

Mitofusin 2, a key coordinator between mitochondrial dynamics and innate immunity

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ABSTRACT

Remodeling of mitochondrial dynamics and mitochondrial morphology plays a pivotal role in the maintenance of mitochondrial homeostasis in response to pathogenic attacks or stress stimuli. In addition to their role in metabolism and energy production, mitochondria participate in diverse biological functions, including innate immune responses driven by macrophages in response to infections or inflammatory stimuli. Mitofusin-2 (MFN2), a mitochondria-shaping protein regulating mitochondrial fusion and fission, plays a crucial role in linking mitochondrial function and innate immune responses. In this article, we review the role of MFN2 in the regulation of innate immune responses during viral and bacterial infections. We also summarize the current knowledge on the role of MFN2 in coordinating inflammatory, atherogenic, and fibrotic responses. MFN2-mediated crosstalk between mitochondrial dynamics and innate immune responses may determine the outcomes of pathogenic infections.

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Introduction

Mitochondrial dynamics are regulated by mitochondrial fusion and fission and the formation of mitochondrial networks. In turn, these processes modulate various biological functions, including mitochondrial metabolism, redox balance, and cell death [1]. Mitochondrial fusion and fission are regulated by a group of guanosine triphosphatases (GTPases) [2,3]. Specifically, mitochondrial fusion is controlled by the GTPases mitofusin-1 (MFN1) and mitofusin-2 (MFN2), which are located in the outer mitochondrial membrane (OMM), and by the GTPase optic atrophy 1 in the inner mitochondrial membrane. Mitochondrial fission is regulated by the dynamin-related protein 1 (Drp1) through interaction with other OMM proteins, such as MiD51 and MiD49 [4,5]. These proteins are essential for mitochondrial quality control and homeostasis, as well as the regulation of numerous biological processes, including immune responses [6,7].

Innate immune responses involving sensing of microbes and generation of antimicrobial effectors are the primary defense in response to pathogenic attacks and damage signals. Accumulating evidence suggests that multilayered molecular crosstalk between innate immune signaling and mitochondrial dynamics regulates the outcomes of pathogenic infections. For example, innate immune signaling

triggered by retinoic acid-inducible gene I-like receptors (RLRs) induces remodeling of the mitochondrial network [8]. RLR activation by viral RNA promotes mitochondrial elongation to enhance the interaction between mitochondrial antiviral signaling protein (MAVS; also known as IPS-1, VISA, or CARDIF) and other signaling proteins of the endoplasmic reticulum (ER) [8]. Toll-like receptor (TLR) 4 signaling has been linked to Drp1-mediated mitochondrial fission and macrophage-mediated inflammatory responses [9], which orchestrate the primary immune responses during infection [10]. In particular, MFN2 seems to be a critical player in linking mitochondrial dynamics, autophagy (xenophagy and mitophagy), and innate immune responses against viruses, bacteria, and parasites [11–14]. Recent findings also suggest that MFN2 regulates inflammatory, atherogenic, and fibrotic responses in a context-dependent manner [15–17]. In this article, we summarize the current knowledge on the role of MFN2 in the crosstalk between mitochondrial dynamics, innate immunity, and immunometabolism in macrophages during infection.

Innate immunity: RLR signaling, inflammasome, and immunometabolism

Innate immune responses are the primary immune defense in response to infectious agents. Innate

immune cells, including macrophages and dendritic cells, express various pattern-recognition receptors (PRRs), which recognize pathogen-associated molecular patterns and damage-associated molecular patterns derived from microbial cells and damaged cellular components. Activation of TLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and other PRRs can trigger complex intracellular signaling pathways. These innate immune pathways are regulated by various kinases, phosphatases, signaling enzymes, adaptors, and protein scaffolds [18–20]. In response to these pathways, antimicrobial peptides and inflammatory cytokines are released to counterattack the invading pathogens. Innate immune responses are tightly regulated to prevent tissue damage due to the over-activation of inflammatory responses [18,19]. In addition to serving as the primary defense, innate immunity is also crucial for the initiation of adaptive immune responses, which protect from subsequent infections by the same pathogen [18,19,21,22]. Moreover, well-characterized immune functions are interconnected to metabolic remodeling in the innate immune cells to shape effector functions and inflammatory responses upon the challenge of diverse pathogens [23–25]. Recent studies have highlighted the involvement of mitochondrial dynamics in the regulation of immunometabolism to influence innate immune functions, as we discuss in the latter part of this review. In this section, we have divided our discussions of RLR signaling, inflammasomes, and immunometabolism, to better explore the inter-related function of MFN2 in the context of these immune response paradigms.

RLR signaling

Cytoplasmic RNA from RNA viruses can activate intracellular RNA-specific PRRs, such as retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5). Recognition of viral RNA fragments by RIG-I and MDA5 initiates signal transduction through MAVS on the surface of mitochondria. MAVS, a key adapter protein of RLR signaling, contains three domains; amino-terminal caspase activation and recruitment domain (CARD), a proline-rich central domain, and a carboxy-terminal transmembrane domain to anchor at the OMM. Upon RIG-I or MDA5 activation, either PRR can bind MAVS through CARD-CARD interactions and induces the formation of large MAVS aggregates, thereby propagating downstream signaling cascade that activates the cytoplasmic kinases, such as tumor necrosis factor receptor-associated factor family member-associated nuclear factor κ -light-chain-enhancer of activated B cells binding kinase 1 (TBK1) and I κ B kinase- ϵ [26–28]. The

activation of protein kinases, in turn, phosphorylate the transcription factors interferon regulatory factor (IRF) 3 and nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B), both of which are crucial transcriptional factors to activate a variety of innate immune-related genes, including type I interferons (IFNs) and pro-inflammatory cytokine genes to regulate antiviral and inflammatory responses during viral infection [26,27]. How an MFN2-MAVS interaction at OMM influences mitochondrial inner compartment is less well understood due to a topologic gap between the OMM and inner mitochondrial membrane (IMM). The IMM protein prohibitins are mitochondrial scaffold proteins involved in mitochondrial signal transduction and homeostasis [29]. Future work is required to understand whether prohibitins may bridge MFN2/MAVS with IMM as a part of prohibitin interactome assembly that is crucial for mitochondrial functions [29].

In addition, RLR-induced antiviral signaling is regulated through extensive post-translational modifications at each step via multiple ubiquitin E3 ligases, deubiquitinases, protein kinases, and phosphatases [30–35]. The detailed mechanisms underlying post-translational modification of RLR-triggered signaling are beyond the scope of this review. The antiviral immune responses are tightly regulated to prevent the uncontrolled secretion of IFNs [36,37]. Emerging evidence suggests that mitochondria are essential for the activation of RLR signaling in response to viral infections. Through complex host-viral interactions, viruses can manipulate the mitochondrial machinery of the host to suppress innate immune activation [38–40].

Inflammasome complex

The inflammasome complex is a large intracellular multi-protein platform that activates caspase-1. In turn, caspase-1 proteolytically cleaves cytosolic pro-interleukin (IL)-1 β and pro-IL-18, and the subsequent release of pro-inflammatory cytokines results in pyroptotic cell death. NLRP3 (NOD-like receptor protein 3) is the most extensively studied inflammasome. Recent evidence suggests that post-translational modifications, protein-protein interactions, and spatiotemporal regulatory mechanisms regulate activation of the NLRP3 inflammasome [41,42]. Furthermore, crosstalk between the ER and mitochondria in mitochondria-associated membranes (MAMs) is essential for inflammasome activation [43]. MFN2-induced tethering between the ER and mitochondria is critical for the formation of MAMs to promote inflammasome-mediated cellular defense [43–45]. Aberrations in MAMs have been implicated in various pathological processes. In particular, alterations in MAMs increase the levels of mitochondrial reactive oxygen species (ROS) and promote intracellular

translocation of mitochondrial components, thereby promoting chronic inflammation and metabolic rewiring [43,44].

Immunometabolism in innate immune cells

Innate immune signals, such as TLR ligands, trigger the differentiation of macrophages into pro-inflammatory M1 macrophages by enhancing aerobic glycolysis and suppressing the tricarboxylic acid cycle. In M1 macrophages, succinate enhances ROS generation, thereby stabilizing hypoxia-inducible factor 1 α (HIF-1 α) and promoting aerobic glycolysis, IL-1 β secretion, and M1 polarization [46–49]. In the early phases of inflammation, an immunometabolic shift to aerobic glycolysis, known as the Warburg effect, is required for cells to fulfill their high energy demands [46,50]. At a later stage of inflammation, metabolic reprogramming in immune cells increases mitochondrial oxidative phosphorylation and fatty acid oxidation (FAO), both of which are required for inflammation resolution and tissue repair [51]. However, recent findings suggest that FAO promotes inflammasome activation [24,52]. Moreover, increased glucose utilization via aerobic glycolysis and the Akt-mammalian/mechanistic target of rapamycin complex 1 pathway is required for lipid metabolism and FAO in activated M2 macrophages and type 2 T helper cells [52–54]. Accumulating evidence suggests that the mitochondrial dynamics shaped by fusion and fission events are intimately linked to the regulation of immunometabolism, thereby leading to diverse outcomes in various immune cell functions [55–58]. Future studies are needed to dissect the immunometabolic profiles in each type of immune cell at different stages of infection and inflammation and elucidate how mitochondrial dynamics interconnect with the molecular networks of immunometabolism to determine infection outcomes.

Components regulating mitochondrial dynamics

Mitochondrial fusion and fission are critical regulators of mitochondrial morphology and function [59]. Mitochondrial fusion is essential for the exchange of metabolites and DNA between neighboring mitochondria, the delivery of metabolites to the cell core from the periphery, and the maintenance of the protein stoichiometry of the mitochondrial DNA replisome [7,60–62]. The GTPase activity of MFN1 and MFN2 is responsible for membrane tethering, fusion, and mitochondrial calcium influx [61,63]. Mitochondrial fission often results in uneven daughter mitochondria; one daughter unit is

eliminated by mitophagy [64]. Fission is essential for the segregation of damaged mitochondria and the maintenance of energy demands in different subcellular regions [64,65]. In addition, fission facilitates apoptosis during extreme levels of cellular stresses through the segregation of damaged mitochondria [65]. Upon selective stresses, including UV irradiation or actinomycin D treatment, mitochondria form a highly interconnected network depending on the mitochondrial inner membrane protein stomatin-like protein 2, but not MFN2 [66]. This response may contribute to an adaptive pro-survival mechanism against selective stresses in the cells [66]. In response to a variety of infectious stresses, mitochondrial dynamics may control the immune activation through multiple mechanisms, which are discussed in the following sections.

The coordination between fusion and fission is a critical regulator of mitophagy and apoptosis, thereby controlling the balance between cell survival and cell death [67]. Despite this, it remains to be determined which signaling pathways play a specific role in the cross-talks between mitochondrial dynamics and other mitochondrial functions. Recent studies showed that the cytoplasmic DNA sensor cyclic guanosine monophosphate -adenosine monophosphate (AMP) synthase (cGAS)/protein stimulator of interferon genes (STING) signaling is involved in a variety of roles in mitochondria, i.e., apoptosis, autophagy, sensing of mitochondrial DNA, and inflammatory signaling in different settings of physiological and pathological conditions [68–71]. Previously, MFN1 deficiency suppresses STING pathway activation to decrease IFN- β induction as well as diminished signaling activation of TBK1 and IRF3 [72]. Given the central role of cGAS/STING signaling in innate and mitochondrial functions, further studies are needed to clarify the molecular links between cGAS/STING signaling and mitochondrial dynamics.

The role of MFN2 in innate immune responses during infection

Overview of MFN2 function

MFN2 participates in the initial step of mitochondrial fusion [73,74]. In humans, MFN2 contains 757 amino acid residues. It is a nuclear-encoded, dynamin-like GTPase harboring an N-terminal GTPase domain and a C-terminus exposed to the cytosol. The GTPase domain of MFN2 hydrolyzes GTP, promoting MFN oligomerization and OMM fusion between adjacent mitochondria [75,76]. Mammalian MFN2 shares ~80% sequence similarity with MFN1 and is essential for OMM fusion. Although the GTPase activity of

MFN2 is lower than that of MFN1, MFN2 has a higher GTP affinity [63]. MFN2 and MFN1 contribute to tethering between the ER and mitochondria [63]. MFN2 also regulates PTEN-induced kinase 1 (PINK1)/Parkin-mediated mitophagy [77]. Upon mitochondrial membrane depolarization, MFN2 interacts with Parkin in a PINK1-dependent manner. Upon phosphorylation by PINK1 [77], MFN2 is ubiquitinated by Parkin; subsequently, MFN2 is degraded through the action of p97, a member of adenylpyrophosphatase associated with diverse cellular activities, that accumulates in mitochondria and is required for Parkin-induced mitophagy [78]. Through this process, MFN2 promotes the removal of damaged or senescent mitochondria [62].

Besides its fundamental role in mitochondrial fusion, MFN2 also regulates various other biological processes, such as cell proliferation and cell death [62,79,80]. Because MFN2 is required for axonal mitochondrial transport in neurons, dysfunction of MFN2 has been associated with several neurodegenerative diseases, such as Charcot-Marie-Tooth disease and Alzheimer's disease [81–83]. Moreover, dysregulated MFN2 expression and function have been implicated in type 2 diabetes mellitus [84] and atherosclerosis [85,86]. In gastric cancer, MFN2 has been shown to exert antitumor effects [80]. By contrast, patients with breast cancer expressing low MFN2 levels show poor prognosis, at least partly due to the ability of MFN2 to inhibit mTORC2 [87]. Future studies are required to uncover the role of MFN2 in different disease conditions, including cancers.

MFN2 and innate immune responses during viral infections

Numerous recent studies have shown that MFN2 is a key regulator of innate immune responses during viral infections. Earlier studies reported that MFN2 inhibited antiviral immune responses by interacting with MAVS [11]. Additionally, MFN2 overexpression inhibited RLR signaling and IRF3 expression; by contrast, MFN2 deficiency enhanced IFN- β secretion and suppressed viral replication [11]. Structural evidence suggests that MFN2 interferes with MAVS homotypic oligomerization to alter the active conformation of MAVS [88]. More recently, MFN2 was found to regulate corticosterone-mediated boosting of influenza virus (H1N1) replication by interacting with MAVS. MFN2 mediates the recruitment of E3 ligase synoviolin 1, thereby promoting MAVS polyubiquitination [89]. Of note, MFN1 may play an opposite role by interacting with MAVS during viral infection. MFN1 binds MAVS and promotes the production of antiviral IFNs

[90]. Further evidence suggests that MAVS interacts with MFN1 to facilitate ER-mitochondrial association, thereby enhancing the downstream signaling of MAVS [8]. Cytomegalovirus-induced mitochondrial fragmentation is one of the immune-escaping strategies viruses employ to inhibit the binding of MAVS to STING1 and suppress antiviral immune responses [8]. Together, these data suggest that MFN1 and MFN2 interact with MAVS to fine-tune innate immune responses during viral infection.

However, it remains unclear how MFN levels are regulated during viral infection. Triggering receptor expressed on myeloid cells 1 (TREM1) has been identified as one of the upstream signaling molecules regulating MFN2 expression. During infection with human immunodeficiency type 1 (HIV-1), MFN1 and MFN2 are upregulated in macrophages in a TREM1-dependent manner. The decreased expression of anti-apoptotic proteins and MFNs is associated with increased levels of apoptosis in macrophages due to alterations in mitochondrial membrane potential (MMP; $\Delta\Psi(m)$) [91]. Thus, TREM1-dependent MFN2 upregulation and inhibition of apoptosis may contribute to the ability of HIV-1 to survive within host cells [91].

Interestingly, MFN1 and MFN2 regulate host defenses against the dengue virus and are cleaved by dengue virus protease NS2B3. During dengue virus infection, MFN1 is essential for efficient antiviral signaling, whereas MFN2 maintains MMP to inhibit cell death [92]. Thus, dengue virus-mediated cleavage of MFNs suppresses mitochondrial fusion and virus-induced cytopathy [92]. Future studies are warranted to reveal the molecular mechanisms by which MFNs regulate antiviral responses and host cell survival in response to different viruses. The intracellular signaling events regulating the expression of MFNs during infection also merit further investigation.

MMP is essential for MAVS-induced antiviral responses [93]. MFN2 is required for MMP homeostasis and IL-1 β secretion after infection with RNA viruses, including influenza, measles, or encephalomyocarditis virus (EMCV) [94]. Conversely, overexpression of the inner mitochondrial membrane protein uncoupling protein 2 alters the MMP and reduces IL-1 β secretion during infection. Mechanistically, MFN2 binds NLRP3 to promote IL-1 β secretion after infection with influenza virus and EMCV [94]. However, it is unclear whether MFN2 is involved in activating the conventional NLRP3 inflammasome complex; whether MFN2 levels affect host defense and pathogenesis during viral infection also remains unclear. Several roles of

MFN2 in innate immune responses during viral infection are summarized in Table 1.

MFN2 and innate immune responses during bacterial infection

Although MFN2 signaling has been mostly studied in the context of viral infection, recent studies suggest a role for MFN2 in regulating the interactions between bacteria and host cells. MFN2 was found to be upregulated in peripheral blood mononuclear cells of patients with active tuberculosis [95]. In addition, mycobacterial antigen 6-kDa early secreted antigenic target and *Mycobacterium tuberculosis* lysate enhanced the interaction between MFN2 and NLRP3, promoting assembly of the inflammasome complex and the production of IL-1 β [95]. MAMs formed through tethering between the ER and mitochondria act as a scaffold for NLRP3 inflammasome activation [43]. MFN2 mediates the formation of MAMs by promoting tethering between the ER and mitochondrial membranes [96–98]. Therefore, MFN2 may play an essential role in

activating innate immune pathways at MAMs and other specialized subcellular regions.

A recent study showed that the energy sensor AMP-activated protein kinase directly interacted with MFN2, inducing autophagy in response to energy stress [99]. Celada et al. confirmed that MFN2 was essential for immune system activation during bacterial infection. MFN2 is required for mitochondrial respiration and the production of ROS. MFN2-mediated ROS production promotes the secretion of cytokines and nitric oxide, induces autophagy and apoptosis, and enhances antigen processing. Myeloid-specific MFN2 deficiency impairs immune responses during infection with *Listeria* and *M. tuberculosis* and during lipopolysaccharide (LPS)-induced septic shock [12,100]. In accordance with these findings, our recent data suggest that myeloid MFN2 is required for inflammatory and antimicrobial responses during infection with *Listeria* or *M. tuberculosis* [14]. MFN2-mediated antimicrobial responses during *M. tuberculosis* infection were partly due to HIF-1 α -induced xenophagy [14]. On the other hand, MFN2 silencing enhanced intracellular

Table 1. The role of MFN2 in innate immune responses during infection.

Pathogen	Model	Effect	Mechanism	Ref.
Viral infection				
EMCV, Measles, VSV	HEK 293T cells; MEFs	Inhibition of RLR-induced antiviral signaling	Interaction with carboxyl-terminal MAVS	[11]
Influenza virus A (H1N1)	A549 cells; Stress mice model	Inhibition of RLR-induced antiviral signaling	Interaction with and degradation of MAVS	[89]
EMCV, Influenza virus, Newcastle disease virus, SeV, Sindbis virus, VSV	HEK 293T cells; MEFs	No effects	ND for MFN2; MFN1 interacts with MAVS and activates type I IFN signaling	[90]
Cytomegalovirus	HeLa; HEK 293T cell	No effects	ND for MFN2; MFN1 interacts with MAVS and activates type I IFN signaling	[8]
Human immunodeficiency virus1	Human monocyte-derived macrophages	Increase in viral reservoir	Inhibition of BCL2L11-mediated MMP disruption by TREM1	[91]
Dengue virus	A549 cells	Attenuation of virus-induced cytopathic effects	Suppression of caspase 3 activation and MMP disruption	[92]
EMCV, SeV, VSV	HEK 293T cells; <i>Mfn1</i> and <i>Mfn2</i> double mutant MEFs	Induction of RLR-induced antiviral responses	Enhancement of adequate MMP and rearrangement of MAVS	[93]
EMCV, Influenza virus, Measles	BMDMs; HEK 293T cells; J774A.1 mouse macrophages	Activation of inflammasome	Interaction with NLRP3 and MAVS complex	[94]
Bacterial infection				
ESAT-6, Mtb lysate	PBMCs; THP-1 cells	Activation of inflammasome	Interaction with NLRP3	[95]
<i>Aeromonas hydrophila</i> , <i>Listeria monocytogenes</i> , LPS, Mtb	BMDMs; <i>Mfn2</i> -cKO mice; L-929 cells; PMs	Induction of antibacterial responses and antigen processing	Increase in mitochondrial ROS and activation of ERK1/2, p38, and NF- κ B	[12]
BCG, <i>L. monocytogenes</i> , Mtb, <i>Mycobacteroides abscessus</i> Mtb	BMDMs; <i>Mfn2</i> -cKO mice; PMs; RAW264.7 cells	Enhancement of aerobic glycolysis and xenophagy	Induction of mitochondrial ROS and HIF-1 α	[14]
	BMDMs; RAW264.7 cells	Increase in bacterial growth	Inhibition of MMP disruption and apoptosis	[101]
Parasitic infection				
<i>Leishmania donovani</i>	Golden hamsters; PMs from BALB/c mice; RAW264.7 cells	Enhancement of antiparasitic microRNAs	Destabilization and compartmentalization of miRNP by mitochondria-ER tethering	[13]

BCG, *Mycobacterium bovis* bacillus Calmette-Guérin; BCL2L11, B-cell lymphoma 2 like 11; BMDM, bone-marrow-derived macrophage; EMCV, encephalomyocarditis virus; ER, endoplasmic reticulum; ERK, extracellular signal-regulated protein kinase; ESAT-6, 6-kDa early secreted antigenic target; HIF-1 α , hypoxia-inducible factor 1 alpha; IFN, interferon; LPS, lipopolysaccharide; MAVS, mitochondrial antiviral-signaling protein; MEF, mouse embryonic fibroblast; *Mfn1*, mitofusin 1; *Mfn2*, mitofusin 2; *Mfn2*-cKO mice, *Mfn2*^{fl/fl}:*LysM*^{Cre} mice; miRNP, microribonucleoprotein; MMP, mitochondrial membrane potential; Mtb, *Mycobacterium tuberculosis*; ND, Not detected; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding and oligomerization domain-like receptor pyrin domain-containing protein 3; PBMC, peripheral blood mononuclear cell; PM, peritoneal macrophage; RLR, retinoic acid-inducible gene-1-like receptors; ROS, reactive oxygen species; SeV, Sendai virus; TREM1, triggering receptor expressed on myeloid cells 1; VSV, Vesicular stomatitis virus

M. tuberculosis growth in macrophages [101], presumably due to differences in experimental conditions. These data strongly indicate that MFN2 is a key player in antibacterial innate and adaptive immune responses by coordinating metabolism. Multiple functions of MFN2 in innate immune responses during bacterial infection are summarized in Table 1.

MFN2 and innate immune responses during parasitic infection

Leishmania donovani infection reduces MFN2 expression levels in host cells, associated with mitochondrial depolarization, decreased mitochondrial dynamics, and reduced turnover of microRNA ribonucleoprotein (miRNP) complexes (Summarized in Table 1) [13]. Decreased MFN2 levels may enhance the stabilization of ER-associated miRNPs because MFN2 is involved in the juxtaposition of the ER and mitochondria [13]. Increased miRNP stability downregulates various cytokines, inhibiting pro-inflammatory responses during *Leishmania donovani* infection [13].

The role of MFN2 in inflammatory and pathological responses

MFN2 and inflammatory responses

Functional analysis of MFN2 levels in macrophages upon antimicrobial and inflammatory responses revealed that myeloid deficiency of MFN2 but not MFN1 inhibited the production of pro-inflammatory cytokines and innate effector molecules (e.g., nitric oxide) [12]. Additionally, MFN2 deficiency in macrophages suppressed innate immune responses, including autophagy, apoptotic cell clearance, and antigen processing [12,14]. MFN2 was also found to be essential for the induction of strong inflammatory responses in response to LPS and non-septic stimuli [12]. However, the role of MFN2 in sterile inflammation remains unclear.

It is well known that low doses of LPS can lead to low-grade chronic inflammatory diseases. Interestingly, super-low doses of LPS lead to MFN1 ubiquitination and degradation, as well as trigger cell necroptosis due to DRP1 activation. Super-low doses of LPS can activate receptor-interacting protein 3 kinase, which is involved in the assembly of the necrosome complex [102]. Although it remains unclear whether MFN2 degradation is due to the super-low dose of LPS, these data strongly suggest that mitochondria-shaping proteins are fundamental for the crosstalk between host inflammatory responses and intracellular necroptosis [102].

A recent study showed that the orexigenic hormone ghrelin increased MMP and ameliorated LPS-induced glycolysis in macrophages. Interestingly, ghrelin-induced IL-12 secretion was dependent on mitochondria elongation and MFN2. Thus, MFN2-mediated mitochondrial fusion may partly mediate the effects of ghrelin on IL-12 production in macrophages [103]. In a recent study, treatment with a mitochondrial fusion promoter significantly increased MFN2 levels and prevented mitochondrial dysfunction, macrophage infiltration, and apoptosis; these events contributed to reduced brain damage in cardiac ischemia/reperfusion injury [16]. However, the molecular mechanisms regulating MFN2 levels remain largely uncharacterized. Activation of the protein kinase C- α (PKC- α)/heme oxygenase-1 (HO-1) pathway increased the expression levels and superoxide dismutase activities of MFN1 and MFN2. However, the PKC- α /HO-1 axis decreased oxidative stress in response to LPS in rat alveolar macrophages [104]. Future studies are needed to identify the upstream regulators of MFN2 that link mitochondrial dynamics, inflammatory responses, and oxidative stress during sepsis and other inflammatory diseases. The roles of MFN2 in controlling inflammatory responses are summarized in Table 2.

MFN2 and fibrotic responses

Mounting evidence suggests that MFN2 regulates profibrotic responses by modulating the function of macrophages. Hepatic macrophage deficiency due to alterations in TREM2 impaired hepatocytic mitochondria and energy production through the release of exosomes containing the MFN2-targeting micro RNA (miRNA) miR-106b-5p. TREM2 deficiency in mice accelerated the progression of nonalcoholic fatty liver disease (NAFLD) and increased the risk of sepsis [105]. MFN2 inhibits transforming growth factor-beta 1 (TGF- β 1)/Smad signaling and the formation of type I, type III, and type IV collagen, thereby ameliorating liver fibrosis and suppressing immune cell infiltration [106]. Hence, MFN2 prevents liver inflammation, fibrosis, and sepsis and is a promising therapeutic target for liver diseases. Moreover, MFN2-deficient macrophages have been shown to promote kidney fibrosis [107]. Future studies are warranted to clarify the molecular mechanisms by which MFN2 regulates fibrotic signals in different tissues and organs. The roles of MFN2 during fibrotic responses are summarized in Table 2.

MFN2 and atherogenic responses

MFN2 appears to inhibit atherosclerotic plaque formation and vascular inflammation by inhibiting extracellular

Table 2. The role of MFN2 in controlling inflammation, fibrosis, and atherogenesis.

Effects	Model	Mechanism	Ref
Inflammation			
Inhibition of metabolic-induced inflammation	BMDMs from <i>Mfn2</i> -cKO mice	Enhancement of IL-12 secretion by ghrelin	[103]
Alleviation of blood-brain barrier breakdown	Cardiac ischemia/reperfusion injured rats	Increase in claudin5 by pretreatment of mitochondrial fusion promotor M1	[16]
Suppression of LPS-induced mitochondrial dynamic disequilibrium	Murine NR8383 macrophage cells	Restoration of MFN1, MFN2, and OPA1 by activation of PKC- α /HO-1 signaling	[104]
Relieving mitochondrial dysfunction in nonalcoholic fatty liver disease and sepsis	BLN.CL2 hepatocytes; Human liver tissue; <i>Trem2</i> ^{-/-} mice	Decrease in a blockade MFN2 of <i>miR-106b-5p</i> through TREM2-mediated exosome	[105]
Fibrosis			
Alleviation of liver fibrosis	AML12 hepatocytes; BMDMs; CCl ₄ -induced liver fibrosis mice; HSC-T16 hepatic stellate cells	Suppression of TGF- β 1/Smad signaling and collagen production	[106]
Protection from kidney fibrosis	<i>Mfn2</i> -cKO, <i>PINK1</i> ^{-/-} , <i>Prkn</i> ^{-/-} mice; BMDMs; Peritoneal macrophages; Renal macrophages	Enhancement of mitophagy through PINK1-mediated MFN2 phosphorylation and recruiting Parkin	[107]
Atherogenesis			
Inhibition of intracellular lipid accumulation	<i>ApoE</i> ^{-/-} mice; RAW264.7 and THP-1 cells	Induction of cholesterol transporters by PPAR γ activation and inhibition of ERK1/2 and p38	[108]
Augmentation of mitophagy in oxidized LDL-exposed status	<i>Apoa1bp</i> ^{-/-} mice; BMDMs; HEK 293T cells; Human carotid tissue	Ubiquitination of MFN2 through interaction between Parkin and N-terminal domain of AIBP	[17]

AIBP, apolipoprotein A-I binding protein (encoded by *Apoa1bp* gene); ApoE, apolipoprotein E; BMDM, bone marrow-derived macrophage; ERK1/2, extracellular signal-regulated protein kinase 1/2; HO-1, heme oxygenase-1; IL-12, interleukin 12; LDL, low-density lipoprotein; LPS, lipopolysaccharides; MFN2, mitofusin2; *Mfn2*-cKO mice, *Mfn2*^{fl/fl}:*LysM*^{cre} conditional knock-out mice; OPA1, optic atrophy 1 (mitochondrial dynamin like GTPase); PINK1, phosphatase and tensin homolog-induced kinase 1; PKC- α , protein kinase C-alpha; PPAR γ , peroxisome proliferator-activated receptor gamma; TGF- β 1, transforming growth factor beta 1; TREM2, triggering receptor expressed on myeloid cells 2

signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase signaling and upregulating peroxisome proliferator-activated receptor-gamma [108]. Mitochondrial apolipoprotein A-I binding protein (AIBP; encoded by *APOA1BP*) is upregulated in atherosclerotic lesions and forms a complex with E3 ubiquitin-protein ligase PARK2 (Parkin), MFN1, and MFN2. AIBP induces autophagy by regulating MFN1 and MFN2 ubiquitination [17]. Therefore, MFN2 may represent a potential target to prevent atherogenic and inflammatory disorders by modulating autophagy and apoptosis in immune cells. The roles of MFN2 in atherogenic responses are summarized in Table 2.

MFN2 links immunometabolism to impact immune responses

Emerging evidence demonstrates the converging roles of mitochondrial dynamics and metabolism to regulate inflammatory and immune functions in various immune cells. For example, activated effector T cells have more fragmented mitochondria, whereas memory T cells maintain fused forms to influence specific characteristics in immunometabolic reprogramming, which is connected to distinct profiles of immune functions [58,109,110]. Conversely, differential metabolic cues also can control the mitochondrial dynamics to acquire specific morphologies that impact the immune functions [56,110]. Clearly, there is a reciprocal relationship

between mitochondrial metabolism and morphologies to finely tune the optimal immune responses to and protect cells from infectious and inflammatory insults. In this section, we focus on the current understanding of MFN2 in cross talks with immune cell metabolism and function.

We have recently shown that MFN2-induced HIF-1 α activation in macrophages is required for xenophagy activation, aerobic glycolysis, and inflammatory responses in response to infectious agents (Figure 1) [14]. HIF-1 α is a key transcription factor regulating aerobic glycolysis, immunometabolic reprogramming, and M1 polarization in macrophages [111,112]. Although MFN2 deficiency does not affect baseline glycolysis in macrophages [12], it is required for the induction of aerobic glycolysis during *M. tuberculosis* infection [14]. Intriguingly, MFN2-mediated HIF-1 α activation is augmented by mitochondrial respiratory chain complex I and ROS and contributes to macrophage-mediated inflammatory responses during infection [14]. Thus, MFN2 activation in macrophages is critical for the induction of inflammation in response to diverse stimuli. The MFN2-induced aerobic glycolysis during infection is at least partly mediated by HIF-1 α . However, it remains unclear why MFN2 but not MFN1 is required for immunometabolic remodeling in macrophages during infection. Furthermore, the mechanisms underlying mitochondrial respiratory chain complex I downregulation in MFN2-deficient macrophages remain elusive [14]. Although most evidence on the role

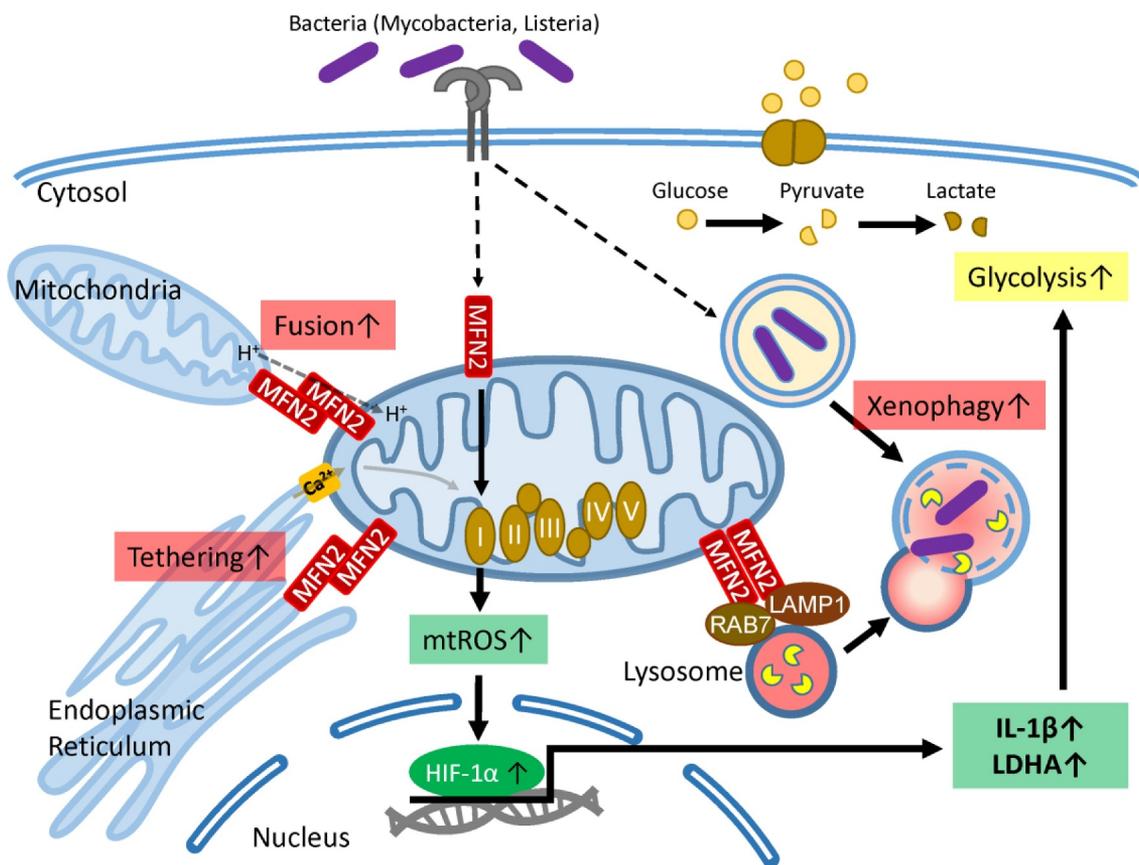


Figure 1. A schematic model of MFN2 and its metabolic roles in macrophages during infection during mycobacterial infection, macrophage MFN2 functions in the enhancement of host defense through activation of inflammatory cytokine generation and xenophagy via interaction with LAMP1. MFN2-mediated innate immune activation depends on the generation of mitochondrial reactive oxygen species (ROS), which are mainly produced by mitochondrial respiratory chain complex I. mitochondrial ROS are required for the induction of HIF-1 α that leads to the production of IL-1 β for inflammatory signaling and gearing aerobic glycolysis up by LDHA. Additionally, MFN2 is crucial for the maintenance of mitochondrial Ca²⁺ homeostasis and mitochondrial membrane potential through tethering mitochondria and endoplasmic reticulum. HIF-1 α , hypoxia-induced factor 1- α ; IL-1 β , interleukin 1 beta; LAMP1, lysosomal-associated membrane protein 1; LDHA, lactate dehydrogenase A; MFN2, mitofusion2.

of MFN2 in innate immunity is derived from mouse models, it is tempting to speculate that MFN2 plays a similar protective function in humans. Elucidation of the MFN2-mediated signaling networks will not only provide important insights into metabolic rewiring in innate immune cells but also uncover therapeutic targets to treat infections.

Conclusion

Accumulating evidence shows that mitochondrial dynamics and innate immune responses communicate and regulate each other to influence the infection outcome. It seems that a coordinated interaction between the mitochondrial network and the innate immune signal is vital for host defense. However, dysregulated mitochondrial architecture and function may lead to aberrant immunometabolism, chronic inflammation, and tissue

damage, resulting in poor infection outcomes. Therefore, the crosstalk between mitochondrial dynamics and innate immunity must be finely controlled to induce optimal antimicrobial responses while preventing unwanted tissue-destructive inflammation. In this regard, it is crucial to mechanistically characterize the roles of each component of mitochondrial fusion and fission during infection and inflammation.

In this article, we highlight the fine-tuning role of MFN2 in host responses against various infections and inflammatory stimuli. MFN2 appears to be a key regulator of innate immunity, as it interacts with MAVS, NLRP3, and various other signaling molecules during viral infections. Furthermore, MFN2 contributes to macrophage-mediated antibacterial responses, including phagocytosis, inflammation, and xenophagy. As MFN2 orchestrates inflammatory, atherogenic, and fibrotic responses, it may represent a promising target for the treatment of inflammatory and pathological conditions. Although

a previous study showed that single nucleotide polymorphisms in *MFN2* were not associated with the risk of leprosy in Chinese patients [113], clinical data on the role of *MFN2* in infectious diseases are limited. Furthermore, the pathophysiological roles of *MFN2* in human infectious diseases will need to be characterized in future clinical studies. Targeting *MFN2* to modulate the balance between innate immunity and pathogenic inflammation may be a worthwhile therapeutic strategy for various infectious and inflammatory diseases.

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Disclosure statement

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Data Availability

Data sharing not applicable – no new data generated.

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