Chapter 10
Mitochondria and Antiviral Immunity

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10.1 Introduction

Mitochondria are unique dynamic organelles that evolved from free-living bacteria into endosymbionts of mammalian hosts (Sagan 1967; Hatefi 1985). They have a distinct ~16.6 kb closed circular DNA genome coding for 13 polypeptides (Taanman 1999). In addition, a majority of the ~1500 mitochondrial proteins are encoded in the nucleus and transported to the mitochondria (Bonawitz et al. 2006). Mitochondria have two membranes: an outer smooth membrane and a highly folded inner membrane called cristae, which encompasses the matrix that houses the enzymes of the tricarboxylic acid (TCA) cycle and lipid metabolism. The inner mitochondrial membrane houses the protein complexes comprising the electron transport chain (ETC) (Hatefi 1985).

The roles for mitochondria in mammalian cells are ever expanding, and include important functions in innate immunity against microbial infection. While the role of mitochondria in oxidative phosphorylation is relatively well understood, their role in calcium homeostasis, lipid metabolism, apoptosis, aging, innate and adaptive immunity are still being elucidated (Duchen 2004a, b) (Fig. 10.1). More recently, there is also an appreciation for the role of mitochondria as key organelles in the metabolic syndrome characterized by diet-induced obesity and inflammation that manifests in conditions such as cardiovascular disease, diabetes, stroke, and cancer: all of which owe their severity to varying degrees of mitochondrial dysfunction. Thus, understanding mitochondrial physiology in order to restore optimal mitochondrial function has been the goal of several therapeutic strategies aimed at curing...
metabolic diseases (Sorriento et al. 2014). In this chapter we present a contemporary overview of the mitochondria and mitochondria metabolic actions in infection and immunity, with focus on innate antiviral immunity.

## 10.2 Mitochondrial Metabolism

Mitochondria are best known for the generation of ATP and the TCA cycle. These processes also generate metabolic products that drive cellular responses involved in innate immunity and immune signaling, including reactive oxygen species. This process starts with glucose that is transported into the cytoplasm and is broken down to pyruvate by the enzymes of the glycolytic pathway. Pyruvate can then be converted into acetyl CoA in the mitochondrial matrix. Acetyl CoA then enters the TCA cycle that generates reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH$_2$) that are used to generate ATP by the mitochondria through OXPHOS (Duchen 2004b; Kadenbach 2012). During OXPHOS, electrons are transferred from NADH and FADH$_2$ through components of the electron transport chain (ETC) located in the inner mitochondrial membrane. NADH and FADH$_2$ transfer electrons to complex I and II, respectively, and subsequently through complexes III and IV, where the electrons mediate the combination
of H\(^+\) and oxygen to form water. The process of electron transport through the ETC is coupled to the pumping of H\(^+\) ions from the mitochondrial matrix to the intermembrane space between the outer and inner mitochondrial membranes, generating an electrochemical gradient known as the membrane potential. H\(^+\) ions are pumped back to the matrix through complex V or ATP synthase, where this process is coupled to the combination of ADP and Pi to form ATP (Hatefi 1985; Saraste 1999) (Fig. 10.2). The electrons that leak from complexes I, II, and III during this process combine with oxygen to form superoxide radicals. Superoxide is converted into \(\text{H}_2\text{O}_2\) by superoxide dismutase. \(\text{H}_2\text{O}_2\) can freely cross membranes and is detoxified by the glutathione peroxidase. \(\text{H}_2\text{O}_2\), superoxides, and other intermediates that form transiently are collectively referred to as reactive oxygen species (ROS) (Kohchi et al. 2009). ROS products, along with microbial products are potent inducers of the innate immune response, and are discussed later in this chapter.

**Fig. 10.2** Oxidative phosphorylation and sources of danger associated molecular patterns (DAMPs): The five complexes of the electron transport chain are located on the inner mitochondrial membrane. The process of transfer of electrons from NADH (to complex I) and from FADH\(_2\) to complex II, and subsequently III, IV and to the final electron acceptor, O\(_2\), is coupled to the pumping of H\(^+\) ions from the matrix to the intermembrane space. The resulting electrochemical gradient that is generated is used by complex V, also called ATP synthase, to generate ATP from ADP and inorganic phosphate. Damage to mitochondria could release DAMPs that can trigger inflammatory responses. DAMPs are shown in red: mitochondrial DNA, mitochondrial transcription factor (TFAM), \(N\)-formylated peptides, mitochondrial ATP and \(\text{H}_2\text{O}_2\) (generated from superoxides (O\(_2\)^{−}) by the action of the superoxide dismutase enzymes SOD1 and SOD2.
10.3 The Innate Immune Response

Innate immunity represents our first line of defense against microbial invasion. It encompasses cell-intrinsic responses, where infected cells initiate an intracellular antimicrobial response that is aimed at suppressing microbial growth and spread. Several of these responses are dependent on mitochondrial metabolic activities and intracellular signal transduction that initiate and support the antimicrobial state (Ohta and Nishiyama 2011). Innate immunity also includes the function of innate immune cells, including, but not limited to macrophages, dendritic cells, and natural killer (NK) cells, which are respectively specialized for killing microbes, presenting microbial antigens to lymphocytes, and killing infected cells—all aimed at restricting microbial replication and spread, and at mediating a protective inflammatory response (Aderem and Ulevitch 2000). Thus, in the scheme of a global immune response to infection, the immune actions are first initiated through innate immune induction within an infected cell or tissue. Viral infection can begin with a single cell and if unchecked, spread to neighboring cells within a tissue, and can disseminate to other sites of the body through movement of blood and lymph. Thus, mammalian cells have evolved to recognize virus infection through a molecular process of nonself discrimination. This process initiates the immune response to virus infection (Takeuchi and Akira 2009).

The process of initiating the innate immune response to virus infection starts when the host cell recognizes conserved molecular patterns within pathogens termed pathogen-associated molecular patterns (PAMPs) (Janeway 1989). PAMPs include nucleic acid, proteins, and lipid/protein complexes that are of viral origin or viral association (Kawai and Akira 2010). Innate immune recognition of these PAMPs is mediated by cellular proteins called pattern recognition receptors (PRRs) (Janeway 1989), that bind to cognate PAMPs, leading to an antiviral response, which when effective can confer viral clearance and result in a self-limiting infection. This scenario likely happens to us on a daily, if not hourly, basis to protect us from viral infection and disease. Problematically, under certain conditions several PRRs might also recognize and react with endogenous (self) molecules that might resemble PAMPs, leading to an inflammatory response, termed sterile inflammation, that occurs in the absence of microbial infection (Rock et al. 2010). Given the wide variety of pathogens that a host may encounter, including viral pathogens, an equally diverse innate response is required to recognize and mount a defense against potential microbial threats. The broad categories of PRRs include, but are not limited to, Toll-like receptors (TLRs), the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), the C type lectin receptors (CLRs), and (RIG-I) (pronounced RIG-eye)-like receptors (RLRs) (Ireton and Gale 2011; Freed and Gale 2014; Brennan and Bowie 2010). PRRs are expressed on the cell surface, cytoplasm and in endosomes to facilitate the recognition of both extracellular and intracellular pathogen-derived PAMPs. The TLRs expressed on the plasma membrane are TLR1, TLR2, TLR4, TLR5, and TLR6, and have been shown to bind microbial components, including those of viral origin. The TLRs predominantly located in endocytic
compartments are TLR3, TLR7, TLR8, and TLR9, and these PRRs bind bacterial or viral nucleic acids (Kawai and Akira 2010; West et al. 2011).

The NLRs are intracellular sensors of PAMPs and danger-associated molecular patterns (DAMPs). NLRs are composed of 20 members that recognize microbial PAMPs or molecules released following cellular stress such as DAMPs. The NLR family members include proteins such as NOD-1, NOD-2, pyrin domain containing 1 (NLRP1), NLRP3, and ice protease activating factor 4 (IPAF, also called NLRC4). NLRP3, the best understood NLR, upon activation, forms a macromolecular complex that mediates the maturation and secretion of proinflammatory IL-1β and IL-18 via the activation of caspase-1. The other NLRs except for NOD-1 and NOD-2, can also stimulate the secretion of IL-1β and IL-18 upon activation (Sutterwala et al. 2014; Yu and Finlay 2008). The NLRP3 inflammasome has been shown to assemble and engage MAVS in response to RNA virus infection, leading to the secretion of active IL-1β (Subramanian et al. 2013). Viral infection-mediated inflammasome activation has been reported in response to both DNA (Barlan et al. 2011; Kanneganti et al. 2006; Nour et al. 2011; Muruve et al. 2008) and RNA viruses (Kanneganti et al. 2006; Franchi and Nunez 2008; Rajan et al. 2011; Negash et al. 2013; Ramos et al. 2012; Kaushik et al. 2012). However the mechanisms by which viral PAMPs stimulate inflammasomes are unclear. While it’s unclear whether direct interactions between viral PAMPs and inflammasomes occur, one report (Mitoma et al. 2013) describes an indirect interaction whereby DHX33, a RNA helicase, binds viral RNA and activates NLRP3 (Fig. 10.3).

The CLR s are receptors that recognize sugar/carbohydrate moieties on proteins. CLR s may recognize the carbohydrate portion as PAMPs or they may bind self-proteins and affect tissue homeostasis and repair. DC-specific ICAM3-grabbing non-integrin (DC-SIGN) receptor is an important member of this family (Robinson et al. 2006).

RNA viruses are recognized largely by the RLRs: The RLR family includes RIG-I itself, melanoma differentiation-associated gene-5 (MDA5) and Laboratory of Genetics and Physiology 2 (LGP2) (Ireton and Gale 2011). While RIG-I and MDA5 sense viral RNA and initiate downstream signaling (Errett et al. 2013; Jiang et al. 2011), LGP2 is believed to have a regulatory function in RLR signaling (Loo and Gale 2011). During the response to West Nile Virus (WNV) infection, LGP2 did not greatly affect innate immune signaling but was crucially important for CD8 T cell responses (Suthar et al. 2012). Recently, LGP2 was shown to help in MDA5–RNA interactions, thereby enhancing MDA5-mediated antiviral signaling (Loo and Gale 2011; Bruns et al. 2014). RIG-I and MDA5 have two N-terminal caspase recruitment domains (CARDs) that are required for signaling, an internal DExD/H box RNA helicase domain and a C-terminal domain involved in viral RNA detection and autoregulation. LGP2 is a non CARD-containing member of the RLR family. RIG-I can recognize viral RNA based on several PAMP motifs including 5′ triphosphate, double stranded (ds) RNA structure, poly-uridine signatures, and 3′ overhang (Saito et al. 2008). MDA5, on the other hand, although its PAMP is not well defined, is thought to recognize complex and long double-stranded RNA (ds-RNA) (Pichlmair et al. 2009). Following RNA binding, the RLR translocate from
the cytosol to mitochondria-associated ER membranes (MAM) to interact with the MAM-anchored and mitochondrial membrane-anchored mitochondrial antiviral signaling (MAVS) protein, leading to innate immune activation. For RLRs, TNF receptor-associated factor (TRAF) family proteins and other adaptors facilitate this signaling by engaging downstream protein kinases that activate the transcription factors interferon regulatory factor-3 (IRF3) (Daffis et al. 2007) and IRF7 (Daffis et al. 2008; Erickson and Gale 2008; Chowdhury et al. 2014) (Fig. 10.3). In myeloid DC and macrophages responding to WNV infection, there is some redundancy with IRF5 also being able to induce IFNβ in a MAVS-dependent manner in the absence of IRF3 and IRF7 (Lazear et al. 2013; Daffis et al. 2009).

Fig. 10.3 RLR and inflammasome signaling processes during viral RNA infection. RLR signaling: During RNA virus infection the sensing of viral RNA by RIG-I/MDA5 leads to their activation and recruitment to MAVS on intracellular membranes including mitochondria where MAVS aggregates to form large-prion-like complexes, and MAM where the RLR/MAVS complexes assemble for signaling. Activated MAVS recruits the E3 ligases TRAF 2/5/6. The E3 ligases polyubiquitinate TRAF2 and other proteins and recruit NEMO. NEMO, in turn, recruits the kinases, IKKα and β, which can lead to NF-κB activation and proinflammatory cytokine induction. NEMO can also recruit IKKe and TBK1 leading to the phosphorylation and subsequent activation followed by nuclear translocation of IRF3 and IRF7 and induction of type I IFN. Inflammasome activation: The NLRP3 inflammasome is sensitive to viral infection. One possible mechanism of NLRP3 inflammasome activation is via the binding of viral RNA by the RNA helicase, DHX33, leading to the activation of caspase 1 and production of mature IL-1β. In addition, mitochondrial ROS produced as a consequence of viral infection activates both the RLR and NLRP3 inflammasome pathways.

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DNA virus infection can be recognized by another set of PRRs including TLR9, which binds CpG motifs in DNA, and cGMP-AMP (cGAMP synthase) (cGAS), which binds to dsDNA and catalyzes production of a 2′-5′ dinucleotide that binds to signal transducer of interferon genes (STING) to drive IRF3 or IRF7 activation (Ablasser et al. 2013). In all cases, when activated, IRF3/7 homodimerize and translocate to the nucleus. Along with activated NF-κB, these factors then bind to specific response elements, leading to the expression of type I IFN, IRF3 target genes and NF-κB-responsive genes. Subsequently, secreted IFN acts both in an autocrine and paracrine manner to induce the expression of IFN-stimulated genes (ISGs). Type I IFN signaling is largely mediated by the JAK-STAT pathway, leading to interferon-stimulated gene factor 3 (ISGF3) expression that binds to the IFN-stimulated response element (ISRE) within the promoter of ISGs. ISGs include inflammatory cytokines and chemokines as well as immune-modulatory genes that impart control of virus replication, spread and regulation of the adaptive immune response. This establishes the “antiviral state” both in virus-infected and bystander cells (Sadler and Williams 2008; Schoggins et al. 2011). Thus, successful innate immune response will limit viral replication while serving to program the adaptive immune response toward antiviral actions.

10.4 Mitochondria and Innate Immunity

Mitochondria and the mitochondria-associated membrane (MAM) play major roles in innate immune signaling against RNA viruses because each functions specifically in RLR signaling. Active RIG-I and MDA5 signal innate immunity through direct association with the adaptor MAVS that is critical for antiviral responses against RNA viruses (Kumar et al. 2006; Sun et al. 2006). MAVS is a 540 amino acid protein with a predicted molecular weight of 56 kDa. MAVS contains an N-terminal CARD domain, a proline-rich region (PRR) and a C-terminal transmembrane domain. MAVS is anchored on the outer membrane of the mitochondria, peroxisomes and MAM. MAM is a specialized extension of the endoplasmic reticulum membrane that makes contacts with the mitochondrial outer membrane (Fig. 10.4) and is discussed later in this chapter (Horner et al. 2011). RIG-I binding to MAVS is dependent upon K63-linked ubiquitination of RIG-I by the E3 ubiquitin ligase tripartite Motif 25 (TRIM 25). Binding of K63 polyubiquitin chains to RIG-I or MDA5 eventually leads to activation of IRF3 (Jiang et al. 2012). Proteins such as human oligoadenylate synthetase L (OASL) that mimic polyubiquitin also enhance RIG-I antiviral activity (Zhu et al. 2014). RIG-I interacts with TRIM25 and the mitochondrial targeting chaperone protein, 14–3–3ε, to form a translocon that delivers activated RIG-I to MAVS on membranes (Liu et al. 2012). The proline-rich region of MAVS is involved in interacting with TNFR-associated factor (TRAF) family members, though it appears that additional contact points for MAVS–TRAF interactions may exist on MAVS (Seth et al. 2005; Xu et al. 2005; Saha et al. 2006), possibly in the CARD region (Tang and Wang 2009; Tang and Wang 2010).
Fig. 10.2. Interaction with RIG-I or MDA5 occurs through the N terminal CARD domain, leading to MAVS oligomerization. These rod-shaped prion-like aggregates appear to form self-perpetuating filaments that amplify signaling, albeit they have only been identified in vitro in cell-free systems and are not yet demonstrated to exist in intact mammalian cells (Hou et al. 2011). MAVS is known to interact with

Fig. 10.4 Proteins associated with mitochondria-associated ER membranes (MAM) tethering. Upon activation by viral infection, mitochondria become activated and are found in close apposition with ER membranes in structures called MAM. MAM allow members of signaling pathways such as RLR signaling and apoptosis induction to come together as a complex to allow for more efficient signal transduction, such as during Ca\textsuperscript{2+} signaling, by forming an “innate immune synapse.” Several proteins have been implicated in the formation of MAM in nonviral systems. How these proteins may interact with MAVS and with one another, especially in the context of viral infections is being defined. MFN2 has been directly implicated in tethering ER to mitochondria. The other proteins that are implicated as MAM constituents may have indirect roles; they might help stabilize MAM or catalyze its formation. MFN1 is located on the outer mitochondrial membrane and interacts with MAVS. Mitochondrial ubiquitin ligase (MITOL) ubiquitinates MFN2 and enhances MAM formation indirectly. Dynamin related Protein 1 (DRP1) is a cytosolic GTPase that has been shown to colocalize with MAM, while phosphofurin acidic cluster sorting protein 2 (PACS2) regulates MAM formation and stability (Adapted from Vance JE (2014) Biochim Biophys Acta 1841: 595–609)
upwards of 30 proteins (Kumar et al. 2006; Belgnaoui et al. 2011). Subsets of these proteins assemble into signaling complexes or signalosomes. The formation of these “MAVS signalosomes” is assisted by proteins such as the outer mitochondrial membrane protein, tripartite motif 14 (TRIM14) that after interacting with MAVS, undergoes polyubiquitination at Lys-365. Upon activation, it recruits NF-κB enhancer modulator (NEMO) to MAVS and allows for the activation of NF-κB and IRFs (Zhou et al. 2014). The ubiquitination and activation of NEMO is promoted by TRAF2, 5, and 6, which are also recruited by MAVS (Liu et al. 2013) (Fig. 10.3). Ubiquitously expressed TV-1 (UXT-V1) is another protein that aids in the formation of the MAVS signalosome by binding TRAF3 and thus facilitates the interaction between TRAF 3 and MAVS (Huang et al. 2012).

Differential usage of TRAF family members as adaptors in interactions with MAVS may regulate IRF3/IRF7/NF-κB and proinflammatory cytokine/ type I IFN (IFN-I) production. While MAVS interaction with TRAF6 and TRAF5 (Tang and Wang 2010) along with TNF receptor associated death domain (TRADD) via receptor interacting protein1 (RIP1) and FAS-associated death domain (FADD) (Michallet et al. 2008) can lead to NF-κB activation, MAVS interaction with TRAF 2/3 (Saha et al. 2006; Liu et al. 2013), TRADD, and TRAF family-associated NF-κB activator (TANK) promotes IKKe and/or TANK binding kinase1 (TBK1)-mediated IRF3 phosphorylation and (IFN-I) production. The nature of the interactions between TRAF and molecules of the RLR pathway and how they are regulated are unclear. A recent report has identified an interaction between the mitochondria-nucleus shuttling protein, FK506-binding protein 51 (FKBP51), TRAF6, and TRAF3 as being important for signaling the expression of (IFN-I) induced by cytosolic dsRNA. This suggests a potential point of regulation, via FKBP51, imposed on the RLR pathway during viral infection (Akiyama et al. 2014).

STING and Translocase of mitochondria-70 (TOM70) are shown to be mitochondrial cofactors for innate immune signaling by MAVS, although this activity is likely to be pathogen-specific (Ishikawa and Barber 2008). TOM 70, along with TOM 20, forms a protein channel on the outer mitochondrial membrane through which nuclear encoded mitochondrial proteins are imported into the mitochondria. TOM 70 interacts directly with MAVS, and this interaction is enhanced in particular during Sendai virus infection (Liu et al. 2010) and is a crucial positive regulator of RLR signaling (Liu et al. 2010). TOM 70 also interacts with HSP90 (Bhangoo et al. 2007), and this tethering allows for close association between HSP90, MAVS, TBK1, and IRF3, presumably allowing for efficient signaling. STING was originally identified as an endoplasmic reticulum (ER)-resident protein that mediates IRF3 activation and stimulator of interferon following recognition of viral nucleic acid (Ishikawa and Barber 2008; Zhong et al. 2008; Sun et al. 2009). Decreased STING expression increased susceptibility to vesicular stomatitis virus (VSV, a RNA virus) as well as herpes simplex virus (HSV, a DNA virus) infection. Subsequent work has more clearly defined a role for STING in intracellular DNA sensing and its role in RNA virus protection may be indirect (Brunette et al. 2012; Wu et al. 2013; Schoggins et al. 2014). STING-mediated antiviral responses are dependent on association with the ER translocon protein known as translocon.
associated protein (TRAP), SEC61 translocon and TBK1, which leads to phosphorylation of IRF3 and IRF7. Thus, close ER-mitochondrial interactions such as those imposed by MAM, are crucial in antiviral signaling.

As noted above, mitochondria produce ROS as a result of their metabolic processes. ROS can impact several signaling pathways to regulate innate immune defenses during virus infection. The cellular stress induced by viral infection is associated with ROS production as observed in human adenovirus (HAdv) (McGuire et al. 2011), hepatitis C virus (HCV) (Nishina et al. 2008), Human Immunodeficiency Virus (HIV) (Kruman et al. 1998), and Epstein Barr virus (EBV) (Lassoued et al. 2008) infections. Mitochondrial ROS (mROS) increases RLR signaling and IFNβ production, which consequently decreases viral replication. While the mechanistic details of how mROS might regulate the RLR pathway during viral infection are unclear, several proteins that regulate this process have been identified. The NOD-like protein, NLRX1 and the globular domain of complement 1q receptor (gc1qR) interact with components of oxidative phosphorylation and increase ROS production (Tattoli et al. 2008; Saha et al. 2013) whereas the cytochrome c oxidase complex subunit COX5B, coordinates with the autophagy pathway through autophagy-related gene 5 (ATG5), to suppress MAVS signaling and decrease ROS production (Zhao et al. 2012).

A crucial requirement for MAVS to function as an adaptor in the RLR signaling pathway is the existence of optimum mitochondrial membrane potential (Koshiba et al. 2011). Fibroblasts lacking both mitofusin 1 (MFN1) and mitofusin 2 (MFN2) and which have low membrane potential, or cells in which the mitochondrial membrane potential is pharmacologically dissipated using protonophores such as carbonyl cyanide m-chlorophenyl hydrazone (CCCP), support TLR3 signaling but not RLR signaling. Interestingly, RLR signaling via MAVS is not itself dependent on de novo ATP production, although many of the RLR signaling proteins bind or hydrolyze ATP during their signaling actions. This relationship suggests that the requirement for mitochondrial membrane potential for MAVS activity reflects needed alterations in mitochondria membrane and MAM interactions that likely form a functional membrane-bound signalosome platform (Koshiba et al. 2011).

10.5 Mitochondria in Sterile Inflammation

Release of mitochondrial components into the extracellular space induces inflammatory reactions (Fig. 10.2). Trauma-induced cell-damage releases DAMPs such as N-formyl peptides, mitochondrial DNA, mitochondrial transcriptional factor (TFAM), mitochondrial ATP, mitochondrial ROS or high mobility group box 1 (HMGB-1) that lead to pathophysiological consequences (Wenceslau et al. 2014; Kono and Rock 2008). HMGB-1, a ubiquitous nuclear protein, functions as a DAMP that can induce apoptosis in Jurkat T cells by lowering the levels of MFN2 that may be required to maintain optimum Ca²⁺ levels in T cells (Wu et al. 2014; Castanier et al. 2010). In addition, HMGB-1 may play a more direct role in
regulating MAVS function by acting as ‘universal sentinels’ of nucleic acid detection (Yanai et al. 2009). Mitochondrial DAMPs activate the NLRP3 inflammasome and amplify the inflammatory response by releasing IL-1β and promoting neutrophil infiltration following trauma (Ma et al. 2014). MAVS is a critical adaptor in addition to apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) in mediating the production of IL-1β from the NLRP3 inflammasome (Subramanian et al. 2013). Mitochondrial ROS may be a major trigger of NLRP3 inflammasome activation. Therefore, inhibition of the NLRP3 inflammasome and the use of ROS inhibitors such as MitoTEMPO can be protective following traumatic events such as intracerebral hemorrhage (Ma et al. 2014). Such inflammatory responses have been observed in immune cells such as gamma-delta cells that upon incubation with mitochondrial DAMPS secrete IL-1β, IL-10 and IL-6 (Schwacha et al. 2014). TLR9 engagement of DNA from damaged cells by immune cells results in an inflammatory response mediated by MyD88 and TRAF6 that eventually results in cell death. However, in non-regenerative terminally differentiated non-immune cells such as cardiomyocytes and neurons, an alternative pathway has been reported where TLR9 binds the sarco/endoplasmic reticulum Ca²⁺-ATPase 2 (SERCA2) protein, reduces its activity, and leads to reduced mitochondrial Ca²⁺. This process then decreases mitochondrial ATP levels and protects the cells from cell death (Shintani et al. 2014). A pathway to prevent inappropriate activation following recognition of endogenous RNA by the RLR pathway has been reported. The superkiller viralicidic activity 2-like (SKIV2L) RNA exosome potently suppresses the activation of the RLR pathway and prevents development of autoimmunity. The importance of this mechanism of handling immunostimulatory RNA is indicated by the finding that deficiencies in SKIV2L have been associated with certain immune disorders (Eckard et al. 2014).

10.6 Mitochondrial and MAM Dynamics in Innate Immunity

Mitochondria are dynamic organelles whose function is regulated by alterations in size, number and interactions with other organelles such as ER and peroxisomes by mechanisms such as fusion, fission and autophagy (Campello and Scorrano 2010). Mitochondrial fusion is regulated by mitofusin1 (MFN1), mitofusin2 (MFN2) as well as by optic atrophy A1 (OPA1) (Chan 2006), whereas mitochondrial fission is regulated by dynamin related protein 1 (DRP1) and fission 1 (FIS1) (Chan 2006). In addition to mediating mitochondrial fusion, mitofusin2 (MFN2) is crucial for mitochondria–MAM interactions (Horner et al. 2011; Horner and Gale 2013). These mitochondrial processes are conserved across organisms and cell types and are critical for cellular function. For example, both mammalian DRP1 and the homologous yeast dynamin related GTPase 1 (DNM1), regulate mitochondrial fission and a DRP1 mutation in mice is implicated in severe developmental defects (Sesaki
et al. 2014). Knockdown of MFN1 and OPA1 (thereby suppressing fusion) results in decreased IRF3 and NF-κB activation, whereas knockdown of DRP1 and FIS1 potentiates IRF3 and NF-κB signaling (Castanier et al. 2010). Thus, fused mitochondria, in general, support enhanced RLR signaling, while fragmented mitochondria do not. Mitochondrial fusion events and formation of MAM support RLR signaling as described earlier. The role for MFN2 in RLR signaling, however, has been unclear. MFN2 is enriched at points of contact between ER and mitochondria in the MAM (Fig. 10.4) and, as such, increases in MAM are associated with enhanced RLR signaling. This supportive role for MFN2 in RLR signaling is potentially at odds with the finding that RLR signaling is inhibited when MFN2 is overexpressed (Yasukawa et al. 2009). It was shown in this study that MFN2 overexpression inhibited RIG-I and MDA5-mediated signaling. It is possible to reconcile these opposing roles if they occur at different times following activation, with the MAM-supportive activity of MFN2 occurring early during the response and the inhibitory role occurring at a point when the RLR pathway needs to be suppressed. Alternatively, MFN2 could be interacting with different, as yet undiscovered, accessory proteins in the above two situations. However, neither of the above two scenarios has been demonstrated and both await experimental evidence.

A crucial part of the dynamic nature of the interactions between mitochondria and the ER is through MAM. As noted above, these membranes are closely associated with ER and mitochondria. MAM was initially identified through electron microscopy studies and later confirmed by cell fractionation studies to contain marker proteins that were highly enriched for this special membrane but not present in high levels in either ER or mitochondria (Cui et al. 1993). Several MAM or MAM-associated proteins have been identified but only a few have been shown to be involved in tethering MAM to mitochondria (Fig. 10.4) (Vance 2014): MFN2 has been directly implicated in tethering ER to mitochondria (de Brito and Scorrano 2008), while MFN1 has been shown to be an outer mitochondrial membrane protein (de Brito and Scorrano 2008) that interacts with MAVS (Castanier et al. 2010). Mitochondrial ubiquitin ligase (MITOL) ubiquitinates MFN2 and enhances MAM formation indirectly (Sugiura et al. 2013). DRP1 is a cytosolic GTPase that has been shown to colocalize with MAM (Friedman et al. 2011) and phosphofurin acidic cluster protein 2 (PACS2) regulates MAM formation and stability (Youker et al. 2009) (Fig. 10.4). Despite these advances, identifying unique markers for MAM has been difficult, as the nature of the MAM seems to vary with cell type and activation status (Vance 2014). It is therefore conceivable that there may be cell type specific enrichment of these proteins or a combination of these and other proteins in the MAM during different viral infections.

MAMs are conserved in organisms ranging from yeast to mammals and have been identified as important in several functions such as importing the lipid, phosphatidylserine (PS) into mitochondria, mitochondrial morphology, calcium homeostasis and promoting cell survival and autophagy (Vance 2014). Mitochondria are important organelles that regulate calcium homeostasis. Recent studies have
revealed that the MAM is a crucial part of Ca\textsuperscript{2+} regulation, as transport of Ca\textsuperscript{2+} from the ER to the mitochondria appears to occur at points of close apposition between the two organelles and conditions that disrupt this contact not only disrupt Ca\textsuperscript{2+} homeostasis, but also ATP production and cell survival (Rowland and Voeltz 2012).

Viral proteins, including the exon 1 protein from cytomegalovirus (CMV) and the HCV core protein have been identified as being associated with MAM (Williamson and Colberg-Poley 2009; Williamson et al. 2012). The pathological significance of localization of viral proteins in MAMs is not clear. Whether these viral proteins are passively transported to the MAM from the ER or whether this represents an active strategy on the part of the virus to subvert host defense needs to be elucidated. The compartmentalization of host proteins in the mitochondria versus the MAM has functional relevance as seen in the case of MAVS cleavage by the viral protease, NS3/4A, during HCV infection (Horner et al. 2011; Horner et al. 2012; Lin et al. 2006). MAVS is localized on mitochondria and peroxisomes as well as in the MAM in HCV-infected cells. Peroxisomal MAVS mounts a rapid response mediated by the transcription factor IRF1 (Ding and Robek 2014). This early response is mediated by the JAK-STAT pathway and resembles a type III IFN response (Ding and Robek 2014; Odendall et al. 2014), while mitochondrial MAVS mounts an IFN-I response with delayed kinetics (Odendall et al. 2014; Dixit et al. 2010). The localization of MAVS in the MAM potentially allows for MAVS to be sterically removed from mitochondria-associated negative regulators, such as NLRX1, that block CARD–CARD interactions between MAVS and recruited RIG-I, thus facilitating potent antiviral signaling. However, during HCV infection, MAM-associated MAVS is specifically subject to cleavage by the HCV NS3/4A protease, whereas the mitochondria-associated MAVS is not. Since RIG-I is recruited to the MAM after infection and HCV targets and cleaves MAM-associated MAVS, the virus thereby effectively blocks IFN\textbeta production to support persistent viral replication and chronic infection. Overall these studies implicate the MAM as a crucial signaling platform from which MAVS and RLRs function to drive innate antiviral immunity.

Apart from being involved as an adaptor in RLR signaling, mediating IFN\textbeta production, activation of MAVS and MAM signaling can have deleterious effects. This outcome was shown in the study by Mukherjee et al. (2013), where they demonstrated that pediatric viral encephalitis attributed to La Crosse Virus (LACV), a bunyavirus, occurs via upregulation of the adaptor protein, sterile alpha and TIR-containing motif 1 (SARM1), a molecule directly involved in neuronal damage, that is induced upon MAVS activation by LACV infection. SARM1-mediated cell death was associated with induced oxidative stress responses and mitochondrial damage. These observations provide an innate immune signaling mechanism for virus-induced neuronal death, and indicate that MAM and mitochondrial signaling of MAVS requires strict control to avoid deleterious effects. The work also reveals potential targets of MAM/mitochondrial signaling that might be considered for development of therapeutics to manage the deleterious effects of such encephalitic viral infections.
10.7 Negative Regulation of Mitochondrial Function and Antiviral Signaling

Viruses trigger multiple PRR pathways upon encountering the host. These pathways act in concert to eliminate the virus. Signaling cross talk between the RLR pathway, NLR pathways and caspase pathways have been identified as mediating both positive and negative regulation of RLR signaling (Ramos and Gale 2011). RLR signaling pathways may be antagonized at the level of PAMP recognition itself where, for example, the ebola virus VP35 protein sequesters dsRNA and prevents viral recognition by RIG-I (Cardenas et al. 2006). The influenza A virus NS1 protein binds RIG-I itself and prevents it from binding its downstream partners (Mibayashi et al. 2007). Negative regulation of mitochondria-mediated innate immunity is exerted at several levels, the most basic of which is the process of mitophagy, whereby the autophagy-related proteins, autophagy-related gene 5 (ATG 5) and/or ATG 12 remove damaged mitochondria and consequently suppress RLR signaling (Tal et al. 2009). Viruses such as measles virus exploit the mitophagy pathway to increase mitophagy and thereby decrease RLR signaling and enhance their replication (Xia et al. 2014). Severe fever with thrombocytopenia syndrome virus (SFTSV), an emerging bunyavirus, targets downstream molecules of the RLR pathway by inducing the formation of inclusion bodies that encapsulate IKKe and TBK1, thereby preventing IRF3 activation and IFNβ production (Ning et al. 2014). IKKe is a novel target for the nucleoprotein (NP) of arena viruses such as Lymphocytic Choriomeningitis Virus (LCMV). LCMV NP can bind the kinase domain of IKKe, and block its autocatalytic activity as well as sequester it away from MAVS and therefore inhibit its ability to phosphorylate IRF3, thereby down-regulating activation of the RLR pathway. However, LCMV NP does not bind the closely related kinase, TBK-1, indicating that the virus specifically targets IKKe (Pythoud et al. 2012). Mitochondrial E3 ubiquitin protein ligase 1 (MUL1) is another negative regulator of RIG-I signaling that interacts with MAVS on mitochondria and catalyzes RIG-I post-translational modifications that inhibit RIG-I signaling. Depletion of MUL1 potentiated RIG-I-mediated NF-κB and IFNβ reporter activity and enhanced responses to poly IC and Sendai virus. Thus, MUL1 is a novel regulator of the RIG-I-like receptor-dependent antiviral response (Jenkins et al. 2013).

MAVS is a major target for the host to regulate antiviral signaling. As noted earlier, the NOD-like protein NLRX1 that has been reported to be localized in the mitochondrial matrix as well as the outer membrane prevents CARD–CARD interactions between MAVS and RLR, thus inhibiting the RLR pathway (Arnoult et al. 2009). Globular head domain of complement component 1q (gC1qR) also directly binds and inhibits MAVS (Xu et al. 2009). Poly (rC)-binding protein 2 (PCBP2), an endogenous protein, similarly recruits atrophin interacting protein 4 (AIP4), catalyzing K48-linked polyubiquitination and degradation of MAVS (You et al. 2009). Similarly, another endogenous protein, PSMA7, the α4 subunit of the 20S proteasome, also induces the proteasomal degradation of MAVS (Jia et al. 2009). Though
the precise mechanisms by which some of the above endogenous proteins operate to suppress MAVS signaling are unclear (Koshiba 2013), the variety and the redundancy in the mode of action of some of these molecules suggests that the RLR pathway is tightly regulated to not only avoid aberrant activation but also to allow for quick down-regulation once the viral threat has been eliminated.

Specifically targeting MAVS to suppress innate antiviral immunity is a strategy employed by several viruses. The hepatitis A virus protease 3ABC, GB virus-B and the HCV protease NS3/4A all cleave and inactivate MAVS, though they cleave MAVS at different sites, likely implicating each site in specific roles of innate immune signaling (Horner and Gale 2013; Li et al. 2005; Chen et al. 2007). Ubiquitination induction and consequent proteasomal degradation is a strategy adopted by Hepatitis B virus X protein that interacts with MAVS and promotes its degradation. While respiratory syncytial virus exploits mitochondrial MAVS to suppress innate immunity (Goswami et al. 2013), UBX-domain containing family member, UBXN1, inhibits MAVS oligomerization in several RNA virus infections including vesicular stomatitis virus, Sendai virus, and dengue virus, thereby inhibiting RLR-mediated antiviral signaling (Wang et al. 2013a). The enterovirus 71 protease 2Apro targets MAVS to inhibit antiviral type I interferon responses (Wang et al. 2013b), while influenza A virus Enhancer of zeste homolog 2 is a negative regulator (Chen et al. 2013) that binds to MAVS and interferes with the interaction between MAVS and RIG-I. Polo-like kinase is another negative regulator of MAVS that disrupts the interaction between MAVS and TRAF3 and thereby negatively regulates IFNβ induction (Vitour et al. 2009). HIV infection results in damage to mitochondrial proteins involved in energy metabolism. Levels of a mitochondrial chaperone, prohibitin, are suppressed in HIV patients. Paradoxically, highly active antiretroviral therapy (HAART) further lowers prohibitin levels in HIV patients (Ciccosanti et al. 2010; Rossi et al. 2014). This understanding of the role of prohibitin in mitochondrial health and the deleterious effects of HAART on prohibitin could lead to the design of better antiretrovirals with fewer nonspecific effects. The numerous viral evasive strategies targeting MAVS that are outlined above point to the pivotal role that MAVS plays in antiviral immunity.

10.8 Apoptosis and Mitochondrial Antiviral Immunity

Mitochondria orchestrate the intrinsic pathway of apoptosis (Wang and Youle 2009). While the primary triggers that drive mitochondria-mediated apoptosis are still not well understood, the earliest detectable change is a increase in outer membrane permeability that triggers the release of proapoptotic molecules such as cytochrome c (Liu et al. 1996), second mitochondria-derived activator of caspase/Direct inhibitor of apoptosis-binding protein with low PI (Smac/DIABLO) (Du et al. 2000; Verhagen et al. 2000), Omi/Htr serine peptidase 2 (HtrA2) (Faccio et al. 2000; Hegde et al. 2002; Martins et al. 2002; Suzuki et al. 2001), endonuclease G (EndoG) (Li et al. 2001), and apoptosis-inducing factor (AIF) (Susin et al. 1996). This
permeabilization is produced by activation of the proapoptotic molecules, BAX and/or BAK ultimately leading to activation of caspase 9, leading to activation of caspase 3, the effector caspase that acts on apoptotic substrates leading to apoptosis. Activity of the BCL2 family of antiapoptotic molecules such as BCL2 and BCL-XL inhibits the activity of BAX and or BAK and thus inhibits apoptosis (Wang and Youle 2009).

Viruses have evolved several strategies to evade mitochondria-induced apoptosis to keep cells viable for longer following infection and thereby continue to propagate virus, or to induce premature apoptosis in innate sentinel cells and thus evade detection. In cytomegalovirus-infected cells, viral mitochondria-localized inhibitor of apoptosis (vMIA) can bind mitochondrial BAX, but not BAK, and thus prevent apoptosis (Arnoult et al. 2004). In influenza A virus-infected macrophages, mitochondrial NLRX1 prevents PB1-F2-induced premature apoptosis by binding to the protein (Jaworska et al. 2014). In a recent report, MAVS was shown to mediate apoptosis following Semliki forest virus infection in a BAX/BAK-independent, but caspase 8/caspase 3 dependent manner. This form of apoptosis did not require IFNβ, IRF3/IRF7, TRAF2 or FADD (El Maadidi et al. 2014). MAVS has also been shown to induce apoptosis in a RLR-independent manner following Sendai virus, HCV and severe acute respiratory syndrome corona virus (SARS CoV) infections (Lei et al. 2009; Huang et al. 2014). IRF3 can also mediate apoptosis by binding to BAX and translocating to mitochondria. Sendai virus infection of IRF3-/- mice leads to persistent infection (Chattopadhyay et al. 2013), suggesting that IRF3-mediated apoptotic removal of infected cells represents an important means of containing viral infection. HCV subverts mitochondria-induced apoptosis by stimulating parkin-mediated removal of damaged mitochondria by mitophagy (Kim et al. 2014), and increasing the rate of mitochondrial fission via Ser 616 phosphorylation of DRP1. Experimental silencing of DRP1 or parkin caused a significant increase in apoptotic signaling, evidenced by increased cytochrome c release from mitochondria, caspase 3 activity, and cleavage of poly(ADP-ribose) polymerase. These results suggest that HCV-induced mitochondrial fission and mitophagy serve to attenuate apoptosis and may contribute to persistent HCV infection (Kim et al. 2014).

10.9 Mitochondria and Adaptive immunity

The role for mitochondrial metabolism in supporting cell growth and proliferation has been well studied in tumor cells. Among immune cells, the relationship between metabolism and function has been better studied in macrophages (O’Neill and Hardie 2013; Shapiro et al. 2011) and T cells (Fox et al. 2005; van der Windt and Pearce 2012; Gerriets and Rathmell 2012). In B cells, the role for mitochondria in maintaining self-tolerance by inducing apoptosis following inappropriate activation has been established (Bouchon et al. 2000; Deming and Rathmell 2006). In dendritic cells, TLR-induced maturation and immunogenicity are dictated by cellular
metabolism such that DC cultured with or without glucose, for example, program T cells toward drastically different fates (Everts and Pearce 2014; Everts et al. 2014).

Upon recognizing antigen presented by antigen-presenting cells, T cells proliferate rapidly over about a 5–10 day period and exert their effector functions. Following this, they decline in numbers, and a small fraction of the originally proliferated cells, called memory cells, are maintained for months to years. Cellular metabolic requirements placed on mitochondria change at different phases of the above process. Mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase that integrates the diverse signals that T cells receive during this process to turn on transcription programs that support the varying metabolic demands (Waickman and Powell 2012).

Several studies have examined the requirement for various aspects of mitochondrial function in T cells during adaptive responses. At the proliferative effector phase response to LCMV infection, the mitochondrial membrane potential was maximal, pointing to a role for mitochondria during the exponential expansion of T cells (Zhu et al. 2014). Quiescent naïve and memory cells, while maintaining low levels of glycolysis, rely predominantly on oxidative phosphorylation (OXPHOS) for their energy and biosynthetic needs. As they undergo antigen-driven proliferation, effector cells make a necessary shift to predominantly use glycolysis while maintaining a low level of OXPHOS. This low level of OXPHOS-mediated ATP production is vital for effector function, as specifically inhibiting mitochondrial ATP production using oligomycin blocks T cell activation and proliferation (Chang et al. 2013). The role for mitochondria-derived ROS in T cell function was studied in a mouse model with T cells deficient for ubiquinol-cytochrome c reductase (UQCRFS1−/−). These T cells had a defect in their ability to generate ROS from complex III of mitochondria (Sena et al. 2013) and resulted in their poor proliferation and cytotoxic potential owing to a deficiency in activation of nuclear factor of activated T cells (NFAT) and subsequent IL-2 production. Interestingly, T cells exposed to elevated levels of ROS showed a deficient ability to respond to influenza A virus and impaired development (Case et al. 2011), suggesting that an optimal threshold of ROS is required for T cells to function normally. Another study that examined the role of mitochondrial metabolism in memory T cells found that IL-15 stimulated mitochondrial biogenesis and expression of carnitine palmitoyl transferase 1a (CPT1a), an enzyme that controlled a rate-limiting step in mitochondrial fatty acid metabolism. This gave the memory cells, but not naïve or effector cells, a higher mitochondrial spare respiratory capacity (SRC) and enhanced ability to transport fatty acids into the mitochondria for oxidation (van der Windt et al. 2012). This enabled memory cells, uniquely, to mount a rapid response upon reexposure to antigen (van der Windt et al. 2012). Our study of the role of MAVS in CD8 T cells during viral infection uncovered a role for MAVS in regulating cell proliferation, calcium homeostasis, and cytokine production, which indicates that MAVS has a crucial role in supporting effector functions in T cells (unpublished data). Thus in T cells, mitochondria have important roles in OXPHOS, lipid metabolism, ROS generation, and Ca^{2+} flux (Pearce et al. 2013) during the adaptive immune response.
Conclusion

Mitochondria stand at the crossroads of innate and adaptive immunity. They not only provide energy and biosynthetic molecules to support the rapid cellular proliferation that is characteristic of the adaptive response, but also provide a platform on which large complexes of antiviral molecules can be assembled to mount effective innate immune responses. Because of their importance to immunity, mitochondria are targeted for regulation of their associated proteins by several viruses. Their roles in antiviral immunity are complex with each cellular subset requiring a different aspect of mitochondrial metabolic function at distinct differentiation states and in responding to different pathogens. The involvement of mitochondria in response to infection as well as in noninfectious metabolic processes make them attractive targets for therapeutic interventions aimed at restoring or enhancing their function. The field of metabolic immunity that focuses on understanding how metabolism affects immune cell fate is relatively new and is expected to progress to reveal insights that will direct new approaches and strategies for enhancing the immune response to microbial pathogens and vaccination.

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