Biochimica et Biophysica Acta 1833 (2013) 225–232

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Mitochondrial-mediated antiviral immunity ☆

Takumi Koshiba *

Department of Biology, Faculty of Sciences, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

ARTICLE INFO

Article history:
Received 18 January 2012
Received in revised form 2 March 2012
Accepted 6 March 2012
Available online 13 March 2012

Keywords:
Antiviral innate immunity
MAVS
Mitochondrial dynamics
RLR pathway
Signal transduction

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

☆ This article is part of a Special Issue entitled: Mitochondrial dynamics and physiology.

* Tel./fax: +81 92 642 2633.
E-mail address: koshiba@kyudai.jp.

0167-4889/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2012.03.005

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-

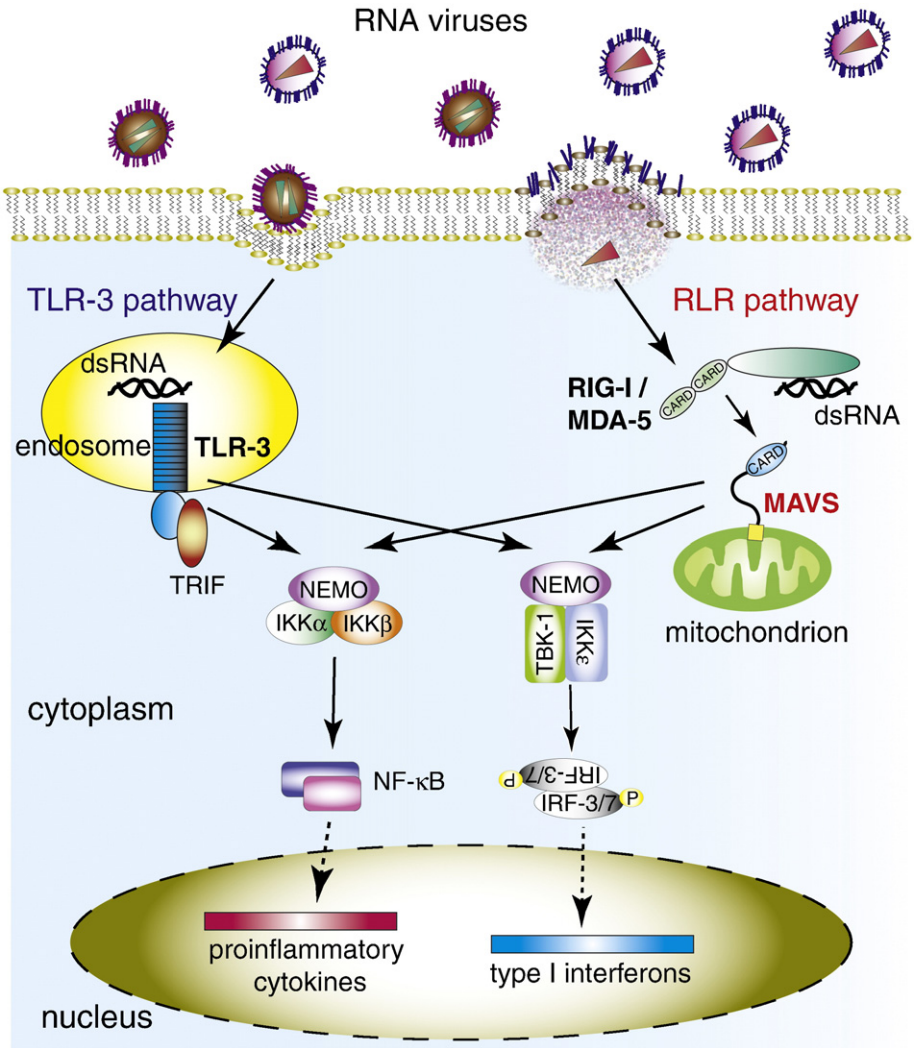

Fig. 1. Overview of innate immunity against RNA viruses in mammals. Viral infections of mammalian host cells are detected by the cells' recognition of virus-derived double-stranded RNA (dsRNA), which initiates two distinct signaling pathways (TLR-3 and RLR). Although these two pathways differ with respect 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.