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Review

Mitochondrial-mediated antiviral immunity ☆

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ABSTRACT

Mitochondria, cellular powerhouses of eukaryotes, are known to act as central hubs for multiple signal transductions. Recent research reveals that mitochondria are involved in cellular innate antiviral immunity in vertebrates, particularly mammals. Mitochondrial-mediated antiviral immunity depends on the activation of the retinoic acid-inducible gene I (RIG-I)-like receptors signal transduction pathway and on the participation of a mitochondrial outer membrane adaptor protein, called the "mitochondrial antiviral signaling (MAVS)". In this review, we discuss unexpected discoveries that are revealing how the organelles contribute to the innate immune response against RNA viruses. This article is part of a Special Issue entitled: Mitochondrial dynamics and physiology.

1. Introduction

Mitochondria, which are compartmentalized by two membrane bilayers (outer and inner membranes), are well known to be involved in a wide variety of functions in eukaryotic cells. They are featured on unique organelles not only by their double-membrane structure but also because they contain their own genome; an approximately 16 kilobase circular mitochondrial DNA (mtDNA) encodes 13 protein genes, which are essential for the respiratory function of mitochondria to generate adenosine triphosphate (ATP) [1].

Serving as cellular powerhouses by virtue of their aerobic respiration, mitochondria also participate in numerous crucial cellular processes, including calcium homeostasis [2–4], apoptosis [5,6], multiple cell signaling [7–10], and aging [11,12]. Within the past decade, one of the most impressive discoveries regarding the novel functions of mitochondria is their mission in cellular innate antiviral immunity in vertebrates, particularly mammals [13–18]. Because mitochondria are believed to have evolved from organisms such as α-proteobacterium, their newly discovered role of branching into the host-cell defense was unexpected. In this review, we discuss recent insights into the fundamental phenomenon of mitochondrial involvement in cellular innate antiviral immunity.

2. Cellular innate immune response against RNA viruses

Innate immunity is an essential and ubiquitous system that defends organisms from infectious pathogens. The innate immune response is typically triggered by the recognition of broadly conserved microbial components known as pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide (LPS) of Gram-negative bacteria, β-1,3-glucans of fungi, peptidoglycans of Gram-positive bacteria, and genetic materials (DNA or RNA) of viruses [19–21]. The recognition of PAMPs by germline-encoded pattern recognition receptors (PRRs) ultimately activates intracellular signaling cascades that result in transcriptional activation, and finally leads to the clearance and killing of infectious microbes [20,21].

RNA viral infection of host cells is sensed by PRR recognition of a PAMP such as double-stranded RNA (dsRNA), that initiated two distinct signaling pathways [21–23]. The first pathway is known to be mediated by Toll-like receptor 3 (TLR-3). Endosomal expressing TLR-3 recognizes virus-derived dsRNA that gains entry into the host cell through endocytosis (Fig. 1). The second pathway is prompted by either of the two retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), RIG-I and melanoma differentiation-associated gene 5 (MDA-5), each of which detects cytoplasmic viral dsRNA [24–27]. Although TLR-3 and RLR pathways differ with respect to their initiating stimuli and downstream effectors, they converge at the point of the activation of the transcriptional factors, nuclear factor κB (NF-κB) and interferon regulatory factor 3 (IRF-3), resulting in the rapid production of type I interferons (IFN-α and -β) and other proinflammatory cytokines that promote the subsequent development of adaptive antiviral immunity [23,28,29].

At almost the same time in 2005, four independent labs found an adaptor molecule acting just downstream from RIG-I/MDA-5, mitochondrial antiviral signaling (MAVS) [13] (also called interferon-β promoter stimulator 1 (IPS-1) [30], CARD adaptor inducing IFN-β (Cardif) [31], and virus-induced signaling adaptor (VISA) [32]). In these studies, Chen and colleagues have revealed that MAVS is located at the mitochondrial outer membrane, and that its proper localization to the

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organelle is required for antiviral signal transduction [13]. Subsequent reports have clearly shown that MAVS cellular deficiency, generated either in knockout mice [33,34] or by the cleavage of virus proteases (NS3/4A and 3ABC) [31,35,36] or caspases [37], abolishes the production of type I IFNs and inflammatory cytokines, underscoring the importance of the link between antiviral innate immunity and mitochondria.

3. Mitochondrial antiviral signaling (MAVS)

MAVS, comprising 540 amino acids in *Homo sapiens*, is a mitochondrial integral outer-membrane protein with a predicted molecular mass of 56 kD (Fig. 2A), although it is assembled to form a supramolecular complex (approximately 600 kD) under physiological conditions [38]. MAVS is encoded in the nuclear genome (not in mtDNA) and is expressed ubiquitously in a variety of tissues and cell types [13,31,32]. So far, it has been reported that some MAVS orthologs are conserved throughout fish species [39–41] (Fig. 2B).

In its structure, MAVS contains an amino terminal caspase activation and recruitment domain (CARD) comprising six helices; three (H1a, H3, and H4) that form a flat positively charged surface and two (H2 and H6) that form an acidic negatively charged surface on the opposite side [42] (Fig. 2A). The RLRs (RIG-I and MDA-5), upstream molecules of MAVS, also contain tandem CARDs at their N-terminals [24,27] that interact with the CARD of MAVS, resulting in the activation of intracellular signaling cascades. At the carboxy terminal region, MAVS contains a single spanning-transmembrane (TM) domain (Fig. 2B) that is responsible for proper mitochondrial localization [13] and its self-association through the stacking of aromatic residues [43]. These properties of MAVS (i.e., mitochondrial localization, oligomerization, and possession of the CARD domain) seem to be the minimal requirements for its cellular function, because overexpression of a MAVS mutant containing only the CARD and TM domains (called mini-MAVS) is sufficient to induce signal transduction [13,35].

However, several lines of study have implicated that the subcellular localization of MAVS is not only on the outer mitochondrial membrane. As well as mitochondrial fission 1 (Fis-1) and mitochondrial fission factor (Mff), both of which are known to co-exist in mitochondria and peroxisomes [44,45], Kagan and colleagues demonstrated that MAVS also exists on the membranes of peroxisome, a metabolic organelle, and that the peroxisomal MAVS is involved in the early induction of IFN-stimulated genes such as viperin, before mitochondrial MAVS induces a sustained antiviral response [46]. In addition to this peroxisomal distribution, another group found MAVS in mitochondrial-associated endoplasmic reticulum membranes (MAM) [47]. Although the multi-

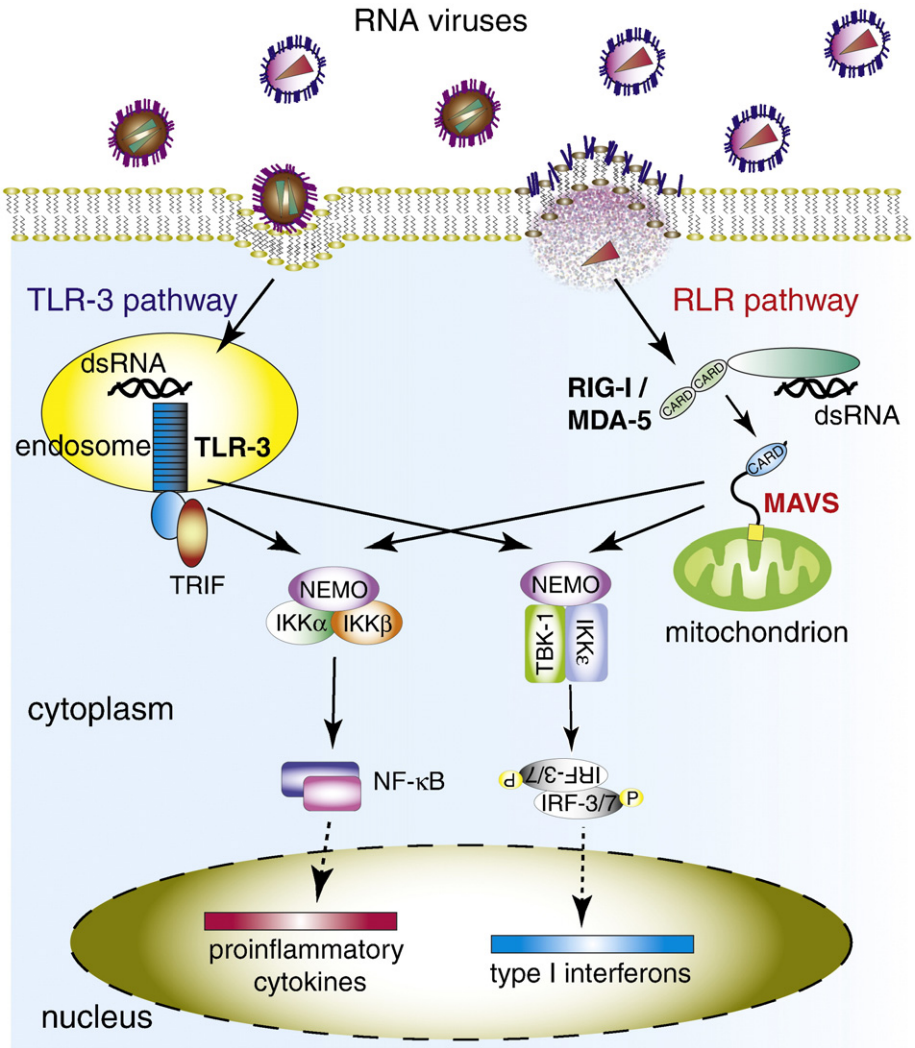

Fig. 1. Overview of innate immunity against RNA viruses in mammals. Viral infections of mammalian host cells are detected by the cells' recognition of virus-derived double-stranded RNA (dsRNA), which initiates two distinct signaling pathways (TLR-3 and RLR). Although these two pathways differ with respect to their initiating stimuli and downstream effectors, they converge at the point of transcriptional activation (NF-κB or IRF-3/7), resulting in the rapid production of type I interferons and proinflammatory cytokines. Mitochondrial-mediated antiviral immunity depends on the activation of the RLR signaling pathway.

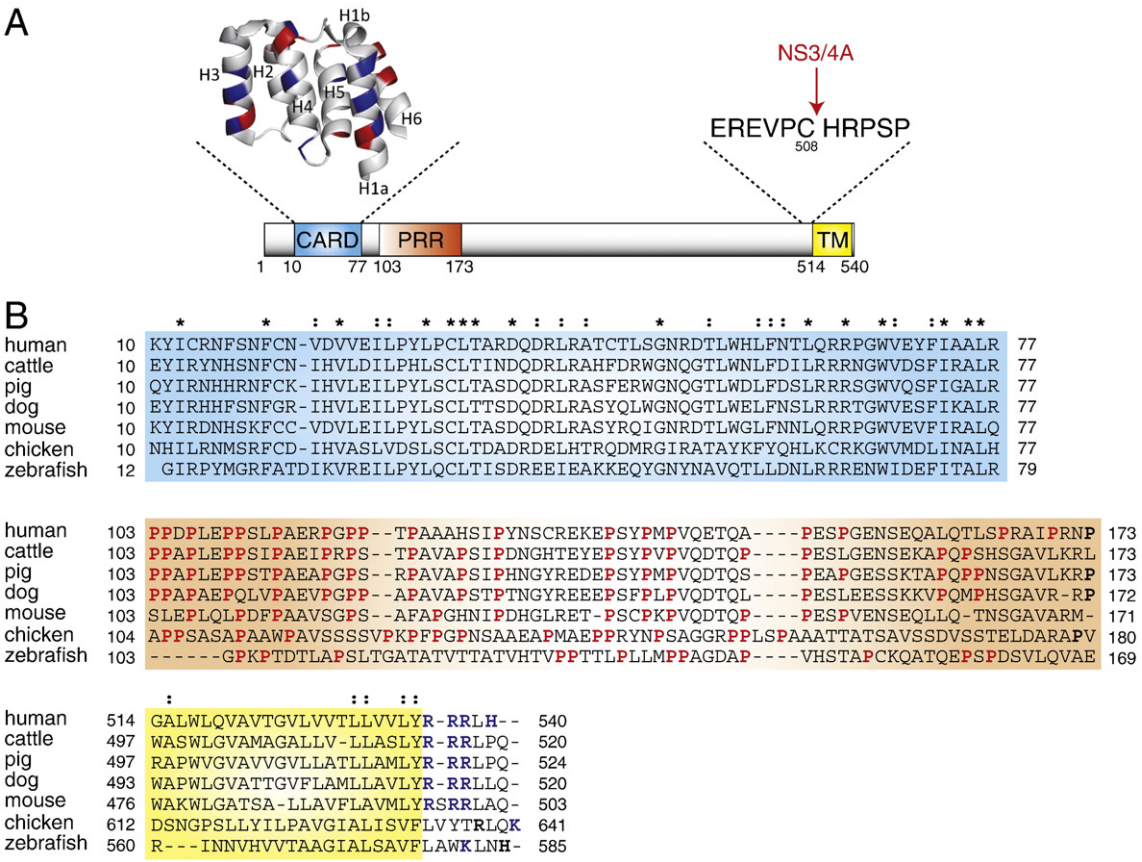

Fig. 2. MAVS domain structure and its sequential alignment among different species. (A). A schematic representation of human MAVS, showing the locations of the CARD domain (CARD), the proline-rich region (PRR), and the transmembrane segment (TM). The amino acid positions are indicated below the structure. The crystal structure of the CARD domain [42] is inserted into the figure. The basic amino acids are colored in blue and the acidic residues are in red. The hepatitis C virus (HCV) serine protease, NS3/4A, cleavage site (Cys^{508}) is located just upstream from TM. (B). Sequential alignment of the CARD, PRR, and TM among different species of MAVS using the Clustal W program. The asterisk (*) indicates the conserved residues among these species, and the colon (:) indicates the residues that have similar properties.

cellular localization of MAVS is in dispute, there is no doubt that these organelles are interconnected and interdependent in cellular metabolism.

Aside from its CARD and TM domains, MAVS contains another functional domain (Fig. 2A and B); a proline-rich region (PRR) that is involved in downstream signaling via its interaction with the tumor necrosis factor receptor-associated factor (TRAF) family, including TRAF2, TRAF3, and TRAF6 [32,48] (*described in the next section*). It remains unclear, however, why a MAVS mutant lacking the PRR retains its signaling capacity [13,35].

4. Activation of MAVS signalosome

Upon RNA viral infection, the RNA helicases (RIG-I and MDA-5) recognize virus-derived RNA ligands, leading to auto-activation by its drastic conformational changes [27,49], and they translocate at the outer mitochondrial membrane to interact with MAVS (Fig. 1). What is the machinery that activates MAVS after the association with RLRs, and how is that machinery regulated? Because these processes are transient populated states during the signaling event, it has been difficult to determine the structure of MAVS directly. A fluorescence-based assay, however, provided important insight into its structural features. Lamarre and colleagues revealed that MAVS dimerization through its TM domain is essential for activating NF-κB and IRF-3, and they proposed a model in which RIG-I-MAVS interaction induces the MAVS dimers [43]. Indeed, Wang and colleague have observed that RIG-I recruitment to MAVS enhances the self-association of MAVS as analyzed by fluorescence resonance energy transfer (FRET) assay, and that the formation of MAVS homodimers would lead to the binding and activation of TRAF3, a downstream molecule of MAVS [50].

It was revealed that, during the activation of MAVS, a scaffold protein, via its dimer formation, MAVS recruits various downstream effectors to form a signaling supramolecular assembly, a "MAVS signalosome" which leads to the upregulation of the NF-κB and IRF-3 pathways (Fig. 3). Many studies have identified adaptors interacting with MAVS, and we describe a couple of examples. TRAF family members, TRAF2, 3, and 6, are known to bind TRAF-interaction motifs (TIM) in the PRR of MAVS [32,48] (Fig. 3; see Positive regulation). TRAF5 has also been shown to associate with MAVS after the activation of the scaffold protein [51]. Another cast of the positive regulators is tumor necrosis factor receptor-associated death domain (TRADD). TRADD also interacts with MAVS and orchestrates the TRADDosome complex, including TRAF3, TRAF family member-associated NF-κB activator (TANK), Fas-associated death domain (FADD), and receptor interacting protein 1 (RIP1); this orchestration leads to the activation of NF-κB and IRF-3 [52]. Translocase of outer membrane 70 (TOM70) has been identified a component of MAVS signalosome, and is bridging TANK-binding kinase 1 (TBK-1)/IRF-3 to mitochondria [53].

Finally, we should note that the stimulator of interferon genes (STING) [54], (an ER-integrated membrane protein that is also called the mediator of IRF-3 activation (MITA) [55], endoplasmic reticulum interferon stimulator (ERIS) [56], and MPYS [57]), also interacts with MAVS (positioned downstream from MAVS) and can activate both NF-κB and IRF-3 pathways [54,55]. As we mentioned earlier

(MAVS in MAM), these discoveries of MAVS-STING interaction further highlight the importance of the interconnectedness and interdependence of mitochondria and ER in antiviral innate immunity.

5. Negative regulators of MAVS signaling

Given that the prominent function of the MAVS signalosome is precisely regulated upon viral infection, it is most likely that the scaffold protein is subjected to control in a quiescent state by negative regulators in non-infected environments. Indeed, we have shown that MAVS forms a stable higher-order complex (~600 kD) on the outer membrane of mitochondria at their resting state [38].

So far, several negative regulators of MAVS, through its binding and/or post-translational modifications, have been investigated (Fig. 3; see Negative regulation). For instance, NLRX1 (also known as NOD9), a novel nucleotide oligomerization domain (NOD)-like receptors (NLRs), is a ubiquitously expressed mitochondrial protein (located at the outer membrane) that inhibits CARD-CARD interactions between RLRs and MAVS, thereby preventing downstream signal transduction [58,59]. However, a thorough biochemical study revealed that NLRX1 localizes to the mitochondrial matrix [60], and the same group found that its overexpression induced reactive oxygen species (ROS), resulting in amplified NF-κB and JUN N-terminal kinase (JNK)-dependent signaling in response to *Shigella* infection [61]. At present, it is still unclear how exactly NLRX1 inhibits MAVS if that distributes at the matrix side, so further analysis will be needed. A receptor for the globular head domain of complement C1q (gC1qR) is also translocated to the mitochondrial outer membrane and binds with MAVS, resulting in the suppression of antiviral immune responses [62].

Some RNA viruses encode protease genes not only to generate their mature proteins required for viral replication, but also because these genes have the potential to suppress antiviral immunity by cleaving putative cellular targets as an evasion strategy. An example of this is the hepatitis C virus (HCV) serine protease, NS3/4A, which cleaves MAVS at the position of 508 (cysteine residue) (Fig. 2A) to ultimately abolish the RLR signaling pathway [31,35]. The hepatitis A virus takes a similar strategy using its 3ABC cysteine protease,

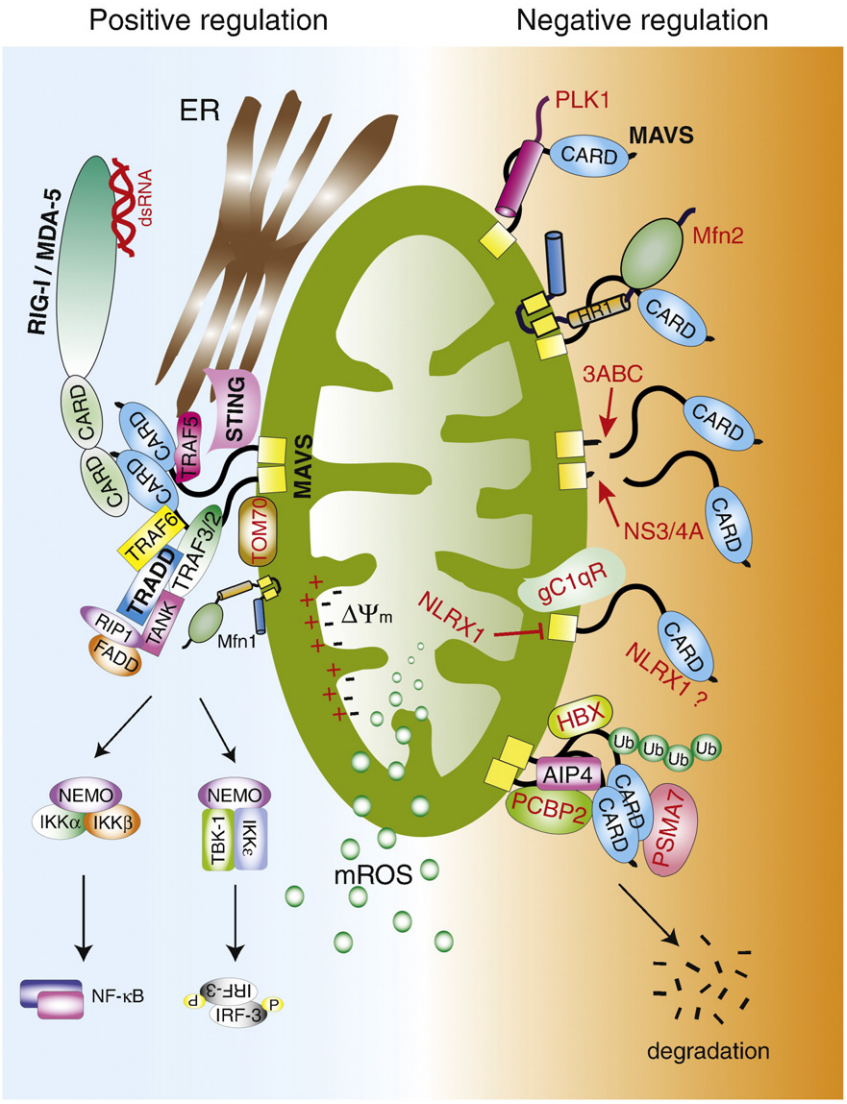

Fig. 3. Positive and negative regulations of MAVS-mediated antiviral signaling. Viral infection can activate RLRs (RIG-I and MDA-5), leading to their translocation to the mitochondria, and RLRs associate with MAVS via a CARD–CARD interaction (Positive regulation). MAVS activation is then triggered by its self-associations. These associations are allowed by recruiting various downstream effectors to form signaling supramolecular assembly (MAVS signalosome), which in turn leads to the activation of NF-κB and IRF-3. The functions of MAVS depend on having normal mitochondrial membrane potential ($\Delta\Psi_m$) from healthy mitochondria. Mitochondrial ROS (mROS) acts as a second messenger for the RLR signaling pathway, and increasing mROS induces the positive regulation of MAVS signaling. On the other hand, MAVS is subjected to control in a quiescent state by several negative regulators under a non-infected environment, or MAVS is promptly terminated after the antiviral response (Negative regulation).

although the cleavage site of the MAVS sequence is unique [36]. Both of the mechanisms of MAVS inhibition are believed to disrupt the mitochondrial targeting of the adaptor protein (Fig. 3). Further, hepatitis B virus X protein (HBX) interacts with MAVS, promoting MAVS ubiquitination; this triggers proteasome-mediated degradation, resulting in the downregulation of the signaling system [63].

On the other hand, poly(rC) binding protein 2 (PCBP2) was reported to act as a negative regulator of MAVS-mediated antiviral signaling by leading MAVS proteasomal degradation via K48-linked polyubiquitination [64]. PCBP2, which induces post-viral infection into the host cells, recruits atrophin-1-interacting protein 4 (AIP4), an E3 ubiquitin ligase, to form a tertiary complex with MAVS, and catalyzes the K48-linked conjugation and degradation of MAVS. As is the case with PCBP2, PSMA7, the α4 subunit of 20S proteasome, negatively regulates antiviral signaling through proteasome-dependent degradation of MAVS, although the details of the mechanism are unclear [65]. These studies provide us with a mechanism by which MAVS signaling is promptly terminated once an antiviral response occurs.

Finally, Polo-like kinase 1 (PLK1) inhibits the MAVS-mediated IFN-β induction by arresting TIM in the C-terminal region of MAVS, thereby disrupting the interaction between MAVS and TRAF3 [66]. In addition to these negative regulators, Mitofusin 2 (Mfn2), a mediator of mitochondrial fusion, is also involved in the RLR pathway [38], as we describe in the following section.

6. Mitochondrial dynamics and antiviral immunity

In many cell types, mitochondria have a tubular morphology and undergo continuous cycles of homotypic fusion and fission, opposing processes that control organelle shape, copy number, and mtDNA maintenance [67–69] (Fig. 4A). Moreover, mitochondrial dynamics play an important role in apoptosis, a fundamental function of mitochondria [70,71]. In mammals, mitochondrial dynamics are controlled by several mitochondrial proteins, including four high-molecular-weight GTPases: mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (OPA1) regulate fusion processes, whereas dynamin-related protein 1 (Drp1) is involved in mitochondrial fission [67–69] (Fig. 4A). Within the past several years, a couple of studies have shed light on the connection between mitochondrial dynamics and antiviral innate immunity.

The first evidence of the role of mitochondrial dynamics in antiviral immunity was the discovery that Mfn2, which mediates mitochondrial fusion, inhibits the RLR pathway through its MAVS-binding via a central 4,3 hydrophobic heptad region (HR1) of Mfn2 [38] (Fig. 3; see Negative regulation). In the study, we showed that an increased abundance of Mfn2 sequesters MAVS in a nonproductive state, thereby preventing the propagation of a downstream antiviral response, reducing or obliterating both IFN-β expression and IRF-3 dimerization. In contrast, the loss of endogenous Mfn2 enhances the virus-induced production of IFN-β and thereby decreases viral replication. Interestingly, we did not observe this inhibitory phenotype with the Mfn2 homolog protein, Mfn1, despite 60% sequence identity [38]. More recently, we found that the Mfn2-mediated inhibition of MAVS signaling is caused by the interference with MAVS–MAVS oligomerization (unpublished results).

Adding to the story of the connection between innate immunity and mitochondrial dynamics, Arnoult and colleagues reported that activation of the RLR pathway via the defective Sendai virus (SeV) strain H4 induces mitochondrial elongation [72]. They also demonstrated that the knockdown of either Mfn1 or OPA1, which blocks mitochondrial fusion, decreases virus-induced activation of the transcription factors, NF-κB and IRF-3, whereas knockdown of Drp1 or Fis-1, which depletes mitochondrial fission, increases RLR signaling. Importantly, they mentioned that mitochondrial dynamics

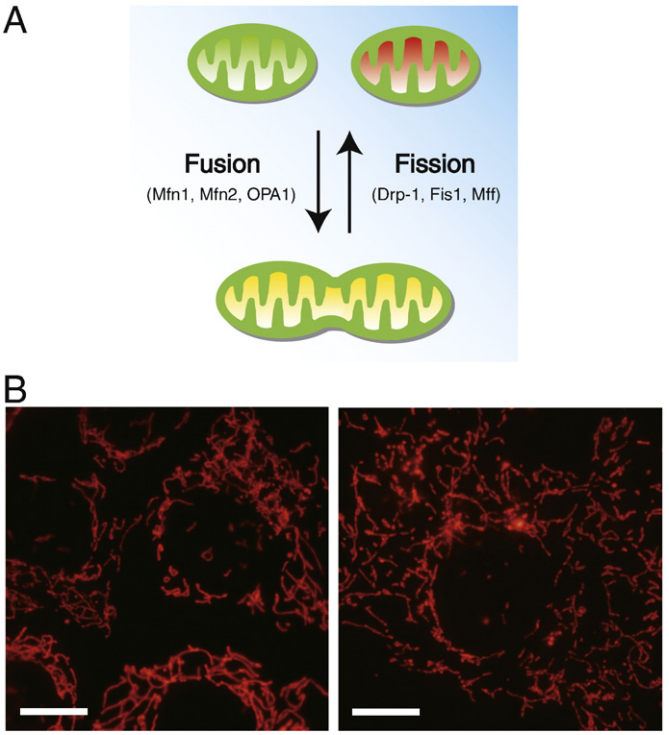

Fig. 4. Mitochondria are dynamic organelles. (A). A schematic representation of mitochondrial dynamics in mammalian cells. Mitochondria are dynamic organelles that undergo continuous cycles of fusion and fission. Molecules involved in mitochondrial fusion and fission are indicated. (B). Mitochondrial morphology in wild-type (left) or *MAVS*-deficient (right) mouse embryonic fibroblasts (MEFs). Mitochondria are visualized by staining with a monoclonal antibody against mtHsp70 (red). Scale bar, 10 μm.

would facilitate MAVS downstream signaling by mitochondria-ER tethering, which is involved in MAVS-STING interaction [72].

Another study reported that viral infection in the host cell triggers MAVS re-distribution on the outer mitochondrial membrane, and this translocation is regulated by Mfn1 because the knockdown of the gene abolishes this rearrangement [73]. Furthermore, those authors proposed a model of viral entrapment by mitochondria via an RIG-I-MAVS complex [73]. Regarding MAVS re-distribution on mitochondria, Chen and colleagues recently provided interesting evidence from an *in vitro* study that viral infection induces the formation of prion-like MAVS aggregates that would potentiate the activation of IRF-3 or recruit TRAF family members, TRAF2 and 6 [74]. In this model, they proposed that RIG-I-MAVS interaction induces rapidly formation of MAVS functional aggregates, and that progressively converts other endogenous MAVS into prion-like aggregates (a hallmark of prion) on the outer membrane of mitochondria. However, it is still unclear whether the aggregates accumulate under physiological conditions, and how cells reform/regenerate these abnormal mitochondria. Therefore much more work is required to understand the linkage of mitochondrial dynamics to MAVS signaling.

7. Mitochondrial functions and antiviral immunity

According to the studies mentioned in the section above, it is obvious that mitochondrial morphology is considerably involved in the MAVS-mediated antiviral signaling pathway. However, further evidence implies that classical mitochondrial functions, such as mitochondrial membrane potential ($\Delta\psi_m$) and mitochondrial reactive oxygen species (mROS), also play key roles in innate antiviral immunity. In fact, the mitochondria in mouse embryonic fibroblasts (MEFs) with null mutation in *MAVS* (*MAVS*$^{-/-}$ MEFs) still exhibit a normal and/or more extended tubular morphology (Fig. 4B). This casts doubt upon

the idea that mitochondrial shape itself affects MAVS signaling. We thus discuss a couple of convincing studies of the mitochondrial functions governing cellular antiviral signaling pathways (Fig. 3).

Mfns-deficient MEFs (both *Mfn1*$^{-/-}$ and *Mfn2*$^{-/-}$) show no detectable mitochondrial fusion and have completely fragmented mitochondria [75,76]. Moreover, the cells display impaired induction of type I IFNs and other proinflammatory cytokines in response to viral infection [77]. Chan and colleagues have reported that the vast majority of Mfns-null cells show widespread heterogeneity of $\Delta\psi_m$, a physiologic function of mitochondria [76]. Indeed, treatment of wild-type cells with CCCP, a protonophore that dissipates $\Delta\psi_m$, remarkably suppresses the antiviral immune responses [77]. In this work, we also showed that in cells overexpressing uncoupling protein-2, which localizes the mitochondrial inner membrane and induces mitochondrial proton leakage [78], the extent of $\Delta\psi_m$ dissipation correlated with the defect in RLR-induced antiviral responses [77]. Further, it is interesting to note that mice lacking *UCP-2* were reportedly resistant to infection by *Toxoplasma gondii*, a protozoan parasite that causes toxoplasmosis, a result of the increased mROS generation; in contrast, such infection is lethal for the wild-type littermates [79]. Future study to evaluate the role of UCP-2 in a viral infection *in vivo* model may prove interesting.

Mitochondrial ROS, which is generated through mitochondrial respiration, are reportedly involved in the RLR signaling pathway. Using autophagy-defective *Atg5*$^{-/-}$ cells, Iwasaki and colleagues demonstrated that the accumulation of dysfunctional mitochondria, which is responsible for increasing mROS levels, enhances RLR signaling [80]. They also showed that cells treated with an antioxidant compound significantly reduced type I IFN levels, whereas rotenone potently increased RLR signaling. In agreement with these findings, another group reported that cellular ROS is essential for RIG-I-mediated IRF-3 phosphorylation and dimerization, the hallmarks of IRF-3 activation [81]. As we mentioned above, UCP-2 has potential role in $\Delta\psi_m$ regulation, and that function is coupled with the attenuation of mROS production [78,79,82]. Therefore, we can also interpret the results to mean that the abundance of UCP-2 leads to the inactivation of MAVS-dependent signaling as the byproduct of mROS-decreasing effect [77].

Finally, a recent paper from Levine and colleagues have revealed that SMURF1, an E3 ubiquitin–protein ligase, acts as a newly mediator in both viral autophagy (Sindbis and herpes simplex viruses) and mitochondrial selective autophagy (mitophagy), uniquely linking between cellular antiviral response and mitochondria [83]. Collectively, these works provide a framework for understanding how the physiologic functions of mitochondria are coupled with its functions in antiviral immunity.

8. Concluding remarks

Mitochondria are well known as the powerhouses of eukaryotic cells. Recent studies indicate that mitochondria also act as a platform for the first line of antiviral defense. In this review, we described the role of mitochondria only in innate immunity against RNA viruses, but the involvement of this double-membraned organelle in immune responses is also important for a broad range of immune responses against other types of inflammation, such as bacterial infection [84–86], sterile inflammation [87–89], and lymphocyte trafficking [90]. Furthermore, it is quite interesting to study the evolutional path of this organelle, in light of the fact that innate immune responses can also be triggered by mitochondrial materials [i.e., mtDNA and mitochondrial *N*-formyl peptides (mtDNA-encoded proteins translated with *N*-formyl methionine residue)] that leak from damaged mitochondria [91,92]. Thus, there is no doubt that mitochondria have key roles in immunity, but further studies are needed to elucidate the basic physiology of mitochondria and how the organelle achieves both cellular metabolism and host defense. Finally, dysfunction of mitochondrial dynamics is also known to be implicated in neurodegenerative diseases, so it will be important to clarify the link between mitochondrial-mediated immunity and neuropathy.

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Glossary

The following abbreviations are used in the text.

AIP4: atrophin-1-interacting protein 4
CARD: caspase activation and recruitment domain
CCCP: carbonyl cyanide *m*-chlorophenylhydrazone
dsRNA: double-stranded RNA
FADD: Fas-associated death domain
gC1qR: receptor for globular head domain of complement C1q
HBX: hepatitis B virus X protein
HCV: hepatitis C virus
IFN: interferon
IKK: inhibitor of NF-κB (IκB) kinase
IRF-3: interferon regulatory factor 3
MAVS: mitochondrial antiviral signaling
MDA-5: melanoma differentiation-associated gene 5
MEF: mouse embryonic fibroblast
Mfns: mitofusins
mROS: mitochondrial reactive oxygen species (ROS)
mtDNA: mitochondrial DNA
NF-κB: nuclear factor κB
NLRX1: NOD-like receptor family member X1
PAMP: pathogen-associated molecular pattern
PCBP2: poly(rC) binding protein 2
PLK1: Polo-like kinase 1
PRR: proline-rich region
$\Delta\psi_m$*:* mitochondrial membrane potential
RIG-I: retinoic acid-inducible gene I
RIP1: receptor interacting protein 1
RLR: RIG-I-like receptor
STING: stimulator of interferon genes
TANK: TRAF family member-associated NF-κB activator
TIM: TRAF-interaction motif
TLR-3: Toll-like receptor 3
TOM: translocase of outer membrane
TRADD: TNF receptor-associated death domain
TRAF: tumor necrosis factor (TNF) receptor-associated factor
UCP-2: uncoupling protein 2