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Review

The essential role of mitochondrial dynamics in antiviral immunity

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A B S T R A C T

Viruses alter cellular physiology and function to establish cellular environment conducive for viral proliferation. Viral immune evasion is an essential aspect of viral persistence and proliferation. The multifaceted mitochondria play a central role in many cellular events such as metabolism, bioenergetics, cell death, and innate immune signaling. Recent findings accentuate that viruses regulate mitochondrial function and dynamics to facilitate viral proliferation. In this review, we will discuss how viruses exploit mitochondrial dynamics to modulate mitochondria-mediated antiviral innate immune response during infection. This review will provide new insight to understanding the virus-mediated alteration of mitochondrial dynamics and functions to perturb host antiviral immune signaling.

1. Introduction

Viral infections are predominantly associated with alterations of cellular physiology. In response, response, the cells upregulate stress response pathways to recover from stress and maintain cellular homeostasis. Mitochondria are the vital intracellular organelles crucial for regulation of various intracellular events such as energy metabolism, innate immunity, and cellular homeostasis (Bratic and Trifunovic, 2010). Mitochondria are highly prone to various cellular stress conditions and undergo damage and dysfunction leading to disruption of vital mitochondrial functions. Owing to their multifaceted role in myriad cellular functions, the maintenance of mitochondrial homeostasis is integral aspect of cellular stress response and homeostasis. Virus infection can directly or indirectly impair mitochondrial function and dynamics. It can be a consequence of physiological stress associated with infection or viral proteins may directly interfere with mitochondrial function and dynamics.

Accumulated damaged mitochondria trigger a vicious cycle of mitochondrial damage and cell death. Cells have evolved a mechanism to rapidly turnover dysfunctional and damaged mitochondria to maintain cellular homeostasis. Mitochondrial dynamics in conjunction with mitochondria-selective autophagy or mitophagy are required for maintaining the mitochondrial quality control. Although not experimentally verified, it is speculated that fission of the mitochondrial network in an asymmetric fashion facilitates the segregation of damaged mitochondria. Subsequently, the damaged mitochondria are flagged for removal by mitophagy, which is initiated by recruitment of respective adaptor proteins that interact with autophagy protein LC3 to facilitate the formation of the mitophagosome. The remnant healthy mitochondria fused back into the existing mitochondrial network through the mitochondrial fusion process. Through this sequence of events, the cells maintain mitochondrial quality and cellular homeostasis. Defects in mitochondrial dynamics and mitophagy have been implicated in many neurodegenerative disorders including Parkinson's and Alzheimer's diseases.

Mitochondria serve as a signaling hub for innate immune signals triggered by the pathogen-associated pattern recognition receptors and facilitate downstream signaling leading to interferon synthesis. Recent studies have demonstrated that the mitochondrial morphodynamics influences the innate immune signaling mediated through the mitochondrial antiviral signaling (MAVS) protein. Viruses can exploit the strategy of altering the mitochondrial dynamics to regulate host innate immune signaling. Alternatively, the viruses can inflict mitochondrial damage and injury to deregulate the host machinery staging the antiviral response. Viruses can also take advantage of the metabolic reprograming elicited by alteration in the mitochondrial morphodynamics to favor their propagation.

In this review, we will highlight the recent literature in the field of viral infections and mitochondrial dynamics and how viruses exploit mitochondrial dynamics, functions and signaling to evade innate immune signaling and favor viral replication and dissemination.

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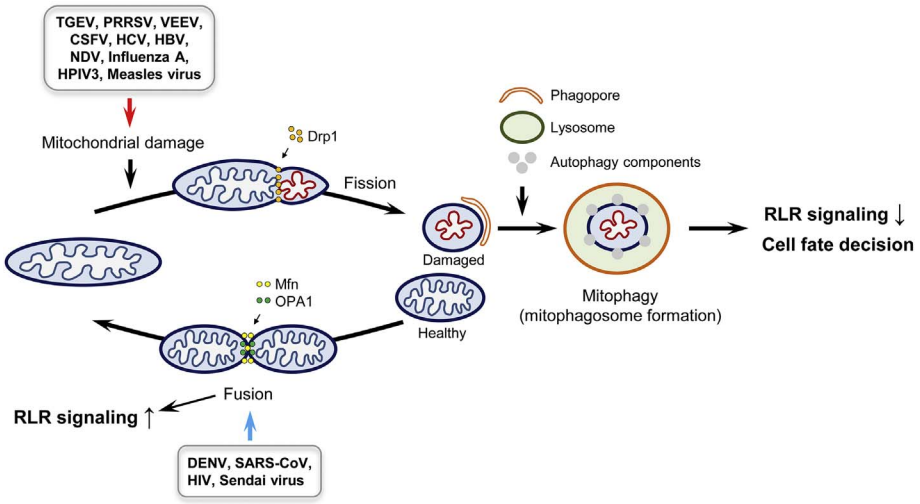

Fig. 1. Mitochondrial dynamics in viral infections. Under normal conditions, mitochondria display tubular morphology. Viral infection-induced stress causes mitochondrial damage. Asymmetric mitochondrial fission facilitates the segregation of the damaged mitochondria from the healthy ones, which are subsequently removed by mitophagy. The remaining healthy mitochondria fuse back into the tubular mitochondrial network. In this way, mitochondria maintain homeostasis and determine cell fate. During infection, viruses are able to modulate functions of cellular factors influencing mitochondrial dynamics (e.g., Drp1, Mfn, and OPA1) shifting mitochondrial dynamics towards either fission (mitochondrial fragmentation) or fusion (mitochondrial elongation) in favor of viral replication and propagation by either dampening innate immune signaling or by maintaining cell viability. RLR, RIG-I-like receptor; TGEV, transmissible gastroenteritis coronavirus; PRRSV, porcine reproductive and respiratory syndrome virus; VEEV, Venezuelan equine encephalitis virus; CSFV, classical swine fever virus; HCV, hepatitis C virus; HBV, hepatitis B virus; NDV, new castle disease virus; HPIV3, human parainfluenza virus type 3; DENV, Dengue virus, SARS-CoV, severe acute respiratory syndrome coronavirus; HIV, Human immunodeficiency virus.

2. Mitochondrial dynamics

In contrast to the earlier belief that mitochondria are solitary rod-shaped subcellular organelles, our current understanding suggests that mitochondria exist as dynamic network, which undergoes frequent cycles of fission and fusion (Fig. 1). The fission and fusion events help in the intermixing and distribution of mitochondrial contents, energy conductance, and responsiveness to cellular cues to maintain mitochondrial functional capacity. The dynamic nature of mitochondria also governs their interaction and communication with other subcellular organelles. Mitochondrial fusion (joining), fission (fragmentation) and transport constitute the three most important aspects of mitochondrial dynamics. Whereas, the integral coordination between mitochondrial dynamics and mitochondria-selective autophagy (mitophagy) drives the mitochondrial quality control process (Westermann, 2010).

2.1. Mitochondrial fission

Mitochondrial fission is initiated by recruitment of the dynamin-1-like protein (Drp1) to mitochondria (Fig. 1). Drp1 is a member of the dynamin superfamily of proteins consisting of a GTPase and GTPase effector domain. Drp1 recruitment and its activity is tightly regulated by post-translational modification such as phosphorylation, nitrosylation, and summoylation (Haun et al., 2013). Drp1 phosphorylation at the serine 616 residue by stress-signal-dependent CDK1 promotes Drp1 recruitment to the mitochondria. This process is mediated by mitochondrial outer membrane proteins including mitochondrial fission factor (Mff), mitochondrial division 49 and 51 (Mid49 and Mid51) that serve as receptors for Drp1 on the outer mitochondrial membrane (Palmer et al., 2011). Subsequently, Drp1 oligomerizes and tightly wraps around the mitochondria thereby constricting and severing the inner and outer mitochondrial membranes (Chan, 2006; Youle and Karbowski, 2005). Mitochondrial fission is also shown to be mediated by the ER tubules and actin filaments, independent of the Drp1 scission activity (van der Bliek et al., 2013). Mitochondrial fission facilitates the segregation of the damaged part of mitochondria from the dynamic mitochondrial network to allow its rapid removal through the mitochondria-selective autophagy process (Jin and Youle, 2012; van der Bliek et al., 2013).

2.2. Mitochondrial fusion

Fusion is a multistep process involving: (1) outer mitochondrial membrane (OMM) fusion and (2) inner mitochondrial membrane (IMM) fusion, which are mediated by Mitofusin 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (OPA1), respectively (Fig. 1) (Chan, 2006). Mitofusins 1 and 2 present on the opposing fusion membranes form homo- or hetero-oligomeric complexes in trans thereby tethering their outer mitochondrial membranes (Detmer and Chan, 2007; Koshiba et al., 2004). Inner mitochondrial membrane fusion is mediated by OPA1. Interestingly, OPA1 presence on adjacent fusing membrane is not essential to facilitate fusion (Song et al., 2009). OPA1 is a multifunctional protein involved in mitochondrial cristae remodeling, bioenergetics and apoptosis. Recent study suggests that selective mitochondrial fusion can be mediated by heterotypic fusion between OPA1 and cardiolipin present on opposing membranes (Liu and Chan, 2017). Mitochondrial fusion allows the joining of healthy discrete mitochondria into the functional mitochondrial network thereby facilitating the isolation of dysfunctional and damaged mitochondria from the network.

2.3. Mitophagy

Unnecessary or dysfunctional cellular components are removed by a self-destructive process known as autophagy. Autophagy is initiated by the formation of phagophore that engulfs the target cargo resulting in the formation of autophagosome, which subsequently fuses with the lysosome, eventually resulting in the delivery of the phagocytosed cargo to the lysosome (Fig. 1). Selective autophagy of mitochondria termed ‘mitophagy’ is one such process involved in rapid removal of dysfunctional or damaged mitochondria. Mitophagy is initiated by two distinct pathways; ubiquitin-dependent and independent pathways. (Georgakopoulos et al., 2017; Khaminets et al., 2016). Ubiquitin-dependent mitophagy is mediated by two major proteins; (1) the ubiquitin kinase PINK1 (PTEN-induced putative kinase 1), a mitochondrial

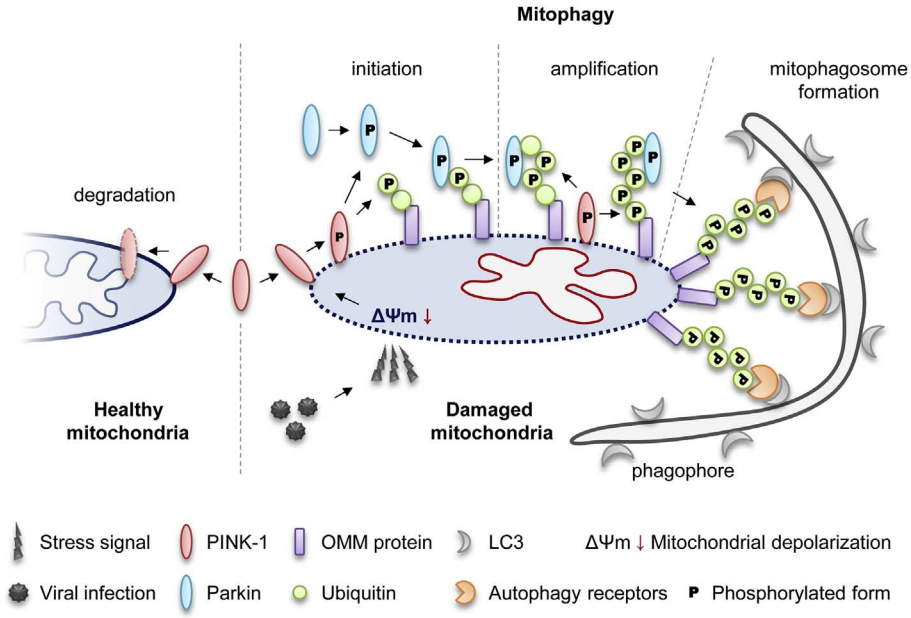

Fig. 2. Process of mitophagy through PINK1 and Parkin pathway. In healthy mitochondria, PINK1 (a mitochondrial serine/threonine protein kinase) is imported rapidly to IMM and subsequently degraded by mitochondrial proteases and proteasome. During viral infection, virus-induced stress triggers mitochondrial depolarization leading to reduced import of PINK1 to IMM, thereby resulting in the stabilization and activation of PINK1. Activated PINK1 initiates selective tagging of damaged mitochondria by phosphorylation of both ubiquitin and Parkin. Activated Parkin builds up ubiquitin chains, which are, in turn, phosphorylated by PINK1 amplifying the signal. The damaged mitochondria tagged with the unique signature of phospho-ubiquitin via PINK1 and Parkin activities are identified by the mitophagy receptors, which interact with LC3. This formation brings the autophagy machinery towards the damaged mitochondria for their subsequent engulfment within the expanding phagophore, resulting in the formation of mitophagosome.

serine/threonine protein kinase, which flags the damaged mitochondria and (2) Parkin, an E3 ligase, as a signal amplifier (Fig. 2) (Lazarou et al., 2015). In heathy mitochondria, cytosolic PINK1 containing a mitochondrial target sequence (MTS) translocates to the mitochondria and is imported rapidly to the IMM by the translocase of outer mitochondrial membrane (TOM) and translocase of inner mitochondrial membrane (TIM). Subsequently, PINK1 is degraded by downstream proteolytic events; involving excision of the MTS by mitochondrial processing protease (MPP), cleavage by presenilin-associated rhomboid-like protease (PARL), and final degradation (Jin and Youle, 2012). In the damaged mitochondria, the loss of membrane potential (ΔΨm) compromises TOM and TIM activity. This prevents the degradation of PINK1 and stabilizes PINK1 on the OMM of the damaged mitochondria (Meissner et al., 2011; Narendra et al., 2010). The stabilized PINK1 at the OMM recruits Parkin ubiquitin ligase, a signal amplifier, which gets activated by phosphorylation and ubiquitination. PINK1 phosphorylates the ubiquitin at Ser65 and the ubiquitin domain of Parkin to further activate Parkin ubiquitin ligase activity (Durcan and Fon, 2015; Kane et al., 2014; Kazlauskaite et al., 2014; Koyano et al., 2014; Narendra et al., 2008; Narendra et al., 2010; Vives-Bauza et al., 2010). In this way, PINK1 and Parkin cooperate to facilitate selective tagging of the damaged mitochondria with ubiquitin chains. This process can be negatively regulated by the deubiquitination mediated by the mitochondria localized deubiquitinase USP30 (Bingol et al., 2014) or by inhibiting PINK1/Parkin recruitment via PKA-mediated phosphorylation of MIC60 (Akabane et al., 2016). The damaged mitochondria tagged with ubiquitin chains are then engulfed by the phagophore resulting in formation of mitophagosome. Subsequently, the mitophagosome fuses with the lysosome to deliver the damaged mitochondria to the lysosome. The PINK-Parkin mediated mitophagy process is depicted in Fig. 2. Recently, Lazarou and Sliter et al. revealed that PINK1 can recruit the two primary mitophagy receptors (optineurin and NDP52), which then recruit other autophagy factors such as ULK1, DFCP1, and WIPI1 (Lazarou et al., 2015). Activated PINK1 is required for recruitment of optineurin (OPTN) and NDP52. Parkin is redundant for autophagy recruitment since autophagy receptors can be recruited in the absence of Parkin, however Parkin is required to increase the mitophagic flux. This suggests that phospho-ubiquitin generated by PINK1 serves as a unique signature for recruitment of the mitophagy receptor proteins and Parkin helps by building the ubiquitin chains for signal amplification (Lazarou et al., 2015). Parkin/PINK1 pathway also promotes TBK1 activation, which then subsequently primes the mitophagy receptors (OPTN, NDP52, and SQSTM1) (Heo et al., 2015; Matsumoto et al., 2015). Heo et al. showed that TBK1 phosphorylates OPTN at S473 and S513, which results in enhanced ubiquitin chain binding. The deubiquitinase USP15 widely expressed in brain and other organs antagonizes Parkin-mediated mitochondrial ubiquitination and mitophagy (Cornelissen et al., 2014).

3. Role of mitochondrial dynamics in viral infection

During viral infection host cells trigger antiviral defense such as; shut down of translation, foreign RNA editing and degradation, interferon production, etc. However, viruses have evolved strategies to escape or evade the host defense system in favor of viral propagation. In case of most RNA viruses, the cytosolic pathogen recognition receptors (i.e., RIG-I and MDA5) recognize viral RNAs and undergo conformational change and oligomerization thereby transducing the signal to the downstream signaling partner MAVS, an antiviral adaptor protein tethered to the OMM and mitochondria-associated membranes (MAM). Activated MAVS then coordinates the assembly of multimeric signaling complex called MAVS signalosome by facilitating recruitment of other host proteins (e.g., TRAFs, TBK1, and IRFs). The MAVS signalosome generates a highly cooperative context dependent signal resulting in the biogenesis of interferons (IFNs). Some viruses [e.g., hepatitis C virus (HCV)] cleave the MAVS protein, thereby suppressing the host antiviral response, which represents one among many strategies exploited by the viruses to target mitochondria and evade host defense strategies (Horner and Gale, 2013).

Autophagy has been implicated to influence viral propagation at multiple steps of viral life cycle. As autophagy rapidly clears the damaged cellular organelles, it generally blocks the induction of cell

death. Hence, autophagy may play a central role in determining the cell fate during viral infection. Alternatively, viruses can modulate autophagy for their replication and to inhibit cell death as a consequence of virus-induced cellular stress. For example, Dengue and Zika viruses utilize autophagy to improve their replication and induction of autophagy by pharmacological agents (e.g. rapamycin) enhances viral dissemination (Datan et al., 2016; Liang et al., 2016). In case of Chikungunya virus, autophagy limits virus-induced cell death and in vivo mortality (Joubert et al., 2012). Accumulating evidences suggest that mitochondrial dynamics, mitophagy, and interaction with MAM can regulate MAVS signalosome formation (Khan et al., 2015). Further, there is a report suggesting that MAVS can regulate mitochondrial homeostasis via autophagy, suggesting the intricate interplay or feedback loop to control mitochondria-mediated innate immunity (Sun et al., 2016).

Thus, it is important to understand the role of mitochondrial dynamics and mitophagy in the two closely connected aspects, acting as a determinant of cell fate and as a determinant of innate immune signaling during viral infection. These two aspects are tightly regulated by many viruses to promote viral persistence. During hepatitis B virus (HBV) or HCV infections, these viruses modulate mitochondrial dynamics to promote mitochondrial fission and mitophagy, to keeping virus-induced mitochondrial injury in check. HBV/HCV induced mitochondrial dynamics also leads to attenuation of IFN signaling in which Parkin-MAVS interactions affects MAVS downstream signaling and the final IFN production, thus crippling innate immunity (Kim et al., 2013a; Kim et al., 2014; Kim et al., 2013b). Both HBV and HCV cause chronic infection and the persistence of the virus in the infected hepatocytes is a major reason underlying the chronic hepatic inflammation leading to the onset of liver disease (Kim et al., 2013a; Kim et al., 2014; Kim et al., 2013b).

In general, it has been considered that bulk autophagy blocks apoptosis. However, recent studies showed that selective mitophagy can affect both cytoprotective and pro-apoptotic conditions (Carroll et al., 2014; Zhang et al., 2014). This might be due to the fact that mitochondria regulates both pro- and anti-apoptotic proteins such as Bcl-2 family, Bax, and Bak (Tsujimoto, 1998). Hence, mitochondrial dynamics, particularly mitophagy, can serve as a major determinant of cell fate during viral infection. Due to the functional significance of mitophagy in viral infection, viruses may modulate mitophagy in distinct fashions independent of autophagy. For example, Dengue virus-induced autophagy inhibits apoptosis to enhance virus replication (Datan et al., 2016; Lee et al., 2008; McLean et al., 2011). On the other hand, Dengue inhibits mitochondrial fission causing mitophagy failure. This process is associated with antiviral immune evasion during Dengue infection (Barbier et al., 2017; Chatel-Chaix et al., 2016).

There are many reports that viruses induce mitophagy to inhibit apoptosis (Gou et al., 2017; Li et al., 2016; Zhu et al., 2016). Transmissible gastroenteritis virus (TGEV), a porcine enteropathogenic coronavirus, induces complete mitophagy to promote cell survival and infection. Zhu et al. show that TGEV-induced mitophagy attenuates cell apoptosis by eliminating virus-induced ROS and enhances TGEV infection. TGEV stimulates DJ-1 protein deglycase to induce mitophagy. DJ-1 is also known as Parkinson disease protein 7. Knockdown of DJ-1 inhibits mitophagy leading to enhanced apoptosis after TGEV infection (Zhu et al., 2016).

As virus-induced mitophagy is a major determinant of cell viability, it is a critical factor to consider in virotherapy using oncolytic viruses. Newcastle disease virus (NDV) and measles virus are among the few of the promising cancer-killing oncolytic viruses. NDV and measles virus induce autophagy along with mitophagy in the non-small cell lung cancer cells (NSCLCs) and exploit mitophagy to favor viral replication by blocking cytochrome c release-triggered apoptosis (Meng et al., 2014). Inhibition of autophagy and mitophagy by pharmacological inhibitors such as 3-methyladenine (3-MA) enhanced oncolysis in NDV-infected NSCLCs. Interestingly, the delayed administration of 3-MA induced more effective oncolysis, since the initiation of autophagy is required for efficient NDV replication. Hence, a delay in 3-MA treatment, which inhibits the initial stages of autophagy process, may result in efficient NDV propagation leading to robust oncolysis in NSCLCs (Meng et al., 2014). In contrast, measles virus does not promote cell death via apoptosis but via necrosis or other mechanisms and measles virus-induced oncolysis was abrogated in autophagy-impaired NSCLCs (Xia et al., 2014b). Since the modulation of autophagy in virus-infected cells differentially affects cell viability in virus-dependent manner, it is very important to understand the role of autophagy in the perspective of individual viruses and to adequately design strategies to maximize oncolytic effect. This understanding will help develop effective therapeutic strategies for virotherapy in combination with autophagy or mitophagy targeting strategies.

4. Modulation of mitochondrial dynamics by viral infection

Mitochondrial dynamics is highly sensitive to changes in the cellular physiological conditions and is rapidly regulated to overcome the stressful conditions and maintain cellular homeostasis. Viral infection is associated with physiological stress and is highly likely that infection-associated stress can affect mitochondrial dynamics. However, some viruses can directly modulate mitochondrial dynamics and mitophagy via the viral proteins to regulate mitochondrial homeostasis and innate immune signaling. For example, the Dengue virus NS4B or NS3 proteins promote mitochondrial fusion by downregulating Drp1, thereby blocking mitochondrial fission (Barbier et al., 2017). Another study shows that Dengue virus NS4B induces elongation of mitochondria by inactivating Drp1. The resultant mitochondrial fusion compromises the integrity of MAMs, the sites of ER-mitochondria association, which are critical for innate immune signaling, thus inhibiting the RLR signaling and interferon production (Chatel-Chaix et al., 2016). In contrast, another study suggests that Dengue virus NS2B3 protease cleaves the MFNs, thereby suppressing mitochondrial fusion (Yu et al., 2015). Yu et al. revealed that MFN1 is required in antiviral RLR signaling pathway and the dominant-negative MFN1 mutant ($MFN1^{T109A}$), which blocks mitochondrial fusion, attenuates the RLR signaling and enhances DENV infection (Yu et al., 2015).

Shi et al. have shown that the SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) ORF-9b protein promotes mitochondrial elongation by physically interacting with Drp1 and facilitating its proteasomal degradation. In addition, the ORF-9b protein also binds to MAVS and promotes K48-linked ubiquitination-dependent proteasomal degradation of MAVS to disrupt MAVS downstream signaling and IFN production (Shi et al., 2014).

Several neurodegenerative disorders are characterized by mitochondrial dysfunction (Johri and Beal, 2012). HIV-associated neurocognitive disorder (HAND) is a one of such neurodegenerative disorder caused by the infection of human immunodeficiency virus-1 (HIV-1) to the central nervous system (CNS), which leads to neurotoxic events and the loss of cognitive and motor functions. HAND patients account for approximately 50% of total HIV patients and 17–20% of HAND patients suffer from HIV encephalitis (HIVE), a neuro-inflammation disorder (Gannon et al., 2011). Recently, abnormal mitochondrial dynamics or mitochondrial dysfunction was identified in human brain samples of HIVE or HAND subjects. Altered mitochondrial proteins were associated with HIV-related neuropathology in the HIV-infected patient samples (Avdoshina et al., 2016; Fields et al., 2016). Similar pathologies were also found in mouse brains of HIV envelope glycoprotein gp120 transgenic mice as well as in primary rat neurons exposed to gp120, suggesting that gp120 is responsible for mitochondrial dysfunction (Avdoshina et al., 2016; Fields et al., 2016). HIV viral protein gp120 induces Mfn1 expression and reduces Drp1 expression, but not Nef or Tat. Since Drp1 mediates mitochondrial fission and Mfn1 promotes mitochondrial fusion, Gp120 shifts the delicate balance of mitochondrial dynamics towards mitochondrial fusion. Drp1

overexpression reduced neuroinflammation and neurodegeneration in the GFAP-gp120-tg mice, suggesting a possible strategy to prevent neurodegeneration in HIV patients by promoting mitochondrial fission (Fields et al., 2016). Another HIV protein, viral protein R (Vpr), is also reported to trigger mitochondrial dysfunction or damage leading to cell death (Huang et al., 2012). HIV-1 Vpr is an integral membrane protein that is localized in the MAM, ER, and OMM regions. HIV-1 Vpr forms vesicles in ER/MAM and transports to the OMM by membrane fusion. Vpr damages the OMM by triggering loss of membrane potential, with subsequent damage to mitochondria. Vpr also promotes Drp1 localization to nucleus from cytosol and proteasome-dependent degradation of Mfn2 by interaction with the CUL4 E3 ubiquitin ligase complex, affecting overall mitochondrial dynamics (Casey et al., 2010; Huang et al., 2012; Wen et al., 2007). In agreement, Drp1 and Mfn2 overexpression prevents Vpr-induced loss of mitochondrial membrane potential (ΔΨm) and apoptotic cell death. (Huang et al., 2012).

Influenza A virus protein PB1-F2 is a key virulence factor contributing to the pathogenicity of the viral infection (Zamarin et al., 2005). PB1-F2 translocates into the IMM space, where it disrupts mitochondrial organization inducing cell death by interacting with mitochondrial proteins adenine nucleotide translocator 3 (ANT3), and voltage-dependent anion channel 1 (VDAC1) (Zamarin et al., 2005). While full-length PB1-F2 (PR8, 88 W, and 58 W strains) localizes to the mitochondria, the C-terminal truncated version of PB1-F2 (designated as 12S variant) from a major population of the low pathogenic subtype, is localized in the cytoplasm (Yoshizumi et al., 2014). C-terminal domain of PB1-F2 is responsible for the interaction with the ANT3, which mediates PB1-F2-induced loss of the mitochondrial membrane potential (Zamarin et al., 2005). Accumulation of full-length PB1-F2 protein causes loss of mitochondrial membrane potential (ΔΨm) leading to mitochondrial fragmentation. In contrast, 12S variant (C-terminal truncated form) does not alter mitochondrial membrane potential. The full-length PB1-F2-mediated attenuation of ΔΨm suppresses the RIG-I signaling pathway and activation of NLRP3 inflammasomes (Yoshizumi et al., 2014). These observations suggest an essential role of PB1-F2 in the virulence of influenza viruses via modulation of host mitochondrial dynamics.

HCV stimulates the expression of Parkin and PINK1 and triggers Parkin translocation to the mitochondria, followed by induction of mitophagy. HCV-induced mitophagy is functionally associated with HCV-mediated impairment of oxidative phosphorylation and depletion of mitochondria, which may result in liver injury (Kim et al., 2013b). It is also reported that HCV core protein physically interacts with Parkin, and inhibits mitophagy by sequestering Parkin. Yeast two-hybrid assays and immunoprecipitation were used to demonstrate that HCV core protein binds to N-terminus of Parkin, comprising the ubiquitin-like domain and RING domain. (Hara et al., 2014). However, the underlying mechanism of how HCV increases Parkin/PINK1 expression and how the Parkin-HCV core protein interaction affects the Parkin-dependent mitophagy remains to be characterized. Classical swine fever virus (CSFV) infection affects mitochondrial dynamics similar to HCV. CSFV downregulates MFN2 expression and stimulates Parkin and PINK1 expression leading to increase in mitochondrial fission and mitophagy (Gou et al., 2017).

Recently, Ding et al. reported Parkin/PINK1-independent regulation of mitophagy by viral protein during human parainfluenza virus type 3 (HPIV3) infection (Ding et al., 2017). HPIV3 or Matrix protein (M) of HPIV3 alone is able to induce mitophagy. Immunoprecipitation followed by mass spectrometry revealed the binding partner of M is a mitochondrial Tu translation elongation factor (TUFM) (Ding et al., 2017), which is known to regulate VSV-induced autophagy (Lei et al., 2012). M mediates TUFM-dependent mitophagy and also serves as mitophagy receptor by interacting with LC3. Interaction of M and TUFM leads to inhibition of type I IFN response. It is further shown that the inhibition of type I IFN response is independent of Parkin/PINK1 and that M protein can induce mitophagy in Parkin-deficient HeLa cells (Lazarou et al., 2015). The HPIV3-M_{K295A} virus, harboring the mutant M protein deficient in binding LC3 and induction of mitophagy, lacks the ability to abrogate the type I IFN production during infection.

5. Role of mitochondrial dynamics in modulation of innate antiviral immune signaling

As mentioned earlier, antiviral response is predominantly mediated by RLR signaling during RNA virus infection. Viral RNAs or pathogen associated molecular patterns (PAMPS) are initially recognized by the helicase domain of RLRs. RLRs and MAVS have similar CARD domains, which facilitates their interaction and oligomerization via CARD-CARD interaction leading to the recruitment of effector proteins in the downstream signaling events (e.g., TRAFs, and TBK1) at mitochondria. The assembled MAVS signalosome activates the transcription factors such as IRF3 or IRF7 to trigger transcriptional induction of IFNs. As MAVS signalosome is mainly formed at the MAM and/or OMM, membrane structures are considered as critical factors (Horner and Gale, 2013). Recent studies, showed a clear link between mitochondrial dynamics and innate immunity (Castanier et al., 2010). For efficient antiviral responses, not only proteins that are associated with mitochondria are important but other features of mitochondria such as morphology, dynamics, and membrane potential also play a crucial role. Castanier et al. observed that Sendai virus promotes mitochondrial elongation during viral infection and the dsRNAs that mimic viral RNAs can activate RLR signaling and promote mitochondrial elongation. Modulation of host proteins regulating mitochondrial dynamics such as Drp1 and MFNs resulted in differential regulation of RLR signaling, indicating that mitochondrial elongation enhances, while mitochondrial fragmentation decreases RLR signaling (Castanier et al., 2010). This study suggests the tight association between RLR signaling and mitochondrial dynamics (Fig. 1). We also observed that the knockdown of genes promoting mitochondrial fission such as Drp1 enhances antiviral responses upon viral infection along with mitochondrial elongation (Castanier et al., 2010; Kim et al., 2014). In contrast, silencing Mfn1 and OPA1 expression results in mitochondrial fragmentation along with reduced antiviral responses upon viral infection (Castanier et al., 2010; Onoguchi et al., 2010). Castanier et al. also demonstrated that Mfn1 binds to MAVS and that the Mfn1/MAVS-mediated mitochondrial fusion promotes ER-mitochondria tethering facilitating MAVS-STING association (Castanier et al., 2010). Onoguchi et al. also revealed the important role of Mfn1-MAVS interaction in RLR signaling. They showed that RLR activation promotes MAVS distribution on the mitochondria forming speckle-like aggregates and that the knockdown of Mfn1 inhibited this speckle-like pattern abrogating RLR signaling. GTPase domain of Mfn1 is critical for interaction with MAVS since the dominant negative GTP-binding-deficient mutant of Mfn1 ($Mfn1^{T109A}$) fails to activate RLR signaling (Onoguchi et al., 2010).

Structure and function of Mfn1 and Mfn2 are very similar in the context of mitochondrial dynamics. However, it seems that both the MFNs distinctly regulate RLR signaling. However, the precise mechanism involved in MFNs-mediated regulation of RLR signaling still needs to be elucidated. Castanier et al. show that MAVS interact with Mfn1, but not with Drp1, OPA1, Fis1, and Mfn2 (Castanier et al., 2010). However, Onoguchi et al. suggests that MAVS interacts with Mfn2. In this study, Mfn2 silencing did not abrogate RLR signaling (Onoguchi et al., 2010). Interestingly, Yasukawa et al. reported that Mfn2 interacts with MAVS via HR1 not the GTPase domain to inhibit RLR signaling, which is in contrast to the effect of MAVS-Mfn1 interaction on RLR signaling (Yasukawa et al., 2009). More detailed studies are required to characterize the RLR signaling to explain the inconsistency found in these studies.

As mentioned earlier, some viruses (e.g., HBV, HCV, NDV, and measles viruses) shift the mitochondrial dynamics towards fission and mitophagy to favor viral replication (Kim et al., 2013a; Kim et al., 2014; Kim et al., 2013b; Meng et al., 2014). Given the role of mitochondria as

a central hub of innate immune signaling, it is easy to speculate that virus-induced disruption of mitochondrial dynamics or mitophagy affects innate immunity. However, viruses can exploit the strategy of altering mitochondrial dynamics to deregulate host innate immune signaling. Also, virus exploits mitophagy to reduce the overall mitochondrial mass to reduce the levels of host machinery staging the antiviral response. In agreement with these scenarios, it has been found that knockdown of autophagy related genes (e.g., ATG7, BECN1, SQSTM1, and RAB7) significantly enhanced virus-induced antiviral immune response during measles virus infection (Xia et al., 2014a). Measles virus infection leads to colocalization of mitochondria with autophagosomes leading to a reduction in overall mitochondrial mass indicating mitochondrial degradation by mitophagy. Particularly, knockdown of SQSTM1 prevented measles virus-induced mitochondrial degradation, suggesting that SQSTM1 mediates measles virus-induced mitophagy contributing to the impaired RLR signaling (Xia et al., 2014a). Other viruses have also been shown to exploit this strategy of reducing the cellular mitochondrial mass to abrogate RLR signaling.

However, Khan et al. found that the inhibition of mitophagy does not affect ISRE activity in HBV expressing cells, suggesting that the effect of Parkin on RLR signaling is independent of its role in mitophagy. Khan et al. demonstrated that HBV-induced Parkin activation suppresses innate immunity via disruption of MAVS signalosome, but not by result of mitophagy. Parkin physically interacts with MAVS and modulates MAVS signaling by facilitating the accumulation of linear ubiquitin chain near the MAVS signalosome that results in the disruption of MAVS downstream signaling (Khan et al., 2016). MAVS also can be ubiquitinated by other E3 ligases such as MARCH5, TRIM25, RNF5, AIP4, RNF125, and TRIM31, and its ubiquitination play a critical role in innate immunity (Heaton et al., 2016; Liu et al., 2017; Yoo et al., 2015). Given that Parkin-dependent mitophagy is also associated with the ubiquitination of mitochondrial outer membrane proteins, ubiquitination might serve as a common factor linking mitophagy and innate immunity. Khan et al. provided a clue in the context (Khan et al., 2016). It is also noteworthy to mention that Parkin can be positively regulated by ISGylation, which is a covalent conjugation of ISG15, a negative regulator of type I interferons (Im et al., 2016). Furthermore, Sun et al. have suggested that MAVS can regulate mitochondrial homeostasis via autophagy (Sun et al., 2016). In short, these accumulating reports suggest a complex interplay between mitochondrial dynamics and MAVS signalosome to control mitochondria-mediated interferon biogenesis.

6. Role of mitochondrial dynamics in viral carcinogenesis

Although many studies have shown that mitochondrial dynamics are altered in cancer cells and that it plays crucial roles in cancer progression (Trotta and Chipuk, 2017), little is known about the role of mitochondrial dynamics in the context of viral carcinogenesis. However, recent study revealed the possible association of viral carcinogenesis with altered mitochondrial dynamics during Epstein–Barr virus (EBV) infection. EBV, a human herpesvirus 4 (HHV-4), is one of the most common viruses in humans and can cause various lymphoid and epithelial malignancies (Young and Rickinson, 2004). The viral latent membrane protein 2A (LMP2A) has been shown to increase the invasive ability and induce epithelial–mesenchymal transition (EMT) in nasopharyngeal carcinoma. Pal et al. showed that LMP2A promoted mitochondrial fission with elevation of Drp1 level and that LMP2A-induced Drp1 elevation enhanced Notch-pathway-mediated cell migration and EMT (Pal et al., 2014). This suggests the important roles of altered mitochondrial dynamics by viruses in EMT and carcinogenesis. The role of mitochondrial dynamics in carcinogenesis or tumorigenesis during infection with other chronic or oncogenic viruses such as HBV, HCV, HIV, or KSHV is yet to be characterized.

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References

Akabane, S., Uno, M., Tani, N., Shimazaki, S., Ebara, N., Kato, H., Kosako, H., Oka, T., 2016. PKA regulates PINK1 stability and Parkin recruitment to damaged mitochondria through phosphorylation of MIC60. Mol. Cell 62, 371–384.
Avdoshina, V., Fields, J.A., Castellano, P., Dedoni, S., Palchik, G., Trejo, M., Adame, A., Rockenstein, E., Eugenin, E., Masliah, E., Mocchetti, I., 2016. The HIV protein gp120 alters mitochondrial dynamics in neurons. Neurotox. Res. 29, 583–593.
Barbier, V., Lang, D., Valois, S., Rothman, A.L., Medin, C.L., 2017. Dengue virus induces mitochondrial elongation through impairment of Drp1-triggered mitochondrial fission. Virology 500, 149–160.
Bingol, B., Tea, J.S., Phu, L., Reichelt, M., Bakalarski, C.E., Song, Q., Foreman, O., Kirkpatrick, D.S., Sheng, M., 2014. The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature 510, 370–375.
van der Bliek, A.M., Shen, Q., Kawajiri, S., 2013. Mechanisms of mitochondrial fission and fusion. Cold Spring Harb. Perspect. Biol. 5.
Bratic, I., Trifunovic, A., 2010. Mitochondrial energy metabolism and ageing. Biochim. Biophys. Acta 1797, 961–967.
Carroll, R.G., Hollville, E., Martin, S.J., 2014. Parkin sensitizes toward apoptosis induced by mitochondrial depolarization through promoting degradation of Mcl-1. Cell Rep. 9, 1538–1553.
Casey, L., Wen, X., de Noronha, C.M., 2010. The functions of the HIV1 protein Vpr and its action through the DCAF1.DDB1.Cullin4 ubiquitin ligase. Cytokine 51, 1–9.
Castanier, C., Garcin, D., Vazquez, A., Arnoult, D., 2010. Mitochondrial dynamics regulate the RIG-I-like receptor antiviral pathway. EMBO Rep. 11, 133–138.
Chan, D.C., 2006. Mitochondria: dynamic organelles in disease, aging, and development. Cell 125, 1241–1252.
Chatel-Chaix, L., Cortese, M., Romero-Brey, I., Bender, S., Neufeldt, C.J., Fischl, W., Scaturro, P., Schieber, N., Schwab, Y., Fischer, B., Ruggieri, A., Bartenschlager, R., 2016. Dengue virus perturbs mitochondrial Morphodynamics to dampen innate immune responses. Cell Host Microbe 20, 342–356.
Cornelissen, T., Haddad, D., Wauters, F., Van Humbeeck, C., Mandemakers, W., Koentjoro, B., Sue, C., Gevaert, K., De Strooper, B., Verstreken, P., Vandenberghe, W., 2014. The deubiquitinase USP15 antagonizes Parkin-mediated mitochondrial ubiquitination and mitophagy. Hum. Mol. Genet. 23, 5227–5242.
Datan, E., Roy, S.G., Germain, G., Zali, N., McLean, J.E., Golshan, G., Harbajan, S., Lockshin, R.A., Zakeri, Z., 2016. Dengue-induced autophagy, virus replication and protection from cell death require ER stress (PERK) pathway activation. Cell Death Dis. 7, e2127.
Detmer, S.A., Chan, D.C., 2007. Functions and dysfunctions of mitochondrial dynamics. Nat. Rev. Mol. Cell Biol. 8, 870–879.
Ding, B., Zhang, L., Li, Z., Zhong, Y., Tang, Q., Qin, Y., Chen, M., 2017. The matrix protein of human parainfluenza virus type 3 induces Mitophagy that suppresses interferon responses. Cell Host Microbe 21, 538–547 (e534).
Durcan, T.M., Fon, E.A., 2015. The three 'P's of mitophagy: PARKIN, PINK1, and post-translational modifications. Genes Dev. 29, 989–999.
Fields, J.A., Serger, E., Campos, S., Divakaruni, A.S., Kim, C., Smith, K., Trejo, M., Adame, A., Spencer, B., Rockenstein, E., Murphy, A.N., Ellis, R.J., Letendre, S., Grant, I., Masliah, E., 2016. HIV alters neuronal mitochondrial fission/fusion in the brain during HIV-associated neurocognitive disorders. Neurobiol. Dis. 86, 154–169.
Gannon, P., Khan, M.Z., Kolson, D.L., 2011. Current understanding of HIV-associated neurocognitive disorders pathogenesis. Curr. Opin. Neurol. 24, 275–283.
Georgakopoulos, N.D., Wells, G., Campanella, M., 2017. The pharmacological regulation of cellular mitophagy. Nat. Chem. Biol. 13, 136–146.
Gou, H., Zhao, M., Xu, H., Yuan, J., He, W., Zhu, M., Ding, H., Yi, L., Chen, J., 2017. CSFV induced mitochondrial fission and mitophagy to inhibit apoptosis. Oncotarget 8, 39382–39400.
Hara, Y., Yanatori, I., Ikeda, M., Kiyokage, E., Nishina, S., Tomiyama, Y., Toida, K., Kishi, F., Kato, N., Imamura, M., Chayama, K., Hino, K., 2014. Hepatitis C virus core protein suppresses mitophagy by interacting with parkin in the context of mitochondrial depolarization. Am. J. Pathol. 184, 3026–3039.
Haun, F., Nakamura, T., Lipton, S.A., 2013. Dysfunctional mitochondrial dynamics in the pathophysiology of neurodegenerative diseases. J. Cell Death 6, 27–35.
Heaton, S.M., Borg, N.A., Dixit, V.M., 2016. Ubiquitin in the activation and attenuation of innate antiviral immunity. J. Exp. Med. 213, 1–13.
Heo, J.M., Ordureau, A., Paulo, J.A., Rinehart, J., Harper, J.W., 2015. The PINK1-PARKIN mitochondrial Ubiquitylation pathway drives a program of OPTN/NDP52 recruitment and TBK1 activation to promote Mitophagy. Mol. Cell 60, 7–20.
Horner, S.M., Gale, M., 2013. Regulation of hepatic innate immunity by hepatitis C virus. Nat. Med. 19, 879–888.
Huang, C.Y., Chiang, S.F., Lin, T.Y., Chiou, S.H., Chow, K.C., 2012. HIV-1 Vpr triggers mitochondrial destruction by impairing Mfn2-mediated ER-mitochondria interaction.

PLoS One 7, e33657.
Im, E., Yoo, L., Hyun, M., Shin, W.H., Chung, K.C., 2016. Covalent ISG15 conjugation positively regulates the ubiquitin E3 ligase activity of parkin. Open Biol. 6.
Jin, S.M., Youle, R.J., 2012. PINK1- and Parkin-mediated mitophagy at a glance. J. Cell Sci. 125, 795–799.
Johri, A., Beal, M.F., 2012. Mitochondrial dysfunction in neurodegenerative diseases. J. Pharmacol. Exp. Ther. 342, 619–630.
Joubert, P.E., Werneke, S.W., de la Calle, C., Guivel-Benhassine, F., Giodini, A., Peduto, L., Levine, B., Schwartz, O., Lenschow, D.J., Albert, M.L., 2012. Chikungunya virus-induced autophagy delays caspase-dependent cell death. J. Exp. Med. 209, 1029–1047.
Kane, L.A., Lazarou, M., Fogel, A.I., Li, Y., Yamano, K., Sarraf, S.A., Banerjee, S., Youle, R.J., 2014. PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. J. Cell Biol. 205, 143–153.
Kazlauskaite, A., Kondapalli, C., Gourlay, R., Campbell, D.G., Ritorto, M.S., Hofmann, K., Alessi, D.R., Knebel, A., Trost, M., Muqit, M.M., 2014. Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser65. Biochem. J. 460, 127–139.
Khaminets, A., Behl, C., Dikic, I., 2016. Ubiquitin-dependent and independent signals in selective autophagy. Trends Cell Biol. 26, 6–16.
Khan, M., Syed, G.H., Kim, S.J., Siddiqui, A., 2015. Mitochondrial dynamics and viral infections: a close nexus. Biochim. Biophys. Acta 1853, 2822–2833.
Khan, M., Syed, G.H., Kim, S.J., Siddiqui, A., 2016. Hepatitis B virus-induced Parkin-dependent recruitment of linear ubiquitin assembly complex (LUBAC) to mitochondria and attenuation of innate immunity. PLoS Pathog. 12, e1005693.
Kim, S.J., Khan, M., Quan, J., Till, A., Subramani, S., Siddiqui, A., 2013a. Hepatitis B virus disrupts mitochondrial dynamics: induces fission and mitophagy to attenuate apoptosis. PLoS Pathog. 9, e1003722.
Kim, S.J., Syed, G.H., Siddiqui, A., 2013b. Hepatitis C virus induces the mitochondrial translocation of Parkin and subsequent mitophagy. PLoS Pathog. 9, e1003285.
Kim, S.J., Syed, G.H., Khan, M., Chiu, W.W., Sohail, M.A., Gish, R.G., Siddiqui, A., 2014. Hepatitis C virus triggers mitochondrial fission and attenuates apoptosis to promote viral persistence. Proc. Natl. Acad. Sci. U. S. A. 111, 6413–6418.
Koshiba, T., Detmer, S.A., Kaiser, J.T., Chen, H., McCaffery, J.M., Chan, D.C., 2004. Structural basis of mitochondrial tethering by mitofusin complexes. Science 305, 858–862.
Koyano, F., Okatsu, K., Kosako, H., Tamura, Y., Go, E., Kimura, M., Kimura, Y., Tsuchiya, H., Yoshihara, H., Hirokawa, T., Endo, T., Fon, E.A., Trempe, J.F., Saeki, Y., Tanaka, K., Matsuda, N., 2014. Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature 510, 162–166.
Lazarou, M., Sliter, D.A., Kane, L.A., Sarraf, S.A., Wang, C., Burman, J.L., Sideris, D.P., Fogel, A.I., Youle, R.J., 2015. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature 524, 309–314.
Lee, Y.R., Lei, H.Y., Liu, M.T., Wang, J.R., Chen, S.H., Jiang-Shieh, Y.F., Lin, Y.S., Yeh, T.M., Liu, C.C., Liu, H.S., 2008. Autophagic machinery activated by dengue virus enhances virus replication. Virology 374, 240–248.
Lei, Y., Wen, H., Yu, Y., Taxman, D.J., Zhang, L., Widman, D.G., Swanson, K.V., Wen, K.W., Damania, B., Moore, C.B., Giguère, P.M., Siderovski, D.P., Hiscott, J., Razani, B., Semenkovich, C.F., Chen, X., Ting, J.P., 2012. The mitochondrial proteins NLRX1 and TUFM form a complex that regulates type I interferon and autophagy. Immunity 36, 933–946.
Li, S., Wang, J., Zhou, A., Khan, F.A., Hu, L., Zhang, S., 2016. Porcine reproductive and respiratory syndrome virus triggers mitochondrial fission and mitophagy to attenuate apoptosis. Oncotarget 7, 56002–56012.
Liang, Q., Luo, Z., Zeng, J., Chen, W., Foo, S.S., Lee, S.A., Ge, J., Wang, S., Goldman, S.A., Zlokovic, B.V., Zhao, Z., Jung, J.U., 2016. Zika virus NS4A and NS4B proteins deregulate Akt-mTOR signaling in human fetal neural stem cells to inhibit neurogenesis and induce autophagy. Cell Stem Cell 19, 663–671.
Liu, R., Chan, D.C., 2017. OPA1 and cardiolipin team up for mitochondrial fusion. Nat. Cell Biol. 19, 760–762.
Liu, B., Zhang, M., Chu, H., Zhang, H., Wu, H., Song, G., Wang, P., Zhao, K., Hou, J., Wang, X., Zhang, L., Gao, C., 2017. The ubiquitin E3 ligase TRIM31 promotes aggregation and activation of the signaling adaptor MAVS through Lys63-linked polyubiquitination. Nat. Immunol. 18, 214–224.
Matsumoto, G., Shimogori, T., Hattori, N., Nukina, N., 2015. TBK1 controls autophagosomal engulfment of polyubiquitinated mitochondria through p62/SQSTM1 phosphorylation. Hum. Mol. Genet. 24, 4429–4442.
McLean, J.E., Wudzinska, A., Datan, E., Quaglino, D., Zakeri, Z., 2011. Flavivirus NS4A-induced autophagy protects cells against death and enhances virus replication. J. Biol. Chem. 286, 22147–22159.
Meissner, C., Lorenz, H., Weihofen, A., Selkoe, D.J., Lemberg, M.K., 2011. The mitochondrial intramembrane protease PARL cleaves human Pink1 to regulate Pink1 trafficking. J. Neurochem. 117, 856–867.
Meng, G., Xia, M., Wang, D., Chen, A., Wang, Y., Wang, H., Yu, D., Wei, J., 2014. Mitophagy promotes replication of oncolytic Newcastle disease virus by blocking intrinsic apoptosis in lung cancer cells. Oncotarget 5, 6365–6374.
Narendra, D., Tanaka, A., Suen, D.F., Youle, R.J., 2008. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J. Cell Biol. 183, 795–803.
Narendra, D.P., Jin, S.M., Tanaka, A., Suen, D.F., Gautier, C.A., Shen, J., Cookson, M.R., Youle, R.J., 2010. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol. 8, e1000298.
Onoguchi, K., Onomoto, K., Takamatsu, S., Jogi, M., Takemura, A., Morimoto, S., Julkunen, I., Namiki, H., Yoneyama, M., Fujita, T., 2010. Virus-infection or 5'ppp-RNA activates antiviral signal through redistribution of IPS-1 mediated by MFN1. PLoS Pathog. 6, e1001012.
Pal, A.D., Basak, N.P., Banerjee, A.S., Banerjee, S., 2014. Epstein-Barr virus latent membrane protein-2A alters mitochondrial dynamics promoting cellular migration mediated by notch signaling pathway. Carcinogenesis 35, 1592–1601.
Palmer, C.S., Osellame, L.D., Laine, D., Koutsopoulos, O.S., Frazier, A.E., Ryan, M.T., 2011. MiD49 and MiD51, new components of the mitochondrial fission machinery. EMBO Rep. 12, 565–573.
Shi, C.S., Qi, H.Y., Boularan, C., Huang, N.N., Abu-Asab, M., Shelhamer, J.H., Kehrl, J.H., 2014. SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome. J. Immunol. 193, 3080–3089.
Song, Z., Ghochani, M., McCaffery, J.M., Frey, T.G., Chan, D.C., 2009. Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion. Mol. Biol. Cell 20, 3525–3532.
Sun, X., Sun, L., Zhao, Y., Li, Y., Lin, W., Chen, D., Sun, Q., 2016. MAVS maintains mitochondrial homeostasis via autophagy. Cell Discov. 2, 16024.
Trotta, A.P., Chipuk, J.E., 2017. Mitochondrial dynamics as regulators of cancer biology. Cell. Mol. Life Sci. 74, 1999–2017.
Tsujimoto, Y., 1998. Role of Bcl-2 family proteins in apoptosis: apoptosomes or mitochondria? Genes Cells 3, 697–707.
Vives-Bauza, C., Zhou, C., Huang, Y., Cui, M., de Vries, R.L., Kim, J., May, J., Tocilescu, M.A., Liu, W., Ko, H.S., Magrane, J., Moore, D.J., Dawson, V.L., Grailhe, R., Dawson, T.M., Li, C., Tieu, K., Przedborski, S., 2010. PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. Proc. Natl. Acad. Sci. U. S. A. 107, 378–383.
Wen, X., Duus, K.M., Friedrich, T.D., de Noronha, C.M., 2007. The HIV1 protein Vpr acts to promote G2 cell cycle arrest by engaging a DDB1 and Cullin4A-containing ubiquitin ligase complex using VprBP/DCAF1 as an adaptor. J. Biol. Chem. 282, 27046–27057.
Westermann, B., 2010. Mitochondrial fusion and fission in cell life and death. Nat. Rev. Mol. Cell Biol. 11, 872–884.
Xia, M., Gonzalez, P., Li, C., Meng, G., Jiang, A., Wang, H., Gao, Q., Debatin, K.M., Beltinger, C., Wei, J., 2014a. Mitophagy enhances oncolytic measles virus replication by mitigating DDX58/RIG-I-like receptor signaling. J. Virol. 88, 5152–5164.
Xia, M., Meng, G., Jiang, A., Chen, A., Dahlhaus, M., Gonzalez, P., Beltinger, C., Wei, J., 2014b. Mitophagy switches cell death from apoptosis to necrosis in NSCLC cells treated with oncolytic measles virus. Oncotarget 5, 3907–3918.
Yasukawa, K., Oshiumi, H., Takeda, M., Ishihara, N., Yanagi, Y., Seya, T., Kawabata, S., Koshiba, T., 2009. Mitofusin 2 inhibits mitochondrial antiviral signaling. Sci. Signal. 2, ra47.
Yoo, Y.S., Park, Y.Y., Kim, J.H., Cho, H., Kim, S.H., Lee, H.S., Kim, T.H., Sun Kim, Y., Lee, Y., Kim, C.J., Jung, J.U., Lee, J.S., 2015. The mitochondrial ubiquitin ligase MARCH5 resolves MAVS aggregates during antiviral signalling. Nat. Commun. 6, 7910.
Yoshizumi, T., Ichinohe, T., Sasaki, O., Otera, H., Kawabata, S., Mihara, K., Koshiba, T., 2014. Influenza A virus protein PB1-F2 translocates into mitochondria via Tom40 channels and impairs innate immunity. Nat. Commun. 5, 4713.
Youle, R.J., Karbowski, M., 2005. Mitochondrial fission in apoptosis. Nat. Rev. Mol. Cell Biol. 6, 657–663.
Young, L.S., Rickinson, A.B., 2004. Epstein-Barr virus: 40 years on. Nat. Rev. Cancer 4, 757–768.
Yu, C.Y., Liang, J.J., Li, J.K., Lee, Y.L., Chang, B.L., Su, C.I., Huang, W.J., Lai, M.M., Lin, Y.L., 2015. Dengue virus impairs mitochondrial fusion by cleaving Mitofusins. PLoS Pathog. 11, e1005350.
Zamarin, D., García-Sastre, A., Xiao, X., Wang, R., Palese, P., 2005. Influenza virus PB1-F2 protein induces cell death through mitochondrial ANT3 and VDAC1. PLoS Pathog. 1, e4.
Zhang, C., Lee, S., Peng, Y., Bunker, E., Giaime, E., Shen, J., Zhou, Z., Liu, X., 2014. PINK1 triggers autocatalytic activation of Parkin to specify cell fate decisions. Curr. Biol. 24, 1854–1865.
Zhu, L., Mou, C., Yang, X., Lin, J., Yang, Q., 2016. Mitophagy in TGEV infection counteracts oxidative stress and apoptosis. Oncotarget 7, 27122–27141.