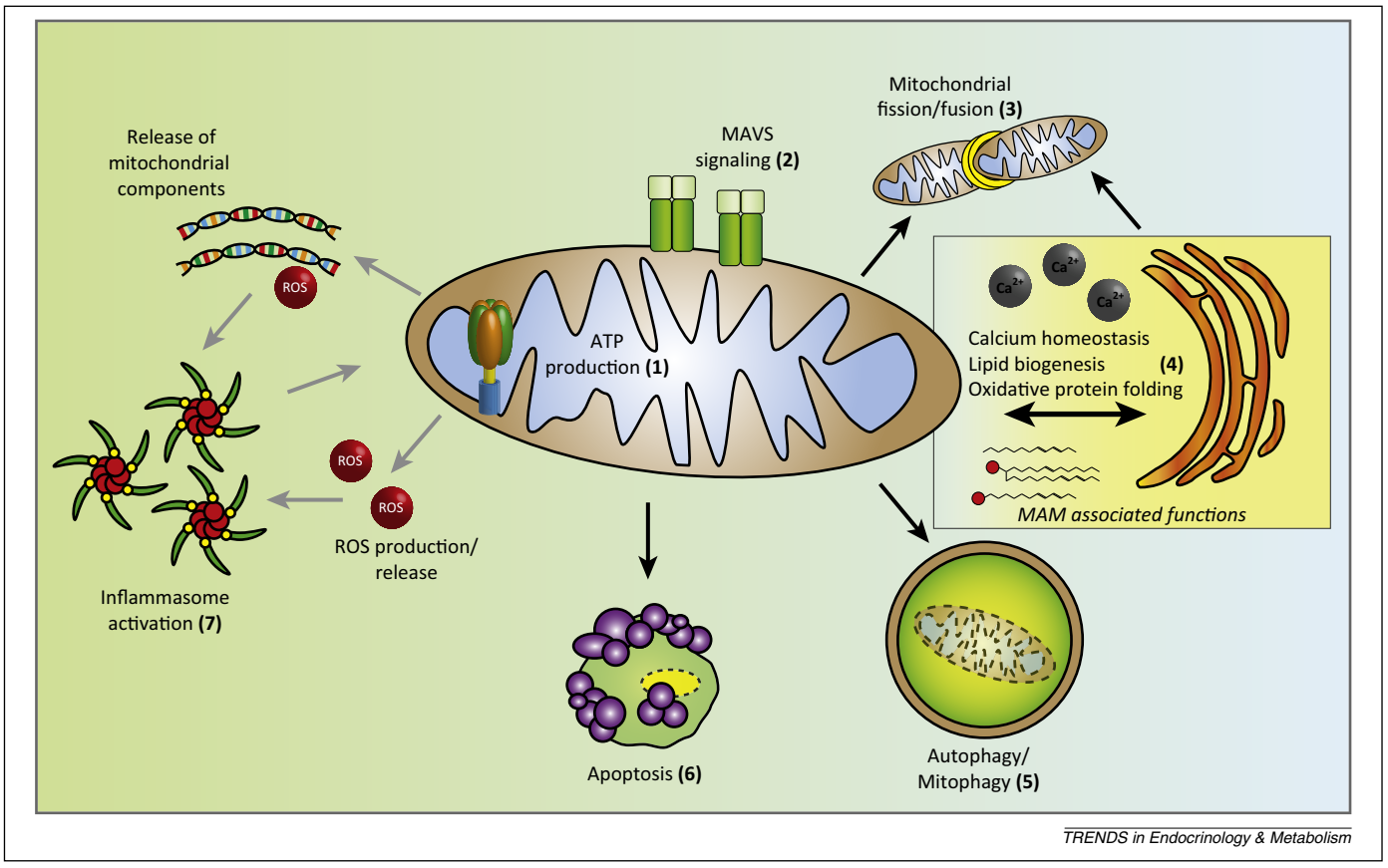

Figure 1. General overview of mitochondrial functions of the cell. The primary function of mitochondria is the generation of ATP (1). In addition, MAVS is expressed on the mitochondrial surface, and provides a signaling platform for immune activation, in particular for antiviral pathways (2). Mitochondrial fission and fusion can be adjusted to meet the demands of the cell or as response to mitochondrial damage (3). The MAM comprises the interface between the mitochondria and the endoplasmic reticulum. In this specialized compartment, mitochondria supply energy and metabolites for lipid synthesis and oxidative protein folding. In addition, calcium homeostasis is tightly regulated at the MAM (4). Released mitochondrial ROS can induce autophagy of cellular components, including mitochondria. Mitophagy degrades damaged or superfluous mitochondria (5). Release of mitochondrial components on large scale is a potent trigger for apoptosis (6). Mitochondria also play an important role in the induction of the inflammasome (7). There is no consensus on the exact order of events (gray arrows). Two main possibilities exist; either the mitochondria become damaged and release their content, leading to activation of the inflammasome. Or the inflammasome becomes activated and induces release of mitochondrial components, creating a feedback loop. Abbreviations: MAM, mitochondria-associated membrane; MAVS, mitochondria antiviral signaling; ROS, reactive oxygen species.

hereditary AID [11]. The result is the inadvertent triggering at subthreshold stimulation levels, for more or less periodic systemic activation of the innate immune response. Presentation of AID features includes: recurrent fever, joint inflammation, erythema, gastric inflammation, and mucosal inflammation [7]. Diagnosis of AID is often a long and difficult process. Because of the low incidence and the fact that activation of the inflammatory response in AID is indistinguishable from pathogen-induced immune activation, it usually takes multiple cycles before the possibility of autoinflammation is recognized. Final diagnosis of hereditary AID can only be made by DNA analysis, such as by next-generation sequencing [12].

We think it is relevant to emphasize here the mechanistic distinction between AID and autoimmune diseases. Autoimmune diseases are disorders of the adaptive, B and T lymphocyte-mediated branch of the immune system, notwithstanding that innate pathways also contribute. In autoimmunity, an important feature is chronic adaptive immune activation, while in autoinflammation, the innate immune system is activated in a recurrent manner that is followed by complete resolution of the inflammation until the next episode of activation. Clinically, autoinflammation is separated from autoimmunity through the lack of adaptive features, autoantibodies and autoreactive T cells [13].

Inflammasomes

Inflammasomes commonly consist of three constituents: a nucleotide-binding oligomerization domain (NOD)-like receptor (NLR), the adaptor protein apoptosis-associated Speck like protein containing a CARD (ASC), and caspase-1. The NLR, which forms the core, determines the type of inflammasome. The exogenous signal that triggers activation determines which type of inflammasome is formed, although the NLRP3 inflammasome responds to several stimuli (including even endogenous stimuli) [9,10], and is therefore special amongst NLRs. It has been suggested that NLRP3 inflammasomes may be activated by a single messenger or an intermediate one, but no consensus has been reached to date [14,15]. Interestingly, of the three general activators that have been suggested (potassium efflux, calcium ions, and ROS) (Figure 1), two are closely related to mitochondria [16–18]. The identification of a single conserved signal is complicated by the existence of a noncanonical pathway, which also activates NLRP3 via caspase-11 [19]. Multiple intermediate signaling pathways may therefore exist that all drive NLRP3 activation. Of note,