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Mitochondrial control of innate immune responses

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Mitochondria are versatile organelles and essential components of numerous biological processes such as energy metabolism, signal transduction, and cell fate determination. In recent years, their critical roles in innate immunity have come to the forefront, highlighting impacts on pathogenic defense, tissue homeostasis, and degenerative diseases. This review offers an in-depth and comprehensive examination of the multifaceted mechanisms underlying the interactions between mitochondria and innate immune responses. We will delve into the roles of healthy mitochondria as platforms for signalosome assembly, the release of mitochondrial components as signaling messengers, and the regulation of signaling *via* mitophagy, particularly to cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling and inflammasomes. Furthermore, the review will explore the impacts of mitochondrial proteins and metabolites on modulating innate immune responses, the polarization of innate immune cells, and their implications on infectious and inflammatory diseases.

KEYWORDS

mitochondria, innate immunity, mtDNA, mitophagy, mitochondrial metabolism, MAVS, cGAS-STING, inflammasome

1 Overview of mitochondria in innate immunity

The mitochondrion is a functionally versatile organelle that has evolved from α-proteobacterium, a prokaryotic organism (1–3). According to the endosymbiont theory, an archaeon engulfed this bacterium about 2 billion years ago, forming a symbiotic relationship to meet its nutritional needs (2, 4–6). This bacterial origin of mitochondria probably explains innate immune responses triggered by recognizing unique mitochondrial components by various receptors (7). Modern mitochondria consist of five distinct components, including an outer and inner membrane, an intermembrane space, cristae formed by the infoldings of the inner membrane, and a matrix (4). One of the critical differences between mitochondria and other cellular organelles is that mitochondria have mitochondrial DNA (mtDNA), the circular DNA that encodes 13 proteins necessary for

oxidative phosphorylation complexes formation, 22 ribosomal RNAs, and 2 transfer RNAs required for mitochondrial RNA (mtRNA) translation (8, 9). Mitochondria are also highly dynamic organelles that change rapidly to meet the demands of various cellular processes (10, 11) *via* the balance of mitochondrial fusion and fission, which is crucial in regulating cellular metabolism, calcium homeostasis, reactive oxygen species (ROS) generation, and mitochondrial quality control (12). Mitochondria are considered the bioenergetic organelles and biosynthetic hubs that use glycolysis-derived pyruvate, fatty acids, and amino acids to generate adenosine triphosphate (ATP) *via* the oxidative phosphorylation process to maintain cellular homeostasis (4) and the intermediate producers for anabolic pathways (4, 13). However, a wide variety of studies have also illustrated mitochondria as signaling hubs that regulate numerous cellular biological events, including metabolism, cell fate determination, and immune responses through forming signaling platforms and releasing mitochondrial ROS (mtROS), mtDNA, and metabolites (4) (Figure 1).

The innate immune system, *via* a plethora of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and DNA sensors, is the first defense line against numerous microorganism invasions and sterile damages, such as those caused by necrotic cells-derived damage-associated molecular patterns (DAMPs) and cytokines (14–16). PRRs recognize distinct pathogen-associated molecular patterns (PAMPs) from pathogenic agents and DAMPs from damaged cells and tissues (17–19). Innate immune responses initiated by PRRs lead to significant production and processing of type I interferons (IFNs), cytokines, and proinflammatory chemokines, which modulate specific adaptive immune responses to eliminate pathogenic agents, repair damaged tissues, and maintain homeostasis (16–18). Mitochondrial functional components such as mtROS, mtDNA, cardiolipin, and the mitochondrial outer membrane (MOM) can directly activate or modulate innate immune responses (7). Meanwhile, dysfunctional mitochondria are involved in multiple inflammatory diseases (20), such as rheumatoid arthritis (RA) (21, 22), systemic lupus erythematosus (SLE) (23, 24), Sjögren's syndrome (25), neurodegenerative diseases (26–28), fibrotic diseases (29), and aging (30, 31). This review will focus on the crucial roles of mitochondria in various innate immune responses, including cytosolic nucleic acid sensing pathways (RLR-mitochondrial antiviral signaling protein (MAVS), and cGAS-STING), inflammasomes, TLRs signaling pathways, and immune cell activation (Figure 1).

2 Mitochondria act as platforms for signaling complex assembly

2.1 RLRs-MAVS signaling

Mitochondria are considered as critical signal platforms to facilitate the RLRs-MAVS signaling cascade by mediating the

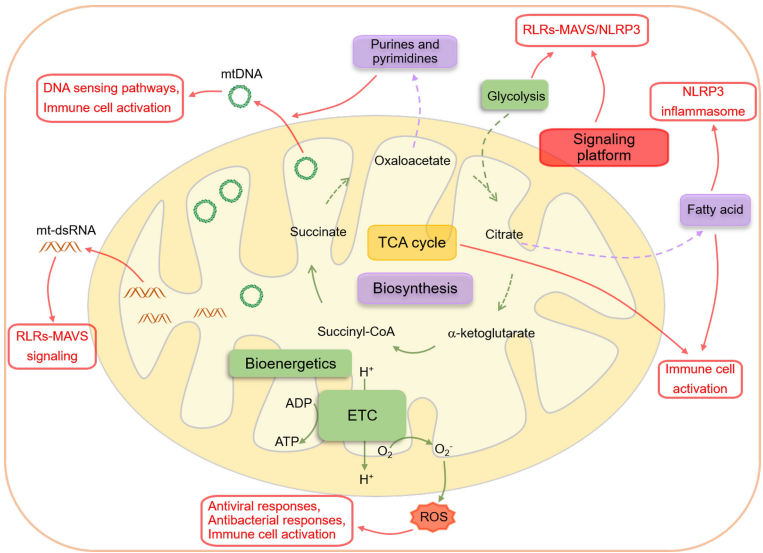

FIGURE 1
An overview of interactions between mitochondria and innate immune responses. Mitochondria are essential metabolic organelles that play an important role in maintaining cellular energy homeostasis through efficiently coupling the TCA cycle to the ETC. The TCA cycle, initiated by acetyl-CoA generated from glycolysis-derived pyruvate dehydrogenation or fatty acid oxidation, produces NADH and FADH2, which supply electrons to the ETC for ATP production (bioenergetics). The intermediates of the TCA cycle also participate in biomacromolecule generation, including glycogen, lipids, nucleotides, and proteins, through anabolic pathways (biosynthesis). In addition to their metabolic functions, mitochondria also serve as signaling hubs that regulate various cellular biological events, particularly immune responses, through several mechanisms. Firstly, the mitochondrial outer membrane acts as a platform for the aggregation of MAVS and the formation of the NLRP3 inflammasome, facilitating the RLRs-MAVS and NLRP3 inflammasome signaling pathways. Secondly, the cytoplasmic release of mtDNA and mtRNA from dysfunctional mitochondria can be recognized by PRRs and directly trigger innate immune responses. Finally, mitochondrial metabolites from the TCA cycle and metabolic byproducts, such as ROS, can precisely modulate the activation of innate immunity.

prion-like aggregation of MAVS (32) (Figure 2). Apart from nucleic acids-sensing TLRs located in endosomes (33), viral RNA can be recognized by RNA sensors in the cytoplasm (34). RIG-I (35) and melanoma differentiation-associated gene 5 (MDA5) (36), which belong to the DExD/H box RNA helicase family, are identified to detect cytosolic viral dsRNA. Upon viral dsRNA association, the conserved caspase activation and recruitment domains (CARDs) of these RNA sensors (37) are exposed and bind to the CARD domains of MAVS (38–41) located in the mitochondrial outer membrane, which drives the prion-like aggregation and activation of MAVS (32, 42). This aggregation recruits kinases TANK-binding kinase 1 (TBK1)/inhibitor of nuclear factor kappa-B kinase ϵ (IKKϵ) to activate the downstream transcriptional factors, interferon regulatory factor 3/7 (IRF3/7), and nuclear factor-κB (NF-κB). mRNAs of type I/III IFNs, interferon-stimulated genes (ISGs), and proinflammatory cytokines (43) are then transcribed and translated to restrict microbial infection, modulate adaptive immunity, and initialize tissue regeneration (44, 45). Intriguingly, the peroxisome (46, 47) and mitochondrial-associated endoplasmic reticulum membranes (MAM) (48) localization of MAVS and MAVS signalosomes have also been suggested, which induce or modulate the expression of ISGs and type III IFNs. Aberrant activation of RLRs-MAVS signaling is known to cause various autoimmune and autoinflammatory disorders (49).

Proteins that regulate mitochondrial dynamics (12), including the dynamin-related family of large GTPases mitofusin 1 (MFN1), mitofusin 2 (MFN2), optic atrophy 1 (OPA1), and dynamin-related protein 1 (DRP1), play critical roles in MAVS function. MFN1 facilitates the redistribution of MAVS on mitochondria to positively regulate RLR-MAVS signaling (50), while conversely, MFN2 represses MAVS aggregation (51). Additionally, both mitochondrial membrane potential ($\Delta\Psi(m)$) and membrane proteins can function as negative regulators of MAVS (7), such as NLR family member X1 (NLRX1), globular head domain of complement component C1q receptor (gC1qR), and Polo-like kinase 1 (PLK1). Activation of RLRs-MAVS signaling, in return, appears to contribute to the elongation of the mitochondrial network *via* interaction between MAVS and MFN1 (50, 52). Notably, disrupting the mitochondrial fragmentation function of DRP1 by TBK1-mediated S412 phosphorylation forms hyper-fused mitochondrial networks, which are required to effectively assemble large MAVS aggregates during innate RNA sensing (45). In this scenario, phosphorylation of DRP1 by TBK1 directly blocks the high-order oligomerization and mitochondrial division function of DRP1 (45). The TBK1-DRP1 axis also participates in nutrient-triggered mitochondrial dynamics and cell fate determination, suggesting that innate immunity also contributes to governing the morphology and physiology of mitochondria (45).

2.2 NOD-like receptor pyrin domain-containing 3 inflammasomes

Inflammasomes are multi-subunit complexes activated under stress conditions to regulate inflammatory responses and induce pyroptotic cell death (53, 54). They consist of a receptor (NLR family and PYHIN protein family members), the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD),

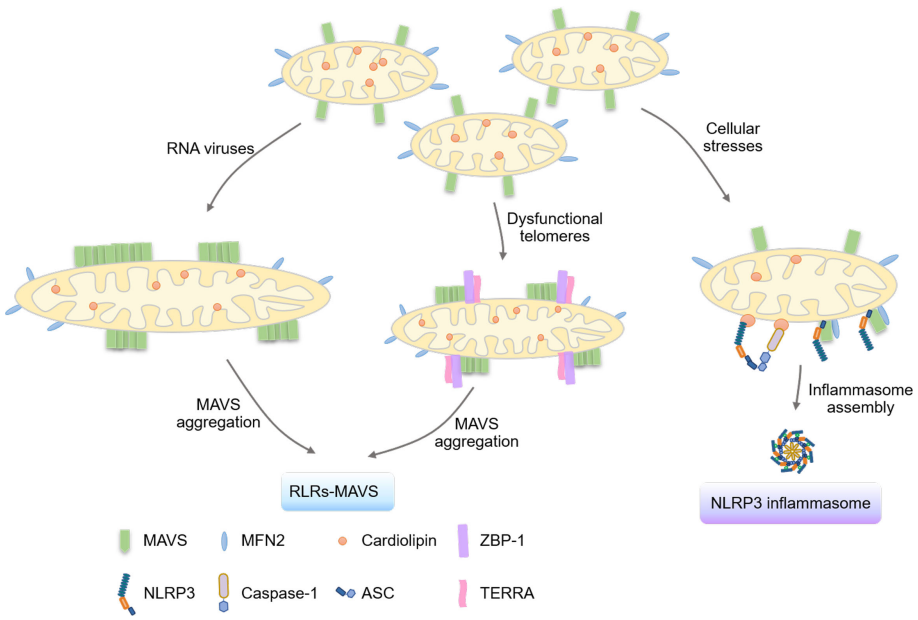

FIGURE 2
Mitochondria serve as platforms for signalosome formation. The mitochondrial outer membrane is critical in activating the innate immune system by serving as the bridging platform for the aggregation of the MAVS protein and the formation of the NLRP3 inflammasome. Upon RNA virus infection, the protein TBK1 phosphorylates and inactivates the mitochondrial fission protein DRP1, critical for the fusion of mitochondria and the aggregation of MAVS for activation. Moreover, the mitochondrial outer membrane serves as a platform for the localization of TERRA-ZBP1 complexes formed under dysfunctional telomeres, leading to the activation of the MAVS pathway. Additionally, mitochondrial proteins such as cardiolipin, MAVS, and MFN2 have been shown to regulate the assembly of the NLRP3 inflammasome by providing binding sites for NLRP3.

and the inflammatory cysteine protease pro-caspase 1 (55). Mitochondria act as scaffolds for NLRP3 inflammasome assembly. NLRP3 translocates from the endoplasmic reticulum (ER) to mitochondria and the MAM to form the NLRP3 inflammasome, which leads to the maturation of caspase-1-dependent proinflammatory cytokines IL-1β and IL-18 (56, 57). Cardiolipin, MAVS, and MFN2 have also been shown to regulate NLRP3 inflammasome assembly. For instance, upon mitochondrial stresses, cardiolipin, the mitochondrial inner membrane-associated phospholipid, is exposed on the mitochondrial surface to serve as the independent binding site for NLRP3 and full-length caspase-1 to assemble and activate the inflammasome (58, 59). Alternatively, MAVS forms a complex with MFN2 (60) to recruit NLRP3 to the mitochondria for NLRP3 inflammasome assembly during RNA viral infection (61–63).

2.3 ZBP1-mediated signaling

A recent study indicated the importance of mitochondrial signal platforms in telomere-mediated tumor suppression and aging. Z-conformation nucleic acid binding protein 1 (ZBP1) (64), an IFN-stimulated gene, functions as a cytosolic Z-nucleic acid sensor to regulate type I IFN signaling, inflammation, cell death, and tissue homeostasis (65). The study showed that mitochondria provide a scaffold for ZBP1-telomeric-repeat-containing RNAs (TERRA) complexes to activate MAVS-dependent interferon response during a replicative crisis (66).

These findings suggest that mitochondrial architecture, rather than a single mitochondria-related protein or product, is essential in maintaining various innate immune responses, which provide a broader perspective for studying the relationship between mitochondria, immunity, and diseases.

3 Regulation of innate immune responses by mitophagy

Maintaining mitochondrial health is crucial for properly functioning the immune system (67, 68). Two primary pathways for dealing with damaged mitochondria are proposed, including mitochondrial quality control mechanisms to immediately process defective or misfolded/mislocalized mitochondrial proteins and mitophagy that delivers irreversibly damaged mitochondria to the lysosome for degradation (31, 69). Mitophagy is mainly controlled by the ubiquitin (Ub)-dependent [PTEN-induced kinase 1 (PINK1)/Parkin RBR E3 ubiquitin-protein ligase (Parkin)] (70) or Ub-independent (specific LIR-containing receptor-dependent) pathways, such as those mediated by BNIP3 (BCL2 interacting protein 3), BNIP3L (BNIP3-like, also called NIX), FUNDC1 (FUN14 domain containing 1), PHB2 (prohibitin 2), BCL2L13 (BCL2-like protein 13), and FKBP8 (FK506-binding protein prolyl isomerase 8) (67, 71).

3.1 Mitophagic regulation of IFN signaling

Mitophagy plays a crucial role in regulating type I IFN signaling activation. Deficient mitophagy caused by autophagy related 5 (ATG5) ablation increases mtROS production and elevates levels of MAVS, promoting the activation of the type I IFN pathway (72). Sequestosome 1 (SQSTM1/p62)-dependent mitophagy (73) and mitophagy induced by viral proteins (71, 74) also regulate the type I IFN response. By contrast, NIX-dependent mitophagy acts as an intrinsic negative regulator of the RLRs-MAVS axis by preventing spontaneous aggregation of endogenous MAVS in the absence of viral infection (75). Besides, the disruption of mitophagy caused by PINK1 and Parkin mutations contributes to the activation of the cGAS-STING signaling pathway *via* cytosolic accumulation of mtDNA (76), which will be elaborated on later.

3.2 Mitophagic regulation of inflammasomes

It has been found that mitophagy helps to repress NLRP3 inflammasome activation by reducing mtROS production and mtDNA release *via* clearing damaged mitochondria (57, 67), while Parkin plays a crucial role in mtROS-NLRP3-mediated inflammatory response by regulating mitophagy activation (77). Defective mitophagy and mtROS accumulation induced by receptor-interacting protein kinase 2 (RIPK2) deletion lead to increased morbidity and mortality by accelerating IL-18 secretion and inflammatory activation during influenza A virus (IAV) infection (78). NF-κB signaling is also vital in anti-inflammatory by inducing the expression of SQSTM1/p62 to promote autophagic clearance of damaged mitochondria in lipopolysaccharide (LPS)-treated macrophages (79). Besides Ub-dependent mitophagy, FUNDC1-mediated Ub-independent mitophagy can control the secretion of inflammasome-related IL-1β (80). Additionally, mitophagy regulates the activation of AIM2 (absent in melanoma 2) (81) and NLRC4 (NLR-family CARD domain-containing protein 4) (82) inflammasomes, revealing a widespread role of mitophagy in controlling inflammasome-mediated innate immune responses.

4 Regulation of innate immune responses by mitochondrial apoptosis

Mitochondria are required to regulate cell apoptosis through the intrinsic pathway, which facilitates many biological processes, including the regulation of inflammatory responses (83, 84). During mitochondrial apoptosis induced by various cellular stresses, the pro-apoptotic effectors BCL2-associated X protein (BAX) and BCL2 homologous antagonist/killer protein (BAK) are activated by BH3-only proteins to assemble the mitochondrial outer membrane permeabilization (MOMP) (84, 85). MOMP allows the release of mitochondrial soluble proteins to activate apoptotic caspases, including cytochrome *c* which binds to apoptotic peptidase

activating factor 1 (APAF1) to form the apoptosome (86), second mitochondrial-derived activator of caspases (SMAC) and high-temperature requirement protein A2 (HtrA2/OMI) which induce the degradation of the caspase inhibitor XIAP (X-linked inhibitor of apoptosis protein) (84).

Mitochondrial apoptosis impacts the type I IFN pathway and inflammation *via* MOMP in several ways (84). Under conditions of caspase deficiency, stimuli induce mitochondrial apoptosis to promote NF-κB signaling through the upregulation of NF-κB-inducing kinase (NIK) resulting from MOMP formation and inhibitor of apoptosis proteins (IAPs) degradation (87). This phenotype has also been observed with SMAC-mimetic compounds treatment (88, 89), but an exception exists. Due to the redundancy of other mitochondrial IAP binding proteins, deletion of SMAC and OMI fails to prevent MOMP-induced IAPs degradation (90, 91). Therefore, further research is needed to explain the mechanism of IAPs depletion by MOMP. Interestingly, MOMP-related IAPs degradation in macrophages can activate caspase 8 to promote the maturation of IL-1β and the activation of NLRP3 inflammasome (92, 93). In addition, the activation of apoptotic caspases-induced potassium efflux also contributes to NLRP3 inflammasome formation (94). Furthermore, mitochondrial nucleic acids, such as mtDNA and mtRNA, released through MOMP, mitochondrial permeability transition pore (MPTP), or voltage-dependent anion-selective channels (VDAC), can robustly activate cytosolic nucleic acids sensing pathways, which will be discussed in the next section. However, the exact role and nature of the mitochondrial inner membrane during these molecular events are still poorly understood.

It is worth noting that in most conditions, mitochondrial apoptosis is non-inflammatory. Apoptotic caspases have been found to inhibit inflammation by directly cleaving inflammatory components such as MAVS, cGAS, and IRF3 (95). Additionally, they can inhibit protein translation and canonical protein secretory processes (84, 96) and induce rapid cell death to remove damaged cells (97). However, other apoptotic caspase-independent mechanisms also contribute to MOMP-dependent anti-inflammatory responses. For example, MOMP induces the release of PNPase-polynucleotide phosphorylase (PNPT1), which degrades mtRNA to block the RLRs-MAVS pathway (98). Mitophagy is another effective approach to maintaining non-inflammatory apoptosis (99). Despite the identification of mitochondrial apoptosis in regulating innate immunity through MOMP, more in-depth studies are still needed to understand the specific pathways and pores or channels associated with the release of mitochondrial-related DAMPs.

5 Innate immune responses triggered by mtDNA

mtDNA is located in the mitochondrial matrix, which associates with the necessary cofactors for mtDNA transcription, replication, and repair (100–103). In 2004, Collins et al. by injecting mtDNA into the joints of mice, demonstrated that oxidized mtDNA might play a role in inflammation, which resulted in inflammation and arthritis (104). This discovery led to a new avenue of research on how mtDNA functions as a critical DAMP under stress conditions. Various innate immune receptors have been known to recognize mtDNA for initiating innate immune responses, as shown in Figure 3.

5.1 Mechanisms of mtDNA release

Although a wide variety of studies have demonstrated the importance of cytosolic mtDNA in innate immunity, the mechanisms explaining the translocation of mtDNA from the mitochondrial matrix to the cytosol are still not well understood. In 2014, two independent studies uncovered that mtDNA is released during mitochondrial apoptosis (105, 106). Follow-up studies demonstrated that apoptosis-related MOMPs allow the rupture of the mitochondrial inner membrane and mtDNA release (107–110). Additionally, under subtle stress-induced non-apoptotic conditions, only a fraction of mitochondria undergoing permeabilization (minority MOMPs) also cause the cytosolic release of mtDNA and the activation of cGAS-STING signaling, the major pathway sensing of mtDNA in the cytosol (111, 112). Furthermore, VDAC, which is used for metabolites and ions transport (113), can oligomerize to form pores in the MOM under oxidative stress conditions (114) and interact with mtDNA and form oligomers in the MOM to permit the release of short mtDNA fragments and trigger type I IFN response (115), while MPTP, formed in the mitochondrial inner membrane under various cellular stress conditions, is considered to regulate the release of small mtDNA fragments (116, 117). Notably, cytoplasmic accumulation of TAR DNA binding protein 43 (TDP-43), a disease hallmark of amyotrophic lateral sclerosis (ALS), can trigger mtDNA release *via* the MPTP and VDAC1 oligomers to upregulate the NF-κB and cGAS-STING signaling (118). Meanwhile, the endonuclease Flap endonuclease 1 (FEN1) has been found to cleave oxidized mtDNA into 600-650 bp fragments that can be released from mitochondria *via* MPTP and VDAC-dependent channels (119). Although MOMP-induced mtDNA release in apoptotic cells has been discussed in detail, the regulations of mtDNA release in living cells under moderate-level stress and the role of the mitochondrial inner membrane in mtDNA release are still not well understood. These mechanisms of mtDNA release are summarized in Figure 3.

5.2 mtDNA triggers cGAS-STING signaling

cGAS is a primary cytosolic DNA receptor that can recognize both exogenous and endogenous DNA and induce the production of 2'3'-cyclic GMP-AMP (cGAMP) (120, 121), which activates the adaptor protein STING (122–125) to elicit type I IFN and inflammatory responses (126). In addition to its role in response to viral and bacterial DNAs (127–131), the cGAS-STING pathway also elicits and controls self-DNA (nuclear DNA and mtDNA)-induced innate immune responses (132), inflammatory diseases

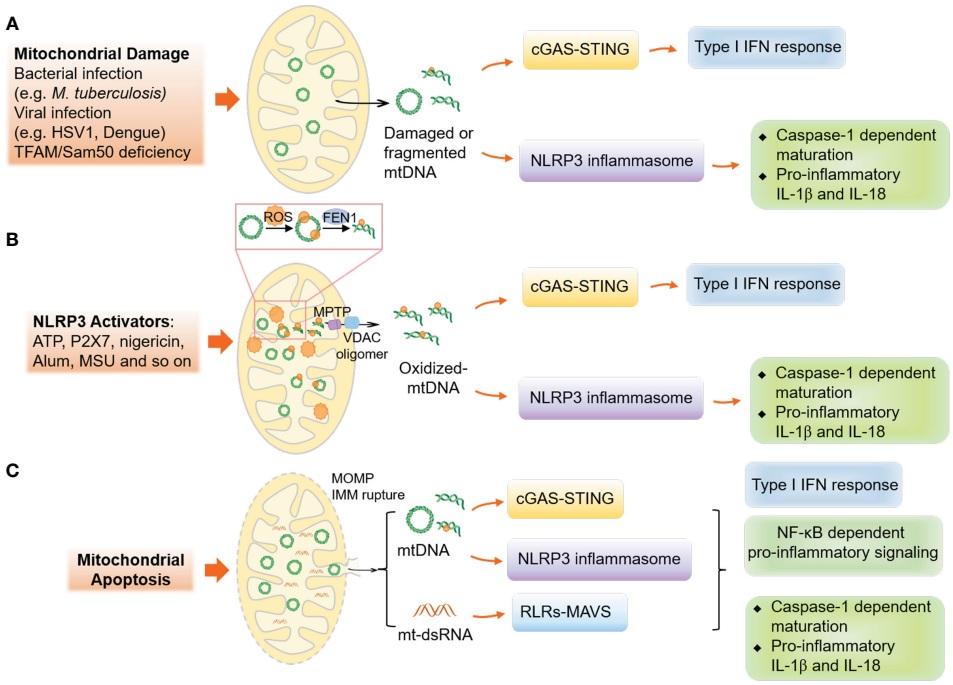

FIGURE 3
Mechanisms of mitochondrial DNA release and mtDNA-associated innate immune responses. **(A)** The disruption or stress of mitochondria, caused by infections like bacterial or viral, can lead to the release of damaged or fragmented mtDNA into the cytoplasm, activating the cGAS-STING and NLRP3 inflammasome responses. **(B)** In non-apoptotic cells, the activation of NLRP3 results in oxidative stress on mitochondria, causing the modification and cleavage of mtDNA by the endonuclease FEN1. The MPTP and VDAC oligomers in the mitochondrial outer membrane facilitate the release of fragmented mtDNA. **(C)** In apoptotic cells, the formation of BAX and BAK oligomers leads to MOMP, causing the release of mtDNA and mt-dsRNA and activating innate immune responses.

(133, 134), antitumor immunity (135–137), neurodegenerative diseases (138), and diverse cellular functions (139) including protein synthesis (140) and glucose metabolism (141).

Various signals can disrupt mitochondrial integrity during pathogen infections. For instance, IAV triggers the release of mtDNA through the proton-selective ion channel (viroporin) activity of the M2 protein in a MAVS-dependent manner and evades the recognition of cGAS by interacting with NS1 proteins and mtDNA (142). Infections of herpes simplex virus 1/2 (HSV-1/HSV-2) have been found to cause stress and elimination of mtDNA, which regulates antiviral responses and ISG expression (143–146). Interestingly, infections with RNA viruses, such as Dengue virus, can activate the cGAS-STING (147–149) and TLR9 pathways (150) by causing mitochondrial stress and oxidized mtDNA release. Certain strains of *Mycobacterium tuberculosis* can also trigger cGAS-STING activation (128, 130, 151) by inducing mtDNA release (152). During pathogen infections, IL-1β secretion can upregulate antimicrobial immune responses by releasing mtDNA to activate the cGAS-STING signaling pathway (153), providing new insights into the mechanisms by which numerous cytokine-related pathways boost inflammatory responses. These results suggest that maintaining mtDNA homeostasis may be a beneficial regulator of innate antiviral immunity.

In addition to pathogen infection, the disruption of mitochondrial DNA integrity, replication, and repair can activate the cGAS-STING pathway (133). For instance, mitochondrial transcription factor A (TFAM) deficiency can cause cGAS-STING activation by damaging the nucleoid structure and accumulating cytosolic mtDNA (8, 145, 154), while depletion of sorting and assembly machinery component 50 (Sam50) (155) and endonuclease G (115) similarly induces mtDNA-related cGAS-STING activation in hepatocytes and other cells. Additionally, chemotherapeutic drugs (156), pyrimidine nucleotide carrier SLC25A33 overexpression, as well as the inhibition of *de novo* pyrimidine synthesis (157), can trigger mtDNA leaking and cGAS-STING activation. As a result, the importance of cGAS-STING in sensing mtDNA and inflammatory-related diseases has made it a highly targeted drug (158).

5.3 mtDNA serves as an inflammasome activator

Nakahira et al. were the first to report that the MPTP-induced cytosolic accumulation of mtDNA and mtROS strengthens NLRP3 inflammasome activation in autophagic protein-deficient macrophages (159). mtDNA oxidized by mtROS is preferred for NLRP3 recognition (79, 160–162). Activating inflammasomes and caspases also regulate mtDNA release by causing mitochondrial damage. Notably, the role of NLRP3 may not promote mtDNA release but rather stabilize it in the cytoplasm (162), while other studies indicate that NLRP3 activation amplifies the mitochondrial damage and mtDNA release (163, 164). Caspase-1 activated by inflammasomes destroys mitochondria by triggering multiple

pathways to promote the production of mtROS, the dissipation of $\Delta\Psi(m)$, and the permeabilization of mitochondrial membranes (163). Moreover, NLRP3 promotes caspase-2 activation and BID cleavage during infection-related ER stress to facilitate mitochondrial permeabilization (164). Further studies are therefore needed to clarify those conflicting data and better understand the relationship between mtDNA and NLRP3.

5.4 mtDNA and TLR9

TLR9 is a member of the TLRs family and is the first TLR discovered to sense bacterial DNA with hypomethylated CpG motifs, and this recognition activates the MAPK and NF-κB signaling pathways, leading to an inflammatory response (134, 165). Interestingly, TLR9 has also been found to recognize mtDNA released into the bloodstream during systemic inflammatory response syndrome (SIRS) and activate a p38-mediated inflammatory response (166, 167). mtDNA released from dying cells can form a complex with the antimicrobial peptide LL-37 to evade the degradation by DNase II and activate TLR9 response (168). In addition, the mtDNA-TFAM complex released from necrotic cells augments proinflammatory response by promoting the activation of receptor for advanced glycation end products (RAGE) and TLR9 (169, 170). Mitochondrial dynamics can also play a role in TLR9-induced inflammation by affecting mtDNA stability (171, 172). The absence of OPA1 in mice results in muscle atrophy and premature death due to the accumulation of damaged mitochondria and disruption of mitophagy, leading to mtDNA-related TLR9-mediated inflammation (173). Circulating mtDNA has been confirmed as an endogenous TLR9 agonist in various studies and has been implicated in several inflammatory-related diseases (9), including rheumatoid arthritis (22), atherosclerosis (168, 174), hypertension (175), acute liver injury (176) and non-alcoholic steatohepatitis (177).

5.5 mtDNA and neutrophil extracellular traps

mtDNA can also play a role in the extracellular space by engaging the cGAS-STING pathway and/or the TLR9 pathway on neighboring immune cells (24, 178, 179), such as in the scenario of neutrophil extracellular traps (NETs) during microbial infection and sterile inflammatory diseases (9, 180). NETs are vast extracellular decondensed-chromatin networks containing a plethora of microbial-killing proteins and DNAs (180, 181). In healthy neutrophils with oxidative damage, entire TFAM-mtDNA complexes are expelled into the extracellular space, and mtDNA can be transported into lysosomes to avoid recognition by TLR9 and maintain the immunological silence of plasmacytoid dendritic cells (pDCs) (179). Conversely, oxidized mtDNA is released in systemic lupus erythematosus (SLE) patients and activates inflammatory responses (179). The formation of oxidized mtDNA-containing NETs can be stimulated by ribonucleotide immune complexes (RNP-ICs) (178) and continuous IFN-α signaling (183), which further strengthens the cGAS-STING pathway. Additionally, lymphocytes and eosinophils can engage the type I IFN response in peripheral blood mononuclear cells by secreting mtDNA-containing webs (184, 185). These findings highlight the importance of mtDNA in both intracellular and extracellular pathways in regulating immune responses.

6 mtRNA in triggering RLR-MAVS signaling

The mitochondrial genome contains both heavy (H) and light (L) strands for the transcription of functional RNAs and several non-coding RNAs (186, 187). Under normal conditions, non-coding RNAs are degraded by the RNA degradosome to prevent the formation of mitochondrial double-stranded RNA (mt-dsRNA) (188, 189). However, during MOMP, mt-dsRNA can be released into the cytoplasm (110, 190), and recognized by MDA5, leading to the activation of the type I IFN response (110, 190). Interestingly, dysfunction of the mtRNA degradosome component, PNPase, can lead to the activation of the type I IFN response by causing the accumulation of mt-dsRNA (190, 191). Additionally, the protein kinase R (PKR) can also detect mt-dsRNA under stress conditions (192) (Figure 3).

7 Regulation of innate immunity by mitochondrial metabolism

The metabolites generated from glycolysis, the electron transport chain (ETC), and the tricarboxylic acid (TCA) cycle play a crucial role in regulating innate immunity, including the type I IFN response, the NLRP3 inflammasome, and immune cell activation.

7.1 mtROS in innate immune responses

mtROS, the "so-called" byproducts of the mitochondrial respiration chain, is generated at complexes I and III of the ETC in response to hypoxia, substrate availability alteration, and abnormal mitochondrial conditions (193). mtROS has been demonstrated to play a crucial role in innate immunity (194) (Figure 4).

7.1.1 mtROS and innate antiviral response

Mitophagy has been shown to regulate mtROS production during viral infection, promoting the RLRs-MAVS signaling (72). In this scenario, cytochrome *c* oxidase 5 b (COX5B), a subunit of the cytochrome *c* oxidase complex, serves as a negative feedback effector of the RLRs-MAVS pathway by repressing mtROS generation upon Sendai virus (SeV) infection (195). On the other hand, the IAV protein M2 positively regulates MAVS aggregation by controlling mtROS production (196). Additionally, the zinc finger protein tetrachlorodibenzo-p-dioxin (TCDD)-inducible

poly (ADP-ribose) polymerase (TiPARP) serves as a PRR for the RNA of the Sindbis virus and can be redistributed by mtROS from the nucleus to the cytoplasm, protecting against viral infection in mice (197). These intriguing findings propose the intricate interplay between mtROS and innate immune signaling pathways in response to viral infections.

7.1.2 mtROS and NLRP3 inflammasomes

The activation of the NLRP3 inflammasome can be triggered by numerous PAMPs and DAMPs that depend on mtROS generation. For instance, inhibiting the function of mitochondrial respiratory complexes I and III by small molecules can induce mtROS generation and NLRP3 activation (56, 57, 198). During oxidative stress, increased mtROS and Ca^{2+} are detected, which promote the formation of MPTP, and increased mitochondrial Ca^{2+} further facilitates the production of mtROS in this situation (199, 200). mtDNA released into the cytoplasm can be oxidized by mtROS, leading to NLRP3 inflammasome activation (162). It is noted that mtROS only activates the NLRP3 inflammasome but not other inflammasome subsets (56). Aldolase A (ALDOA) also plays a role in maintaining NLRP3 inflammasome activation by restricting activation of the AMP-activated protein kinase (AMPK) and mitophagy (201).

7.1.3 mtROS and neutrophil activation

mtROS also significantly contributes to neutrophil activation, such as neutrophil degranulation, NET formation (178), Ca^{2+} ionophores induced NETosis (202), and cytokines production (203). *In vitro* studies have shown that inhibiting the production of mtROS by the antioxidant SkQ1 can accelerate the apoptosis of the chemotactic peptide fMLP-activated neutrophils (204). However, in synoviocytes, reducing the mitochondrial membrane potential and increasing ROS production through methotrexate (MTX) treatment can induce mitochondrial apoptosis (205).

7.1.4 mtROS in antibacterial and anti-parasite activities

Evidence suggests that mtROS functions as a crucial agent in antibacterial defense (194). For example, accumulation of mtROS has been observed in TLR1, 2, and 4-activated macrophages to enhance the bactericidal activity of these cells by activating the downstream NF-κB response (206), which is achieved through TRAF6-mediated ubiquitination and enrichment of ECSIT (evolutionarily conserved signaling intermediate in Toll pathways), a protein involved in mitochondrial respiratory chain assembly (207). Additionally, mtROS is necessary to trigger p38 signaling upon TLR4 activation (194). In addition to TLRs responses, the IFN-γ signaling pathway also boosts the production of mtROS through the nuclear receptor estrogen-related receptor α (ERRα) to clear cellular Listeria monocytogenes (208). Patients with tumor necrosis factor receptor-associated periodic syndrome are more sensitive to LPS stimulation due to increased mtROS and inflammatory cytokines (209).

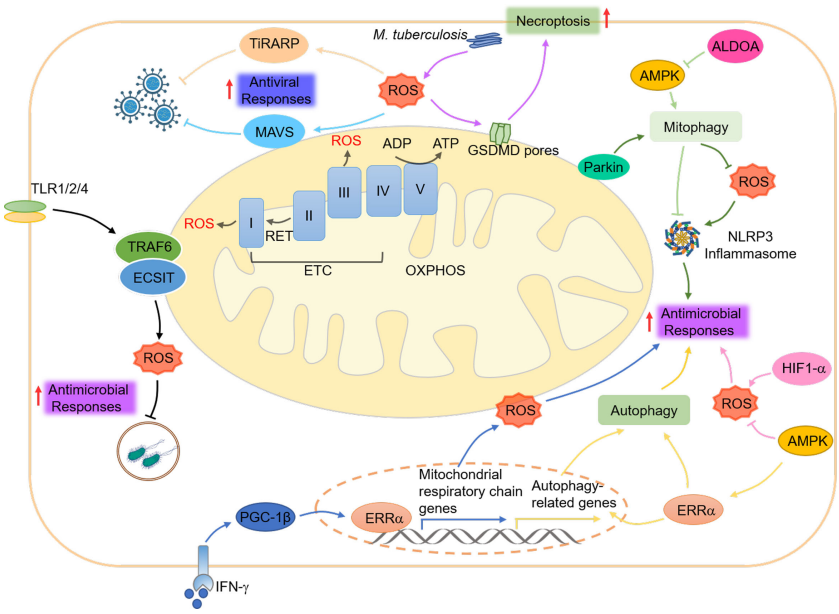

FIGURE 4
Mitochondrial ROS and innate immunity. mtROS is produced at complexes I and III of the ETC in response to hypoxia, changes in substrate availability, and abnormal mitochondrial or cellular conditions. mtROS plays a role in coordinating innate immune responses, including antiviral signaling through the RLRs-MAVS, antimicrobial responses through the NLRP3 inflammasome and TLR pathways, and necroptosis through GSDMD. The cellular metabolism regulator AMPK helps to maintain a balance of mtROS and promote antimicrobial responses by inhibiting their generation, while HIF1-α enhances their production. AMPK also regulates the activation of the NLRP3 inflammasome by suppressing mtROS and promoting autophagy, which ERRα regulates through post-translational and transcriptional mechanisms. Additionally, the key regulator of mitophagy, Parkin, controls mtROS production and the activation of the NLRP3 inflammasome. Finally, increased cytosolic mtROS have been found to drive the mitochondrial localization of GSDMD, leading to the formation of a mitochondrial GSDMD pore and the acceleration of necroptosis.

The metabolic balance regulators AMPK and mechanistic target of rapamycin (mTOR) contribute to antimicrobial responses by regulating mtROS production. For example, during some pathogenic bacterial infections, AMPK inhibits mtROS production, while hypoxia-inducible factor 1α (HIF-1α) upregulates its generation to maintain proper levels and promote antimicrobial responses (210, 211). HIF-1α also combines with mTOR to control antimicrobial signaling through glycolysis, with mTOR promoting mtROS accumulation in monocytes (212, 213). However, in *Trypanosoma cruzi*-infected macrophages, mTOR inhibition increases mtROS production and NLRP3 inflammasome activation to clear cytoplasmic parasites (214). Interestingly, in *Mycobacterium tuberculosis*-infected Lrrk2^{G2019S} mice, increased cytosolic mtROS can directly associate with gasdermin D (GSDMD), a member of the plasma membrane pore-forming family involved in pyroptosis, to form mitochondrial GSDMD pore, promoting mtROS release and necroptosis, leading to hyperactivation of inflammation and severe immunopathology (215). These studies illuminate the crucial role of mtROS in precisely regulating the autophagy-inflammasome axis to control innate immune activation.

7.2 Glucose metabolism and MAVS signaling

Glucose metabolism has been shown to suppress RLR-induced interferon production through lactate, which directly binds to MAVS and disrupts its mitochondrial localization (216). MAVS directly binds to hexokinase-2 (HK-2) in its resting state to maintain its kinase activity and proper glycolysis process (216). However, research has also shown that the cytosolic phospholipase A2 (cPLA2) disrupts the interaction between MAVS and HK-2 in astrocytes, leading to increased NF-κB-related inflammation (217) (Figure 5). Notably, a recent study revealed a critical role of AMPK in potentiating both RLRs-MAVS and cGAS-STING signaling and antiviral responses *via* direct AMPK-mediated phosphorylation of TBK1 at S511 residue (141). These mutual interactions between glucose metabolism and innate immunity indicate an intricate and delicate network of immune responses related to mitochondria.

7.3 Mitochondrial metabolism and NLRP3 inflammasomes

Interplay of N-acetylglucosamine (GlcNAc) with hexokinase can lead to inflammatory responses in the host by disrupting hexokinase localization and activating NLRP3 inflammasomes (218) (Figure 5). Similarly, inhibiting glycolysis after the priming step through chemical treatment can activate the NLRP3 inflammasome (219). Free fatty acids (FAs) from diet or FA synthesis can activate the NLRP3 inflammasome (220–222). Therefore, activation of AMPK during fasting or caloric restriction suppresses FA-induced NLRP3 inflammasome activation by promoting autophagy and limiting ROS production (220, 223), in contrast to its role in potentiating nucleic acid signaling (141). Besides, in a state of low blood glucose, fatty acid oxidation provides energy and leads to the production of ketone bodies like β-hydroxybutyrate (BHB), which inhibit the activation of the NLRP3 inflammasome by inhibiting K^+ efflux (224). By activating citrate synthase and inhibiting FA uptake, BHB reduces the level of mitochondrial acetylation, which represses NLRP3 inflammasome formation, mitochondrial dysfunction, and heart fibrosis (225). Butyrate, a short-chain fatty acid (SCFA), by contrast, inhibits NLRP3 activation by reducing pro-IL-1β levels (226).

7.4 Mitochondrial metabolism and macrophage polarization

Macrophages can be differentiated into two main distinct lineages on the type of activation signals they have received: M1 macrophages, characterized by a proinflammatory phenotype, and M2 macrophages, characterized by an anti-inflammatory and pro-fibrotic phenotype (227, 228). Studies have shown that oxygen consumption and reliance on mitochondrial metabolism differ between M1 and M2 macrophages (228–230). For example, M1 macrophages show reduced while M2 macrophages exhibit increased mitochondrial metabolism. Notably, the inhibition of the ECT through reverse electron transport (RET) increases the production of mtROS, stabilizes HIF-1α, and enhances the inflammatory response, favoring M1 macrophage polarization (228). Moreover, inhibiting fatty acid oxidation promotes M1 macrophage activation and suppresses M2 macrophage phenotypes (228).

Metabolites from the TCA cycle also play a vital role in controlling macrophage polarization by regulating macrophage chromatin modifications, DNA methylation, and protein post-translational modifications (231) (Figure 5). Acetyl-CoA, the starting point of the TCA cycle (231–235), provides acetyl groups for acetylation and influences the production of proinflammatory molecules such as nitric oxide (NO), ROS, and prostaglandin E2 (PGE2) in response to stimuli such as LPS (236). Acetyl-CoA in IL-4-related M2 macrophages, however, increases histone acetylation and M2 macrophage-related gene expression (237). The immune-responsive gene 1 protein (IRG1) produces itaconate (238, 239), which has been found to accumulate in response to *Mycobacterium tuberculosis* infection (182) and LPS stimulation (240) and exert anti-inflammatory effects (241). On the other hand, α-ketoglutarate (α-KG) promotes M2 polarization in LPS-stimulated M1 macrophages through epigenetic reprogramming and suppression of the NF-κB signaling pathway (242). Succinate similarly contributes to macrophage activation by stabilizing HIF-1α and increasing the transcription of IL-1β (243, 244), while fumarate accumulates in LPS-activated macrophages (243, 245) and modulates pro-inflammation by inhibiting lysine-specific histone demethylase 5 (KDM5) enzyme (246). These repeated observations indicate an essential role of mitochondrial metabolites in the polarization and activation of macrophages.

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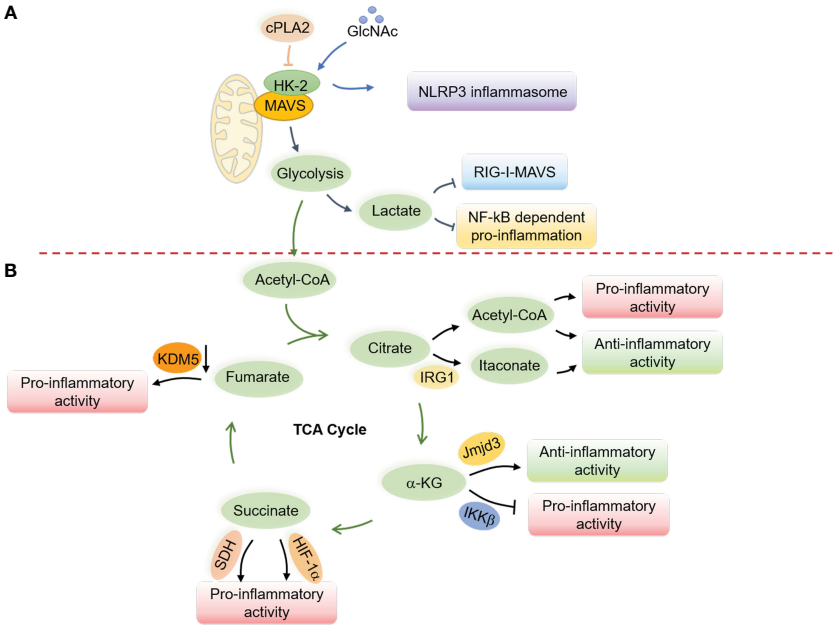

FIGURE 5
Regulation of innate immune responses and macrophage activation by mitochondrial metabolism. **(A)** Glucose metabolism regulates the RLRs-MAVS signaling and the NLRP3 inflammasome through the hexokinase 2 (HK-2) and lactate generation. In a resting state, MAVS interacts with HK-2 to maintain its kinase activity and proper glycolysis process, while lactate production interrupts the mitochondrial localization of MAVS to suppress the RLRs-MAVS signaling. cPLA2 disrupts the interaction of MAVS and HK-2, thereby boosting NF-κB-related inflammation. GlcNAc, derived from the peptidoglycan of the bacterial cell wall, can interact with HK-2 to promote its redistribution into the cytoplasm and facilitate the activation of the NLRP3 inflammasome. **(B)** Metabolites from the TCA cycle control macrophage polarization by regulating chromatin modifications, DNA methylation, and post-translational modifications of proteins. Elevated cytosolic acetyl-CoA increases histone acetylation to promote the expression of inflammatory molecules and determine macrophage polarization. Itaconate, derived from cis-aconitate, engages anti-inflammatory activity in LPS-stimulated macrophages by inhibiting mtROS production, reducing succinate dehydrogenase (SDH) activity, blocking the inhibitor of NF-κB, the NF-κB-binding protein (IκBζ), and stabilizing nuclear factor erythroid 2-related factor 2 (Nrf2). α-KG engages anti-inflammation *via* Jmjd3-dependent metabolic and epigenetic reprogramming and inhibits the proline hydroxylation of IKKβ to repress pro-inflammation. Succinate facilitates proinflammatory activity by enhancing ROS production through stabilizing HIF-1α and being oxidized by SDH. Fumarate increases proinflammatory activity by inhibiting the KDM5 histone demethylase activity, thereby promoting the gene transcription of TNFα and IL-6 cytokines.

8 Concluding remarks and perspective

Mitochondria are essential cellular organelles that play a critical role in maintaining the energy balance of cells by linking the TCA cycle to the ETC. This efficient energy transfer from the TCA cycle to the ETC allows cells to generate ATP, an energy source for various cellular processes. In addition to their metabolic functions, mitochondria serve as signaling hubs that regulate various cellular biological events, particularly innate immune responses. This complex relationship between mitochondria and innate immunity involves several processes maintaining mitochondrial homeostasis. Firstly, mitochondria act as scaffolds for signaling molecules, facilitating the activation of innate immune responses by forming signal complexes. For instance, the aggregation of the antiviral signaling molecule MAVS on the mitochondrial outer membrane acts as a platform for forming the antiviral response. Similarly, the assembly of the NLRP3 inflammasome on the mitochondrial outer membrane serves as a platform for activating the inflammatory response. These scaffold functions of mitochondria play a crucial role in regulating innate immune responses. Secondly, mitochondrial metabolism also plays a key role in regulating innate immune responses. For example, the production of ROS and metabolites from the TCA cycle, including citrate, itaconate, and succinate, regulate the secretion of inflammatory cytokines, antimicrobial responses, and immune cell activation. The precise mechanisms underlying the regulation of these metabolic products in modulating innate immune responses are complex and still require further investigation. Finally, intracellular detritus from damaged mitochondria, such as mtDNA and mtRNA, serve as DAMPs that can directly activate antiviral and inflammatory responses. This mechanism of innate immune activation directly links mitochondrial dysfunction and innate immune responses and highlights the importance of mitochondrial homeostasis in regulating innate immunity.

Mitochondrial dysfunction lies at the heart of a wide array of human diseases, encompassing neurodegenerative conditions, chronic inflammation, autoimmune disorders, and metabolic diseases. Various interactions have been identified between innate immunity and various aspects of mitochondria, including their membranes, dynamics, components, and metabolites. Despite this, our comprehension of the role of mitochondria-related immune responses in the onset and progression of diseases remains incomplete. The specific nature of the signaling inputs and mechanisms governing mtDNA release, a major contributor to

inflammatory responses, is not yet fully understood. Moreover, mitochondrial dysfunction is implicated in age-related diseases, particularly those involving the uncontrolled release of mitochondrial components such as mtDNA, ATP, succinate, and mtROS during aging. What causes the close association between mitochondrial integrity and aging, or conversely, is the loss of mitochondrial integrity a key driver of the aging process? In addition, various pathogen infections can trigger minor MOMP through non-lethal stimuli. Is this phenomenon a beneficial immune warning system or a detrimental factor in developing mitochondria-associated diseases? We anticipate that integrating cutting-edge techniques like high-throughput screening, omics analyses, and tissue imaging, together with the application of diverse genome-editing technologies, will significantly advance our understanding of the complex interplay between mitochondria, inflammation, and disease.

In conclusion, the relationship between mitochondria and innate immunity is a complex and multifaceted phenomenon involving various processes that maintain mitochondrial homeostasis, including mitochondrial metabolism, mitochondrial dynamics, and quality control. Further investigation is needed to fully understand the precise mechanisms of these interactions and their potential implications for developing novel therapeutic strategies against infectious and inflammatory diseases. Aberrant innate immune responses associated with dysfunctional mitochondria are related to various pathologies, including infectious, autoimmune, neurodegenerative, and cancerous diseases, and require further study to unravel the underlying mechanisms and develop new therapeutic targets for improving human health.

Author contributions

SC and PX designed the review; ZL helped with the discussion; SC and PX wrote the review article. All authors have read and approved the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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