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Review

Mitochondrial Functions in Infection and Immunity

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Mitochondria have a central role in regulating a range of cellular activities and host responses upon bacterial infection. Multiple pathogens affect mitochondria dynamics and functions to influence their intracellular survival or evade host immunity. On the other side, major host responses elicited against infections are directly dependent on mitochondrial functions, thus placing mitochondria centrally in maintaining homeostasis upon infection. In this review, we summarize how different bacteria and viruses impact morphological and functional changes in host mitochondria and how this manipulation can influence microbial pathogenesis as well as the host cell metabolism and immune responses.

Highlights

Bacteria and viruses have evolved specific ways of targeting mitochondria to perturb mitochondrial function that can prove to be beneficial for these microbes.

Many bacteria and viruses use specific virulence mechanisms to modulate mitochondrial dynamics, leading to either mitochondrial fusion or fission.

Mitochondrial metabolism can also be impacted by bacterial and viral infections.

While in some cases bacteria and viruses induce the mitochondrial cell death pathway, in others cell death is inhibited promoting intracellular bacterial and viral proliferation.

Mitochondria regulate different innate immune signaling pathways induced upon bacterial or viral infections.

Mitochondrial Morphology

Mitochondria are important organelles in the cell involved in a plethora of different functions, from energy production and fatty acid oxidation to regulating cell cycle and cell death. Mitochondria originated from an endosymbiotic relationship between bacteria and ancestral eukaryotic cells billions of years ago [1]. During evolution, mitochondria evolved to perform significant functions fostering the endosymbiotic relationship within the eukaryotic cells while still retaining their own DNA (mtDNA), and transcription and translation machineries. mtDNA encodes only 13 proteins and ~99% of mitochondrial proteins are nuclear encoded.

Mitochondrial networks are dynamic in nature, undergoing cycles of fission and fusion that are mediated by a dedicated set of dynamin-related GTPases. Mitofusin 1 and 2 (MFN1 and MFN2) and optic atrophy 1 (OPA1) coordinate their functions to bring about mitochondrial fusion. Mitochondrial fusion essentially involves fusion of the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM). MFN1 and MFN2, which are OMM proteins, interact with each other in a homo- and heterotypic manner involving GTP hydrolysis, which eventually leads to the fusion of the OMM. Fusion of the IMM is mediated by OPA1, which is a GTPase-protein anchored in the IMM. OPA1 is proteolytically cleaved into different fragments, including a long (L) form and a short (S) form, in the intermembrane space (IMS) of the mitochondria by two membrane-bound metalloproteases OMA1 and YME1L. L-OPA1 has been associated with mitochondrial fusion [2,3]. Loss of these mitochondrial fusion-mediating proteins (MFN1, MFN2, and OPA1) leads to mitochondrial fragmentation [4,5]. Mitochondrial fusion is an essential cellular process that helps to merge fragments of mitochondria, mediating the exchange of mtDNA, proteins, and metabolites [6]. Mitochondria can also break their network down into smaller fragments in a process termed 'mitochondrial fission'. The most critical factor regulating this process is the cytosolic GTPase-protein dynamin-related protein 1 (DRP1), also called dynamin-1-like protein (DNM1L). Under conditions of mitochondrial fragmentation, DRP1 is recruited from the cytosol to the OMM, where it forms oligomeric structures wrapping around the mitochondrial scission site and, eventually through GTP hydrolysis, undergoes a conformational change that results in membrane constriction and scission [7]. On the OMM, DRP1 interacts with mitochondrial fission factor (MFF) and mitochondrial dynamics proteins (MiD49 and MiD51), which serve as receptors for its recruitment [8,9]. Consistent with their role

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in mitochondrial fission, loss of MFF, MiD49, and MiD50 leads to mitochondrial hyperfusion and defected DRP1 recruitment to the mitochondria [10–12]. There is no known regulator of IMM fission, and it is not understood how the IMM and OMM coordinate in the process of fission.

Mitochondrial fission is required for removing damaged parts of mitochondria, which get eventually cleared by mitophagy. Mitochondrial fission also has a critical role in replicating mitochondria during cell cycle. There are also specific sites on mitochondria that serve as designated sites for mitochondrial fission. These sites are often where the tubules of endoplasmic reticulum (ER) physically contact mitochondria. These ER–mitochondria contact sites induce a constriction, where DRP1 is eventually recruited [13]. Furthermore, the receptors of DRP1, MiD49, and MiD51 are also present at the ER–mitochondria contact sites, suggesting that these sites are involved in the recruitment of DRP1 and subsequent mitochondrial fission [13,14]. It is not clearly understood how much of mitochondrial fission is driven by ER and whether the role of ER in mediating mitochondrial fission depends on specific stimuli or if it is a general phenomenon under all conditions that promote mitochondrial fission.

Given the central role of mitochondria in regulating a range of cellular activities, their role in regulating host response to an infection is plausible. Multiple studies have reported the subversion of mitochondrial functions upon microbial infections. Different pathogens have evolved ways of targeting the mitochondria to influence their intracellular survival, dissemination by mediating mitochondria-induced cell death, or evading host immunity. Research into the microbial strategies of impacting mitochondria has yielded a wealth of knowledge about their pathogenesis mechanisms. Additionally, pathogens could serve as essential tools in understanding the missing links in mitochondrial dynamics and function. Historically, studying bacterial internalization and their intracellular life-cycles elucidated mechanistic details of endocytic trafficking and vesicular biology. It will be fascinating to understand using similar strategies mitochondrial fission–fusion cycles and the key players involved in regulating the processes that are as yet unknown. In this review, we explore how bacteria and viruses manipulate the mitochondria and how this manipulation can influence microbial pathogenesis. Furthermore, we discuss how mitochondria influence the host immune response against infections and other stimuli.

Modulation of Mitochondrial Dynamics upon Infection

Several bacteria have developed strategies to subvert mitochondrial dynamics to benefit their intracellular niche. An effective way of subverting the mitochondrial function can be beneficial for intracellular bacteria since mitochondria can produce reactive oxygen species (ROS), which can be detrimental for the survival and proliferation of intracellular bacteria. A common theme among bacteria that target mitochondrial dynamics is that they form a niche to proliferate inside host cells. However, there are clear exceptions to this rule, as exemplified by *Helicobacter pylori*, an extracellular bacterium that targets mitochondria (discussed later). Moreover, most of the bacteria targeting mitochondrial morphology generally cause fragmentation of the mitochondria, thereby perturbing their function significantly. An interesting example is the intracellular Gram-positive bacterium *Listeria monocytogenes*. Infection with *L. monocytogenes* leads to rapid mitochondrial fission, causing fragmentation of the mitochondrial network, with effects that are dependent on its pore-forming toxin listeriolysin O [15]. Perturbation of mitochondrial dynamics by knocking down components of the fusion (MFN1 and MFN2) and fission (DRP1) machineries impacts the intracellular survival of *L. monocytogenes*, suggesting that the bacterium actively deploys listeriolysin O to fragment mitochondria for its sustenance inside the cell [15]. Interestingly, mitochondrial fission caused by *L. monocytogenes* is independent of DRP1 [16], pointing towards other mechanisms of mitochondrial fission that are as yet unknown. Similar to *Listeria, H. pylori* also targets mitochondria via its secreted vacuolating cytotoxin VacA, which localizes

to mitochondria [17]. VacA induces fragmentation of the mitochondrial network and subsequent release of cytochrome C, which are both dependent on the activity of DRP1 [18]. DRP1-dependent mitochondrial fragmentation is also observed in *Shigella flexneri* infections [19]. Knockdown of the *DRP1* gene by small interfering (si)RNA reverses mitochondrial fragmentation, and reduces the infectious foci counts and the plaque size, suggesting a decrease in cell-to-cell spreading of bacteria [19]. Furthermore, *Legionella pneumophila* secretes an effector called MitF through its type IV secretion system, which induces DRP1-dependent mitochondrial fragmentation in macrophages [20]. Blocking mitochondrial fragmentation leads to a decrease in intracellular replication of *L. pneumophila* [20]. By contrast, *Chlamydia trachomatis* preserves the elongated mitochondrial network for its intracellular proliferation. *C. trachomatis* upregulates a host miRNA (miR-30c-5p), which is key in maintaining the mitochondrial structure and intracellular proliferation of the bacteria [21]. While during the early infection phase, *C. trachomatis* induces mitochondrial elongation, it does resort to enhancing mitochondrial fragmentation during the late phases of infection [22]. Mitochondrial elongation is associated with enhanced respiratory activity and increased ATP production, which in turn promotes bacterial proliferation, thus making mitochondria a critical focal point in the intracellular life-cycle of *C. trachomatis* [22] (Figure 1).

All these observations invoke an intriguing question: given the bacterial origin of mitochondria, do these bacteria use similar mechanisms to attack other bacterial populations to maintain their own niche? Bacteria secrete soluble factors, including microcins and bacteriocins, to inhibit the growth of other competing bacteria. In addition, mechanisms such as contact-dependent inhibition (CDI) are in place where certain bacteria use type V or VI secretion systems to restrict the growth of other bacteria by direct contact [23]. It will be exciting to determine whether bacteria use similar mechanisms to interact with mitochondria and if this arm of defense against bacterial competition serves a dual role.

Similar to bacteria, many viruses also target mitochondrial functions to establish a proliferative niche for themselves and subsequently disseminate by killing the cells. Influenza A viral protein PB1-F2, which is a key virulence factor for the viral infection, targets mitochondria, leading to mitochondrial fragmentation due to the loss of mitochondrial membrane potential [24]. By contrast, dengue viruses inhibit DRP1, thus inducing mitochondrial fusion and elongation of the mitochondrial network via a nonstructural protein NS4B. Mitochondrial fusion is required for intracellular proliferation of the virus and evasion of the antiviral innate immune signaling [25,26]. Moreover, ORF-9b, a virulence factor of severe acute respiratory syndrome coronavirus (SARS-CoV), induces proteasomal degradation of DRP1, thereby leading to mitochondrial fusion, which eventually limits host cell interferon (IFN) responses against the virus [27]. Similarly, the HIV envelope protein gp120 causes a reduction in DRP1 levels, leading to mitochondrial hyperfusion [28]. These studies and other research [29] have clearly established a role of mitochondrial dynamics and their interplay with antiviral immunity upon a viral invasion. Since many of the viral proteins that target mitochondria are essential for viral replication, they might serve as critical drug targets for generating therapeutics against viral infections.

Modulation of Mitochondrial Metabolism upon Infection

The mitochondrion is the central organelle that regulates the metabolism of macromolecules, including carbohydrates, amino acids, and fatty acids. Glucose, which is the major source of energy, is converted to pyruvate in the cytoplasm via glycolysis. Under normal conditions in most cells, pyruvate is shuttled into mitochondria, where it is oxidized via the tricarboxylic acid (TCA) cycle, eventually generating ATP through the electron transport chain of the mitochondria in a process called oxidative phosphorylation (OXPHOS). OXPHOS is an efficient process; complete oxidation of a single molecule of glucose generates 36 molecules of ATP. Even though

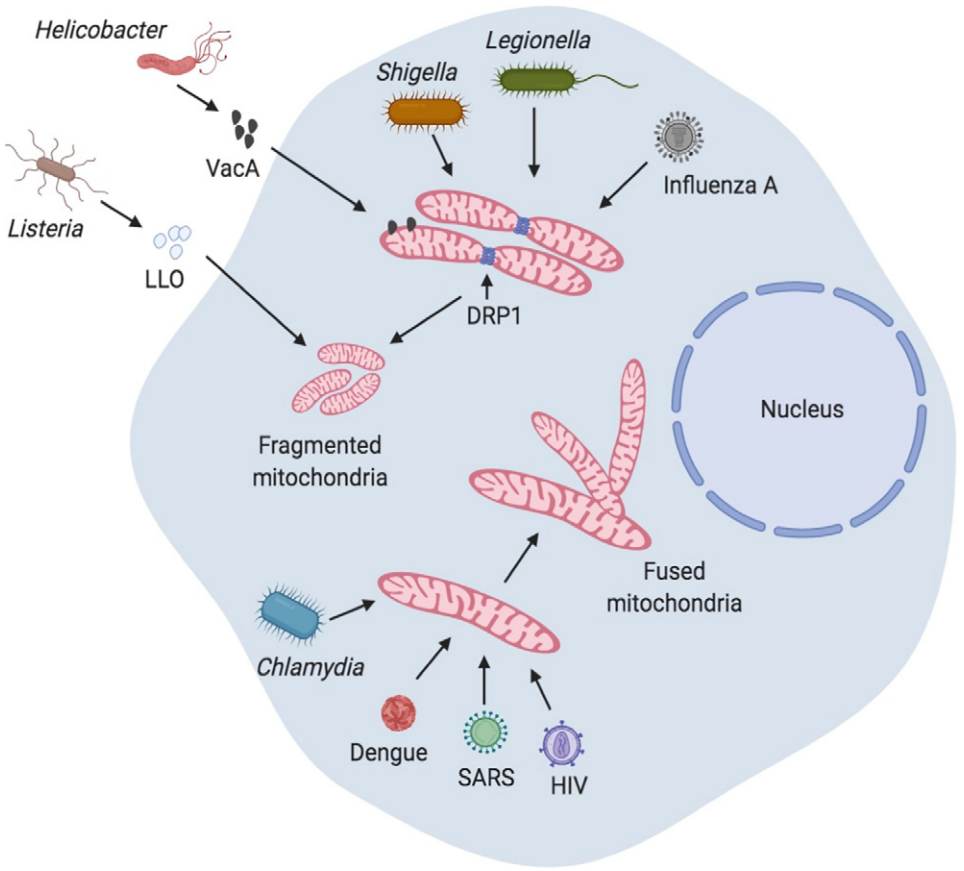

Figure 1. Modulation of Mitochondrial Dynamics upon Infection. Bacteria and viruses induce changes in mitochondrial morphology. *Listeria* secretes Listeriolysin O (LLO), a pore-forming toxin that induces an unconventional form of mitochondrial fragmentation that is independent of dynamin-related protein 1 (DRP1). Vacuolating cytotoxin VacA from *Helicobacter* localizes to mitochondria and induces mitochondrial fragmentation, the release of cytochrome C into the cytosol, and subsequent cell death. *Shigella* and *Legionella* also induce mitochondrial fragmentation in a DRP1-dependent manner. By contrast, *Chlamydia* infection leads to mitochondrial fusion, which is required for its intracellular proliferation. Viruses can also modulate mitochondrial dynamics. Influenza A leads to the dissipation of mitochondrial membrane potential, which ultimately causes mitochondrial fragmentation. Dengue virus inhibits DRP1 and induces mitochondrial fragmentation, which is necessary for its replication and immune evasion. Similarly, severe acute respiratory syndrome (SARS) virus and HIV cause DRP1 degradation, thereby bringing about mitochondrial fragmentation. Created with BioRender (www.BioRender.com).

OXPHOS is energetically efficient, it is metabolically slow. Rapidly dividing cells (e.g., cancer cells or activated immune cells) that have a high metabolism need quick energy production to maintain their activity. These cells resort to an alternative form of ATP production, termed aerobic glycolysis (also called the Warburg effect), in which pyruvate generated from glycolysis is converted to lactate in the cytoplasm, generating two ATP molecules for every glucose molecule (Figure 2).

Many bacteria are known to modulate cellular metabolism. They can actively remodel the host cell metabolism to enhance their intracellular survival or the remodeling can be a result of the host response towards bacteria to ramp up the immune response. In either case, the end result is generally a slowdown of the TCA cycle and an induction of aerobic glycolysis. One of the best-known bacteria that perturbs metabolism is *Mycobacterium tuberculosis.* Macrophages and T cells

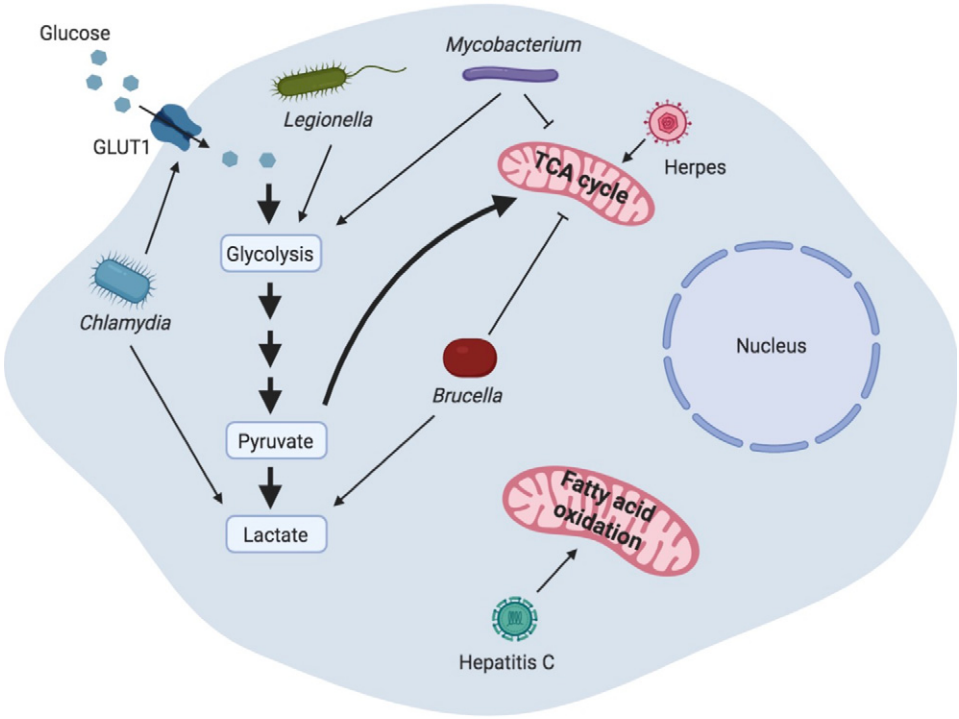

Figure 2. Modulation of Mitochondrial Metabolism upon Infection. Many bacteria and viruses hijack cellular metabolism for their own benefit. *Mycobacterium* is the best-known bacterium that influences host metabolism by enhancing aerobic glycolysis. Epithelial cells and immune cells infected with *Mycobacterium* exhibit a reduction in the tricarboxylic acid (TCA) cycle and a corresponding increase in the glycolytic flux. Elevated aerobic glycolysis is also observed in *Mycobacterium*-infected lung granulomas in animal models of infection and in patients with active tuberculosis. *Legionella* also promotes glycolytic flux similar to *Mycobacterium*, thus enhancing aerobic glycolysis. *Brucella* infection promotes lactate production via aerobic glycolysis, while suppressing the TCA cycle. *Chlamydia* enhances the levels of the glucose transporter GLUT1, leading to augmented glucose uptake and increased glycolytic flux, which is necessary for its intracellular growth. Viruses also perturb metabolic pathways for their replication and subsequent dissemination. Herpes virus induces the TCA cycle, thereby promoting mitochondrial respiration, while Hepatitis C perturbs mitochondrial fatty acid oxidation. Created with BioRender (www.BioRender.com).

infected with *M. tuberculosis* exhibit increased levels of glycolytic enzymes and transporters for glucose uptake and reduced levels of TCA cycle and OXPHOS enzymes, suggesting that *M. tuberculosis* infection induces a metabolic state similar to the Warburg effect [30]. Human alveolar macrophages also display a similar shift towards aerobic glycolysis, which is essential to curb the intracellular growth of bacteria. Inhibition of this metabolic switch leads to reduced production of proinflammatory cytokine IL-1β and enhanced growth of intracellular bacteria [31]. Similarly a switch towards aerobic glycolysis was also observed in a rabbit model of active tuberculosis (TB), in *M. tuberculosis*-infected lung granulomas of guinea pigs, and in lung granulomas from patients with TB [32–34]. *M. tuberculosis* also enhances the levels of aerobic glycolysis in human peripheral blood mononuclear cells (PBMCs) dependent on Toll-Like Receptor 2 (TLR2) and the AKT-mTOR pathway [35]. Another *Mycobacterium* species, *Mycobacterium avium*, also induces aerobic glycolysis in infected cells, which is dependent on the presence of IFN-γ [36]. Additionally, *Brucella abortus*, an intracellular bacterium causing chronic human and live-stock disease, can alter host cell metabolism to benefit its own growth and proliferation in cells. The metabolic shift induced by *B. abortus* is characterized by reduced TCA metabolism, reduced amino acid consumption, altered mitochondrial localization, and augmented lactate production [37]. Chemical inhibition of

glycolysis and lactate production attenuates the intracellular survival of *B. abortus* [37]. Furthermore, infection with *C. trachomatis* also rewires cellular metabolism. *C. trachomatis* infection causes upregulation of the glucose transporter Glut1 and downregulation of TIGAR, which is an inhibitor of fructose-2,6-bisphosphate, thereby altering glycolysis [38]. These findings are in line with *C. trachomatis* being an obligate intracellular bacterium the growth of which depends on the uptake of glucose from the host cells [39]. Similarly, *Chlamydia psittaci* induces metabolic perturbations and alterations of mitochondrial function characterized by increased glutamate and lactate production and accumulation of glycogen due to higher consumption of glucose by infected cells [40]. Macrophages infected with *L. pneumophila* also exhibit an abrupt halt of mitochondrial respiration and an increase in glycolysis, thus tipping the balance towards aerobic respiration, which is required for intracellular bacterial replication [20]. Thus, it is now clear that bacteria influence host metabolism. It will be interesting to further explore what kind of effectors and molecular mechanisms bacteria use to hijack the mitochondrial metabolism. To obtain a complete picture, it will also be important to address the outstanding mechanistic questions as to how sensing of certain bacteria, such as *M. tuberculosis*, leads the host cell to remodel its cellular metabolism to restrict bacterial proliferation.

Viruses also tweak mitochondrial metabolism to maintain a suitable replication niche. Interestingly, viruses can induce different effects on the host metabolism, which specifically depend of the type of virus. For example, two related herpes viruses [human cytomegalovirus (HCMV) and herpes simplex virus type-1 (HSV-1)] induce different effects on host metabolism. While HCMV enhances glycolytic flux, HSV-1 leads to induction of the TCA cycle [41]. HCMV appears to directly impact metabolism by elevating mitochondrial biogenesis, which is accompanied by increased respiration, both of which are required for HCMV replication [42]. Measles virus also enhances mitochondrial functions characterized by reduced ROS levels and enhanced mitochondrial membrane potential in infected cells, and this perturbation is required for persistent infection [43]. Hepatitis C virus (HCV) infection enhances mitochondrial fatty acid oxidation [44] and, concordantly, pharmacological inhibition of the transport of long-chain fatty acids into mitochondria restricts viral replication [45]. From numerous studies, it has become apparent that different viruses target different nodes of mitochondrial metabolism, including β-oxidation and the TCA cycle. However, we are still far from a clear understanding as to what the mechanisms of mitochondrial targeting are and why there exists such a diversity of metabolic perturbations caused by different viruses.

Modulation of Mitochondria-Induced Cell Death upon Infection

Mitochondria directly impact cell death via the intrinsic apoptosis pathway. The major players regulating cell death through this pathway belong to the B cell lymphoma 2 (Bcl-2) protein family. Some of these proteins are pro- while others are antiapoptotic in function. Major factors carrying out apoptosis include Bcl-2-associated X protein (Bax) and Bcl-2 homologous antagonist/killer (Bak), which, upon activation, localize to the OMM and induce OMM permeabilization (MOMP) [46]. MOMP leads to the release of proapoptotic factors, including cytochrome c and second mitochondrion-derived activator of caspases (SMAC/DIABLO), from the mitochondria into the cytoplasm. Cytochrome c interacts with the cytosolic protein apoptotic protease activating factor 1 (APAF1) in the cytoplasm and forms a specialized protein complex, called the apoptosome. The apoptosome cleaves procaspase-9 into active caspase-9, which subsequently cleaves and activates the executioner caspases 3/6/7, resulting in cell apoptosis [46].

Many pathogenic bacteria hijack this pathway to influence their own survival by either promoting cell death to obtain nutrients and disseminate further or suppressing cell death to enable their

proliferation inside the infected cells. For example, *Shigella flexneri* induces the loss of mitochondrial membrane potential, leading to disruption of mitochondrial function that causes cell death in macrophages [47] and non-myeloid cells [48]. Blocking the damage to mitochondria is sufficient to reverse the cell death phenotype, suggesting that *S. flexneri* actively uses strategies to perturb mitochondrial function [48]. Macrophages infected with *M. tuberculosis* also exhibit dissipation of mitochondrial membrane potential and a MOMP phenotype [49]. Virulent *M. tuberculosis* induces the translocation of Bax to mitochondria, leading to MOMP, the release of cytochrome-c in the cytoplasm, and eventually cell death [49]. In addition, a virulence factor called SipB produced by *Salmonella enterica* and delivered via the type III secretion system (T3SS) targets mitochondria in macrophages and induces cell death [50]. Similarly, *H. pylori* vacuolating toxin VacA activates DRP1 and induces its localization to mitochondria, leading to mitochondrial fragmentation, MOMP, activation of Bax, and release of cytochrome c into the cytoplasm. All these effects are rescued by inhibition of mitochondrial fragmentation, suggesting that *H. pylori* actively induces disruption of the mitochondria that leads to cell death [18]. Additionally, *Pseudomonas aeruginosa* secretes an effector, called ExoT, through its T3SS, which activates the mitochondrial intrinsic pathway of cell death by inducing higher levels of the proapoptotic proteins Bax, Bid, and Bim, loss of mitochondrial membrane potential, and release of cytochrome c [51].

There are also several bacteria that inhibit cell death instead of promoting it. This is seen as a strategy to protect their niche inside the cells where they replicate. For example, *L. pneumophila* secretes an effector called SidF through its T4SS, which inhibits apoptosis by suppressing the effects of the Bcl2 family proapoptotic proteins BNIP3 and Bcl-rambo [52]. SdhA is another *L. pneumophila* T4SS effector, which prevents apoptosis of the infected macrophages. Macrophages infected with the *L. pneumophila sdhA* mutant display enhanced cell death, thereby hindering the intracellular proliferation of the bacteria [53]. *Coxiella burnetii* uses an effector, named CaeB, to limit MOMP, thereby inhibiting the intrinsic apoptosis pathway [54]. CaeB expression in HEK293 cells leads to its localization to mitochondria, suggesting that this effector manipulates mitochondrial physiology, which then modulates cell death [54]. Additionally, *C. trachomatis* and *Chlamydia pneumoniae* induce proteasomal degradation of the proapoptotic proteins Bim, Puma, and Bad without affecting the transcript levels [55,56]. Degradation of these proteins eventually leads to suppression of cytochrome c release into the cytosol and inhibition of cell death, which assists the proliferation of the bacteria in the cells. A *C. trachomatis* effector called CPAF is responsible for inhibiting cell death by promoting the degradation of proapoptotic proteins [57]. While there are many different pathways that induce the demise of a cell, the mitochondrial pathway is widely targeted by bacteria to manipulate the host. It requires further investigation to understand whether there is crosstalk between cell death pathways when cells are challenged with a bacterial infection or whether bacteria also use similar effectors and mechanisms to target other forms of cell death. Bacterial modulation of the mitochondrial cell death pathway appears logical in terms of keeping the immune system silent, since it triggers apoptosis, which is an anti-inflammatory form of cell death (Figure 3).

Since many pathogenic bacteria modulate the mitochondrial cell death pathway, it is plausible that bacteria induce damage to the epithelial barrier by inducing cell death, thereby disseminating to other organs and ultimately leading to sepsis. Indeed, perturbed mitochondrial morphology, a dysfunctional mitochondrial electron transport chain, and enhanced oxidative stress have been reported in sepsis [58]. However, specific strategies to restore mitochondrial homeostasis in sepsis have not yielded promising results in humans [59], even though results from animal experiments were encouraging [60]. This suggests that bacteria use multiple strategies to disseminate and evade the immune system, of which mitochondrial targeting appears to be only one.

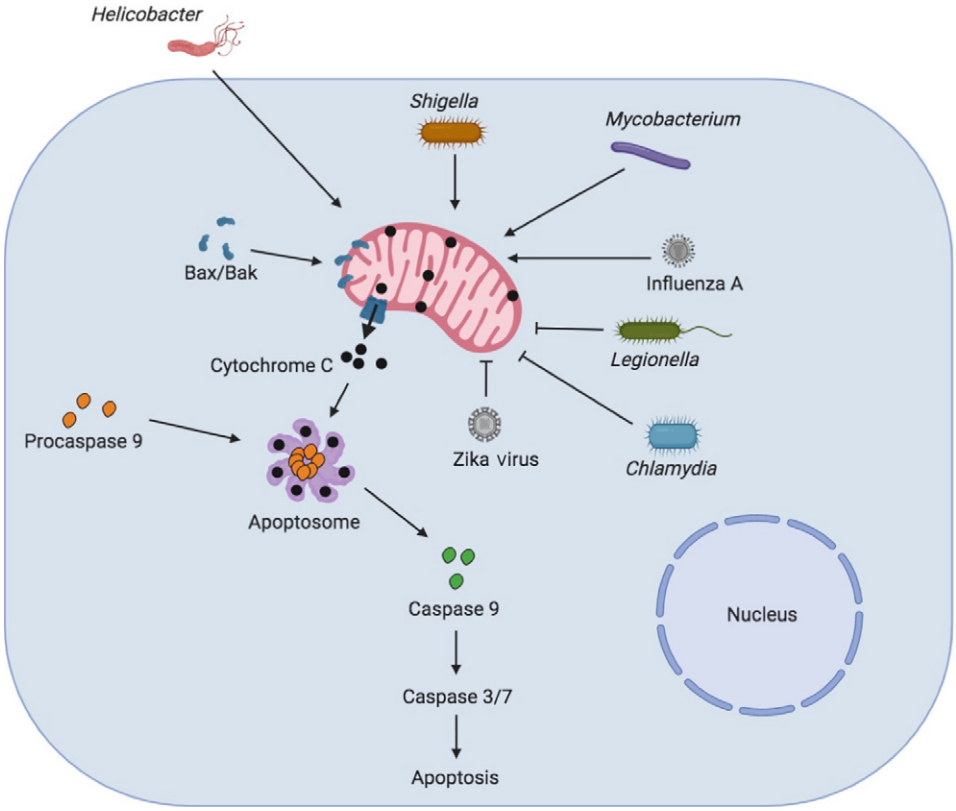

Figure 3. Modulation of Mitochondrial Apoptosis Pathway upon Infection. B cell lymphoma 2 (Bcl-2) family proteins, including include Bcl-2-associated X protein (Bax) and Bcl-2 homologous antagonist/killer (Bak), regulate the mitochondrial cell death pathway. Bax and Bak are proapoptotic proteins that localize to mitochondria and induce outer mitochondrial membrane permeabilization (MOMP), leading to the release of proapoptotic factors, such as cytochrome C, into the cytosol, which induce cell death by activating Caspases 9, 3, and 7 via the apoptosome complex. Bacteria and viruses influence this pathway and modulate the host response. *Helicobacter*, *Shigella,* and *Mycobacterium* infections lead to mitochondrial disruption that stimulates the mitochondrial apoptotic machinery and causes cell death. By contrast, bacteria such as *Chlamydia* and *Legionella* block the mitochondrial cell death pathway to promote their intracellular proliferation. Different viruses also exert varied effects on the mitochondrial cell death pathway. Influenza A enhances cell death, which helps in its dissemination, while Zika virus blocks cell death. Created with BioRender (www.BioRender.com).

Similar to bacteria, viruses can also modulate cell death for their own replication and dissemination. For example, Influenza A utilizes the mitochondrial cell death pathway by targeting its virulence factor PB1-F2 to the IMM space, where it disrupts mitochondrial organization, thereby inducing cell death [61]. Similarly, an HIV protein, called the viral protein R, translocates to OMM upon viral infection, inhibits Mfn2, and disrupts mitochondrial membrane potential, leading ultimately to cell death induction [62,63]. Interestingly, in contrast to HIV and Influenza A, some viruses, including Dengue [64], Zika [65], and Chikungunya [66] viruses, promote autophagy in the host, which inhibits cell death and promotes viral replication and dissemination. Similarly, measles virus enhances mitophagy in host cells, which limits apoptosis, but induces necrotic cell death in the later stages due to reduced levels of ATP [67]. Studies of viral infections have highlighted the involvement of autophagy and its interplay in different forms of cell death. These interesting studies have also revealed how certain aspects of bacterial infections match viral strategies, while others differ, in the context of modulating cell death.

Mitochondria and Innate Immunity

Multiple studies have established a crosstalk between signaling via the innate immune receptors and the mitochondria. Innate immune receptors, also known as pathogen recognition receptors (PRRs), are either cytosolic or membrane bound. The most-studied PRRs include the membrane bound TLRs and the cytosolic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). Ligand-activated TLRs or NLRs lead to the induction of downstream signaling cascades, causing the activation of major immune-regulatory transcription factors, such as AP-1 and NF-κB, ultimately leading to the production of cytokines and chemokines. Here, we describe the role of mitochondria in regulating innate immune responses.

Mitochondria and TLR Signaling upon Infection

TLRs are highly conserved transmembrane receptors that bind to their ligands, called microbe-associated molecular patterns (MAMPs) or danger-associated molecular patterns (DAMPs). Ligand binding leads to activation of TLRs and downstream signaling, resulting in a variety of cellular responses, including the activation and nuclear localization of the transcription factor NF-κB and the subsequent production of proinflammatory cytokines and interferons. Ten human (TLR1–10) and 12 mouse TLRs (TLR1–9, TLR11, 12, and 13) have been identified and characterized so far. In humans, TLR1, 2, 4, 5, 6, and 10 are localized to the plasma membrane and TLRs 3, 7, 8, and 9 are localized intracellularly in the endosomal membrane. While TLRs are activated significantly by bacterial or viral components, several studies have highlighted the role of mitochondrial components in modulating TLR signaling. mtDNA is similar to bacterial DNA in that both share hypomethylated CpG motifs that activate TLR signaling. Purified human and murine mtDNA injected intra-articularly led to arthritis in mice, while this effect was not observed with nuclear DNA, revealing the inflammatory nature of mtDNA [68]. In addition to mitochondrial components being proinflammatory, mitochondria themselves regulate TLR signaling in response to MAMPs. Activation of TLRs 1, 2, and 4 leads to the recruitment of mitochondria to macrophage phagosome and enhances mitochondrial ROS production. After TLR activation, the TLR adaptor protein TRAF6 interacts with, and ubiquitinates, a mitochondrial respiratory chain assembly factor, ECSIT. Ubiquitination of ECSIT leads to enhanced mitochondrial ROS production, which augments intracellular bacterial killing [69]. ECSIT interacts with TRAF6 and the serine/threonine kinase TAK1 upon lipopolysaccharide (LPS) stimulation, which activates TLR4 signaling. These protein interactions are deemed necessary for NF-κB activation upon LPS stimulation [70]. Activation of TLR signaling upon viral infections is also modulated by mitochondria. The OMM protein MARCH5 positively regulates TLR7 signaling by poly-ubiquitinating TANK (a TRAF-binding protein) and impairing its ability to bind to TRAF6 [71]. Additionally, the transcription factor NFAT1 is known to translocate into mitochondria in murine microglia with LPS stimulation, inhibition of which leads to reduced levels of cytokines and suppression in ROS production, suggesting a link with mitochondrial regulation of TLR signaling in microglia [72]. Bacterial infection also upregulates mitochondrial biogenesis through the upregulation of the PGC family of transcriptional co-activators [73–75]. This induction of mitochondrial biogenesis is also dependent on TLR2 and TLR4, signifying that the innate immune function feeds into the regulation of mitochondrial function [73]. Moreover, it was recently reported that methicillin-resistant *Staphylococcus aureus* (MRSA) induces the generation of mitochondria-derived vesicles that contain ROS and that help in the clearance of intracellular bacteria dependent on TLR signaling [76]. Even though there is substantial evidence for the involvement of mitochondria in TLR signaling, there are significant gaps that need to be addressed, in particular how mitochondria sense activation of TLRs and how they play into regulating downstream signaling. It will also be of interest to determine whether different TLRs follow similar mechanisms of mitochondrial involvement and whether the loss of mitochondrial functionality completely dampens TLR responses phenotypically. Ongoing and future work will address these conundrums.

Mitochondria as an Activation Platform for NLR Signaling

In addition to the membrane-bound TLRs, PRRs exist in the cytosol that detect cytosolic PAMPs and DAMPs. The most widely studied cytosolic PRRs are the NLRs. NLRs activate inflammasomes, which are multiprotein complexes that act as platforms for the activation of pro-inflammatory caspase-1. Active caspase-1 then proteolytically cleaves pro-IL-1β, pro-IL-18, and pro-IL-33 to produce mature cytokines, which are secreted out of the cell [77,78]. Caspase-1 also cleaves gasdermin D, which shuttles to the cell membrane, where it causes pore formation that ultimately leads to pyroptosis, an inflammatory form of cell death [77,78]. Some inflammasomes, such as NLRP3 and NLRC4, are well studied, while the mechanistic and functional details of others, such as NLRP6, NLRP7, and NLRP12, remain lacking. Functional links between mitochondria and the NLR signaling have been reported, as described later.

One of the first seminal studies describing the link between mitochondrial function and NLR signaling reported that the NLRP3 inflammasome and its adaptor protein ASC localize to the mitochondria upon activation [79]. The study revealed that a block in mitophagy led to an accumulation of damaged ROS-producing mitochondria, which induced the activation of the NLRP3 inflammasome [79,80]. Subsequently, the mitochondrial-associated adaptor protein MAVS was identified as an interaction partner important for the association of NLRP3 with mitochondria [81,82]. MAVS also promoted NLRP3-induced production of mature IL-1β, revealing an important role of mitochondria in mediating NLRP3 function [81,82]. Another mitochondrial protein, MAPL (also known as MUL1), localizes to the OMM and regulates NLRP3 activity. SUMOylation of NLRP3 by MAPL results in suppression of its activity [83]. Furthermore ,mtDNA [84,85] and the mitochondrial lipid cardioliopin [86] act as potent activators of the NLRP3 inflammasome. By contrast, NLRP3 inducers also bring about aberrant perturbation of mitochondrial homeostasis by diminishing the concentration of NAD^+, which consequently leads to accumulation of acetylated α-tubulin and subsequent microtubule remodeling, which is also necessary for NLRP3 localization to mitochondria [87]. Moreover, another member of the NLR family, NLRX1, interacts with MAVS in the OMM, and this interaction downregulates IFN-β production upon viral infection [88]. Loss of NLRX1 promotes virus-induced type I IFN production and decreases viral replication [88]. Overactivation of NLRX1 causes enhanced ROS production [89–91]. NLRX1 has also been reported to target the mitochondrial matrix and interact with UQCRC2, a matrix protein of the respiratory chain complex III. This interaction is required for ROS production [90]. Besides ROS production, NLRX1 was recently shown to function as a mitophagy receptor in *L. monocytogenes* infection [92]. Additionally, activation of the NLRC4 inflammasome has been associated with mitochondrial damage. *P. aeruginosa* infection leads to increased production of ROS and release of mtDNA into the cytoplasm, which activates the NLRC4 inflammasome [93]. Thus, it will be interesting to determine how the less understood inflammasomes, such as NLRP6, NLRP7, and NLRP12, react upon mitochondrial perturbations and whether conditions that activate these inflammasomes also influence mitochondrial physiology.

Mitochondria and Other Innate Immune Pathways

Mitochondria also have an essential role in regulating the function of other innate immune receptors. The mitochondrial protein MAVS influences the function of retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), which are specialized PRRs involved in the recognition of viruses by the innate immune system [94]. The RLR family members RIG-I, melanoma differentiation-associated 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) sense viral RNA in the cytoplasm and lead to downstream activation of a potent immune response, which activates the transcription factors IRF3, IRF7, and NF-κB, culminating in the production of type I IFNs and other proinflammatory cytokines. Viral infection induces aggregation of MAVS on the mitochondrial membrane, which is mediated by RIG-I, and these MAVS aggregates are capable of

activating IRF3 to generate an antiviral immune response [95]. The mitochondrial fusion protein MFN2 also regulates RLR signaling via MAVS. MFN2 directly interacts with MAVS; overexpression of MFN2 leads to a decrease in RIG-I and MDA5, thereby reducing antiviral immunity [96]. Interestingly, MAVS is also located on peroxisomes, and peroxisomal and mitochondrial MAVS work in conjunction to promote IFN production and antiviral immunity [97,98].

Finally, the cGAS-STING pathway has also been reported to have a mitochondrial dimension. This pathway senses cytosolic DNA and generates a downstream immune response driving type I IFNs and other proinflammatory cytokines. mtDNA present in the cytosol is sensed by cGAS and the cGAS-STING pathway is turned on. mtDNA stress induced by a deficiency in the transcription factor TFAM, leads to an escape of mtDNA into the cytosol, where it engages the DNA sensor cGAS, promoting STING-IRF3 signaling and ultimately culminating in a type I IFN response [99]. Mechanistic studies on the regulation of cell death and inflammation governed by mitochondria revealed that the absence of proapoptotic caspases promotes the cells to induce the cGAS-STING pathway and antiviral immunity upon MOMP [100,101]. Even though MOMP induced by Bax/Bak proteins has been associated with the escape of mtDNA into the cytoplasm [102], the exact mechanism whereby mtDNA can escape to the cytosol remains unknown. Further investigations are needed to ascertain whether additional mechanisms exist that release mtDNA into the cytoplasm to induce cGAS-STING signaling.

Concluding Remarks

Given the importance of mitochondria as a highly versatile player in governing different aspects of host responses from bacterial infections to innate immunity, it is understandable that various intracellular bacteria have evolved specific tactics to hijack mitochondrial functions to create a viable niche for themselves. Similarly, extracellular bacteria have devised ways of targeting mitochondria to induce cell death to avail themselves with nutrients. Even viruses have dedicated virulence factors that modulate mitochondrial function to influence their replication and dissemination. Downstream of an infection, it is fascinating that a plethora of immune responses, be it against bacteria or viruses or LPS stimulation, are strongly impacted by mitochondria (see Outstanding Questions). Thus, it will be exciting to extrapolate this current understanding and delve into how these fundamental processes governed by mitochondria can be translated into active therapeutics to boost immunity against pathogens or to keep overt immune responses under control in the case of inflammatory disorders.

Outstanding Questions

Can microbes that manipulate mitochondrial morphology be used to uncover the missing mechanistic links of mitochondrial fission and fusion?

How do pathogens perturb mitochondrial metabolism and what benefits does that confer on them?

How does altered mitochondrial metabolism upon infection affect cellular immune responses?

Can therapeutics targeting mitochondria bolster immune responses against microbial infections and limit the spread of infection?

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