Molecules and Cells

Minireview

Mitophagy and Innate Immunity in Infection

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Mitochondria have several quality control mechanisms by which they maintain cellular homeostasis and ensure that the molecular machinery is protected from stress. Mitophagy, selective autophagy of mitochondria, promotes mitochondrial quality control by inducing clearance of damaged mitochondria via the autophagic machinery. Accumulating evidence suggests that mitophagy is modulated by various microbial components in an attempt to affect the innate immune response to infection. In addition, mitophagy plays a key role in the regulation of inflammatory signaling, and mitochondrial danger signals such as mitochondrial DNA translocated into the cytosol can lead to exaggerated inflammatory responses. In this review, we present current knowledge on the functional aspects of mitophagy and its crosstalk with innate immune signaling during infection. A deeper understanding of the role of mitophagy could facilitate the development of more effective therapeutic strategies against various infections.

Keywords: infection, inflammation, innate immunity, mitochondria, mitophagy

INTRODUCTION

As the "powerhouses of the cell", mitochondria are important organelles that provide adenosine triphosphate (ATP) for fundamental cell functions. Septic and damaged mitochondria result in excessive production of reactive oxygen species (ROS) and the oxidant peroxynitrite, and alter the electron transport chain (Kurose et al., 1993; Taylor et al., 1995). Increased tumor necrosis factor (TNF) levels during inflammatory conditions result in excessive mitochondrial damage and oxidative stress, thereby dysregulating mitochondrial function, altering mitochondrial morphology, and inhibiting respiration (Schulze-Osthoff et al., 1992). Mitochondria play critical roles in a variety of biological responses, including inflammation, proliferation, and survival/death, and are thus potential targets for various diseases (Cloonan and Choi, 2013; Dromparis and Michelakis, 2013).

Mitochondria undergo constant fission and fusion to maintain important mitochondrial functions and maximize oxidative capacity under stress conditions (Cloonan and Choi, 2013; Gomes and Scorrano, 2013; Youle and van der Bliek, 2012). By promoting complementation, the fusion of two mitochondria helps rescue them from stress, whereas fission is required for mitochondrial quality control via the removal of damaged mitochondria. Such continuous changes are functionally associated with mitochondrial metabolism and dependent on mitophagy (Youle and van der Bliek, 2012). Mitophagy is a selective form of autophagy that is critical for mitochondrial quality control and function to prevent the accumulation of potentially harmful mitochondria that could cause excessive inflammatory responses (Tal and Iwasaki, 2011). Defective mitophagy is associated with inflammatory cytokine secretion and dysregulation of immune cell homeostasis, thus contributing to inflammatory and autoimmune disease pathologies (Montava-Garriga and Ganley, 2020; Xu

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et al., 2019).

Various pathogens and their components modulate mitophagy to affect the innate immune response and promote pathogen replication in host cells. However, little is known about the crosstalk between mitophagy and xenophagy during infection. Several cargo receptors, such as p62/SQSTM1 and nuclear dot protein 52 kDa (NDP52), are shared by the mitophagy and xenophagy pathways (Gkikas et al., 2018). Key regulators of mitophagy, such as PTEN-induced putative kinase 1 (PINK1) and Parkin/PARK2, are also important for controlling infection and inflammation (Gkikas et al., 2018). In this review, we discuss recent findings on the roles of mitophagy in the regulation of the innate immune response and inflammation during infection. In addition, we highlight the mechanisms by which pathogens modulate mitophagy and consider the role of key mitophagy regulators in antimicrobial responses.

OVERVIEW OF MITOPHAGY

Mitochondria are morphologically dynamic organelles; mitochondrial quality is sustained through biogenesis of new mitochondria, fusion and fission, and elimination of damaged mitochondria via mitophagy (Yoo and Jung, 2018). Mitochondrial fission is mainly regulated by a dynamin GTPase protein, dynamin-related protein 1 (Drp1), whereas mitochondrial fusion is controlled by two large GTPases, mitofusin (Mfn) 1/2 and optic atrophy type 1 (OPA1) (Cho et al., 2010). Mitochondrial fission can produce an impaired daughter mitochondrion, which is eliminated by autophagosomal engulfment (Yoo and Jung, 2018). Mitophagy removes damaged mitochondria during infection, inflammation, and various neurodegenerative diseases (Pickles et al., 2018; Xu et al., 2019).

The recognition of target mitochondria by the autophagosome occurs through interaction among microtubule-associated protein 1 light chain 3 (LC3) and LC3 adapters in either an ubiquitin (Ub)-dependent or independent manner (Fig. 1) (Pickles et al., 2018). The PINK1/Parkin pathway regulates Ub-dependent mitophagy. Mutations in *PINK1* and *Parkin* cause autosomal recessive Parkinson disease (PD) (Klein and Westenberger, 2012). To date, several proteins have been shown to be related to PD pathogenesis, including α-synuclein (α-syn), PINK1, Parkin, DJ-1/PARK7, and leucine-rich repeat kinase 2 (LRRK2) (Klein and Westenberger, 2012). Several mitophagy mechanisms in response to various stresses have been reported in distinct cellular contexts. Generally, mitophagy can be classified into Parkin-dependent and -independent pathways, which exhibit crosstalk (Pickles et al., 2018). During normal cellular activity, the stability of mitochondrial kinase PINK1 is regulated by presenilin-associated rhomboid-like (PARL) protease, depending on mitochondrial membrane potential (Jin et al., 2010). PINK1 accumulation on the outer mitochondrial membrane (OMM) leads to the recruitment of Parkin to sites with impaired mitochondria (Jin et al., 2010; Shi and McQuibban, 2017). Accumulated PINK1

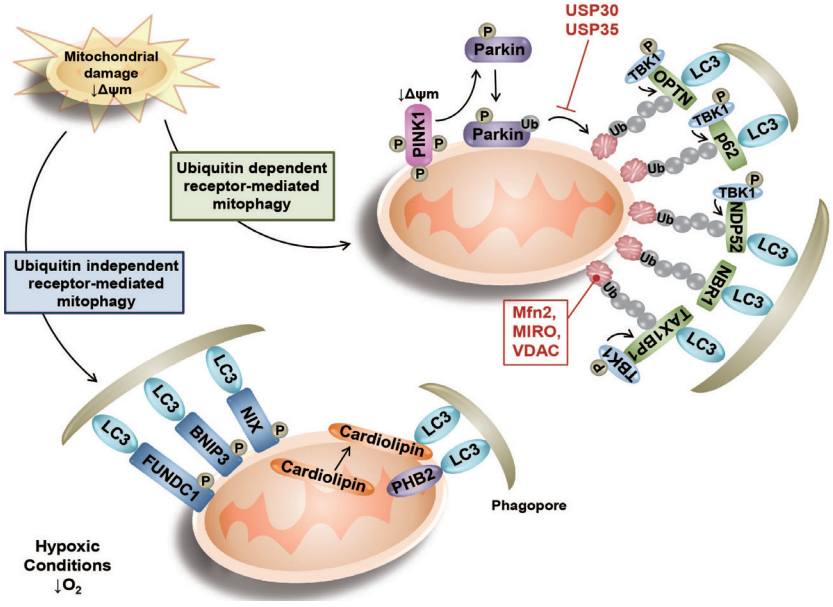

Fig. 1. Mechanistic overview of mitophagy. Adaptor protein-mediated mitophagy is dependent on the PINK1/Parkin pathway. In damaged mitochondria that have lost their mitochondrial membrane potential (ΔΨm), PINK1 accumulates and phosphorylates ubiquitin, which recruits the E3 ligase Parkin. Parkin ubiquitinates outer mitochondrial membrane (OMM) proteins such as Mfn1/2, MIRO, and VDAC. The poly-ubiquitinated proteins serve as binding sites for selective autophagy adaptors including OPTN, p62, NDP52, TAX1BP1, and NBR1. These proteins contain LC3-binding sites (LIR), leading to the encapsulation of mitochondria by the autophagosome. TBK1 phosphorylates OPTN, thereby enhancing its binding ability. Receptor-mediated mitophagy relies on other OMM proteins, including BNIP3, NIX, and FUNDC1. In addition, inner mitochondrial membrane proteins, such as PHB2 and cardiolipin, function as receptors in the response to mitochondrial damage.

then phosphorylates Ub at serine 65 and activates Parkin to trigger mitophagy via a feedforward mechanism (Narendra et al., 2008; 2010). Notably, the phosphorylation of Parkin increases its E3 ligase activity and affinity to enhance recruitment of phospho-Ub (p-Ub), promoting ubiquitination of OMM protein substrates including voltage-dependent anion channel-1 (VDAC1), MFN 1/2, and Miro 1 on the surface of mitochondria, and enhancing mitophagy (Gegg et al., 2010; Geisler et al., 2010; Liu et al., 2012b). Ub-tagged OMM proteins bind to several LC3-interacting region (LIR)-containing autophagy adapters, such as p62, optineurin (OPTN), neighbor of BRCA1 gene (NBR1), NDP52, and TAX1 binding protein 1 (TAX1BP1) (Choi et al., 2017; Geisler et al., 2010; Heo et al., 2015; Hollville et al., 2014; Wong and Holzbaur, 2014), which interact with LC3 to engulf mitochondria via the autophagosome. In addition, several deubiquitinating enzymes (DUBs) have been reported to regulate mitophagy. The formation of p-Ub or poly-Ub chains is consistently reversed by deubiquitinases, such as USP30 and USP35, which reverse mitophagy by removing Ub chains generated by Parkin on the OMM (Bingol et al., 2014; Wang et al., 2015). Although Parkin is a crucial regulator of mitophagy, accumulating evidence indicates that mitophagy can be induced even in the absence of Parkin. PINK1 can also recruit receptors such as OPTN and NDP52 by generating p-Ub on mitochondria to trigger mitophagy directly in Parkin-deficient cells (Burman et al., 2017; Lazarou et al., 2015), suggesting that Parkin is not essential for mitophagy but rather amplifies the tagging signal.

Not only Ub-mediated LC3 adaptor proteins but also several protein receptors have an LIR motif, which allows direct binding to LC3 to promote mitophagy. BCL2-interacting protein 3 (BNIP3) and its homolog BNIP3-like (BNIP3L/NIX) can also induce mitophagy in Parkin-deficient cells (Ney, 2015; Novak et al., 2010; Quinsay et al., 2010). In addition, FUN14 domain-containing protein 1 (FUNDC1) is a mitophagy receptor that responds to hypoxia-induced mitophagy. The phosphorylation of FUNDC1 by Src kinase and casein kinase II (CK2) inhibits its interaction with LC3 under normoxia (Chen et al., 2014; Liu et al., 2012a). However, under hypoxia, FUNDC1 is dephosphorylated by phosphoglycerate mutase 5 (PGAM5) but can also be phosphorylated by Unc-51 such as autophagy activating kinase (ULK) 1, which induces mitophagy (Chen et al., 2014; Wu et al., 2014). However, Hirota et al. (2015) also reported that inhibition of FUNDC1 does not significantly affect hypoxia-induced mitophagy. In addition, it was recently reported that prohibitin 2 (PHB2), an inner mitochondrial membrane protein that contains an LIR motif, functions as a mitophagy receptor through interaction with LC3 during mitophagy (Wei et al., 2017).

OVERVIEW OF INNATE IMMUNITY AND INFLAMMATION DURING INFECTION

The innate immune system is the primary host defense against pathogenic microorganisms or dangerous stimuli (Ishii et al., 2008). Therefore, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are major inflammatory stimuli. These patterns include the bacterial cell wall, DNA, lipoproteins, and carbohydrates (Tang et al., 2012). Macrophages are major players in innate immunity and exhibit phagocytosis, pro-/anti-inflammatory effects, and antimicrobial activity (Silva, 2011). Upon infection, innate immune cells including macrophage subsets recognize a variety of PAMPs through their pattern-recognition receptors, including Toll-like receptors (TLRs) and cytoplasmic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (Ishii et al., 2008; Kawai and Akira, 2011; Martinon et al., 2009). PAMP or DAMP detection by innate immune receptors triggers intracellular signaling pathways to activate the nuclear factor (NF)-κB pathway and synthesis of proinflammatory cytokines and chemokines, leading in turn to the recruitment of leukocytes in response to infection/inflammation and promotion of their effector functions, as well as to the production of antimicrobial proteins (Ishii et al., 2008; Murray and Wynn, 2011). A complicated signaling network that is mediated via numerous types of innate immune receptors can drive innate effector cells into a state of inflammatory, antibacterial, or tissue repair responses (Ishii et al., 2008; Murray and Wynn, 2011). In addition, much work has been devoted to different types of inflammasome activation such as NLRs and absent in melanoma 2 (AIM2) inflammasomes (Cui et al., 2014). Several types of NLRs, including the NLR family, pyrin domain containing 3 (NLRP3) and nucleotide-binding domain, and leucine-rich repeat-containing family caspase recruitment domain containing 4 (NLRC4), activate an inflammatory caspase, resulting in maturation and secretion of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18. Inflammasome activation is an intrinsic host defense mechanism that occurs in response to various pathogens; however, excessive and uncontrolled activation leads to tissue damage and is harmful to the host (Cui et al., 2014; Krakauer, 2019).

An extensive array of pathogens and their components trigger or inhibit host autophagy/xenophagy of innate immune cells during infection (Ogawa et al., 2011; Randow and Munz, 2012; Sorbara and Girardin, 2015; Tang et al., 2012). The activation of host autophagy and/or innate immune pathways is a crucial effector mechanism against intracellular pathogens and induces host defense mechanisms while limiting unwanted tissue damage (Bento et al., 2015; Hawn et al., 2015; Paik et al., 2018; Sumpter and Levine, 2010). In addition, several immune receptors or players, including NOD1/2, NF-κB, TANK-binding kinase 1 (TBK1), and interferon (IFN)-γ, play a role in the regulation of autophagy/xenophagy during infection to prevent an excessive response or promote host antimicrobial activity (Krakauer, 2019; Pilli et al., 2012; Sorbara and Girardin, 2015). Many pathogens also exploit or modulate host innate immune responses by interacting with the key signaling molecules of host cells to escape immune control, membrane trafficking, and xenophagy (Asrat et al., 2014; Colonne et al., 2016; Niller et al., 2017; Pareja and Colombo, 2013). Numerous in-depth studies have been carried out on autophagy and innate immune signaling, and the functions and consequences of crosstalk between the two pathways have been extensively reviewed in terms of infection and inflammation. Nonetheless, the crosstalk of mitophagy with innate immune signaling during infection has

not been well studied.

In this review, we provide an overview of the functions of mitophagy during infection and discuss current knowledge of the strategies used by microbes to manipulate mitophagy in host cells and escape innate effectors. We propose that reciprocal regulation between mitophagy and innate immunity is a critical determinant of the host defense response to infection and forms the basis of a larger interacting network consisting of mitochondrial homeostasis, antimicrobial immunity, and metabolic reprogramming. Understanding the regulatory mechanisms incorporating these pathways is crucial for developing effective antimicrobial immunotherapies.

CROSSTALK BETWEEN MITOPHAGY AND INNATE IMMUNITY

The innate immune response to pathogens may influence or perturb mitochondrial homeostasis, including mitochondrial dynamics (Jin et al., 2017a; Mohanty et al., 2019). Upon infection or inflammation, autophagy and innate immune pathways can be integrated to promote the host antimicrobial response and prevent excessive inflammation. The PINK1/Parkin pathway plays a crucial role in the activation of mitophagy and regulates innate immune responses during infection. Mitophagy and xenophagy are regulated by common cargo receptors, including NDP52 and p62. In addition, mitophagy activation is regulated by multiple players in innate immune signaling, suggesting that mitophagy and the innate immune response are closely interconnected. Dysregulated mitophagy can provide feedback on the inflammatory response to serve as an amplification loop for exuberant inflammasome activation. An understanding of the crosstalk between mitophagy and the innate immune response will facilitate the manipulation of mitochondrial function to control host defense, immunity, and inflammation.

Functions of the PINK1/Parkin pathway in infection

In response to lipopolysaccharide (LPS) stimulation, the loss of mitochondrial membrane potential leads to calcium/calmodulin-dependent protein kinase I activation and mitophagy, which is mediated by PINK1/Parkin and DJ-1-dependent mechanisms (Zhang et al., 2017). In a model of polymicrobial sepsis, *pink1* or *park2* deficiency led to increased host sensitivity and inflammasome activation, suggesting that the PINK1/Parkin pathway is critical for host protection during systemic inflammation (Kang et al., 2016). In addition, Parkin protected against sepsis-induced cardiac contractility and maintained mitochondrial metabolic function by activating cardiac mitophagy (Piquereau et al., 2013). The ability of DJ-1, an ROS scavenger that binds to p47phox of the NADPH oxidase complex, to clear bacteria is impaired during sepsis (Amatullah et al., 2017). Although that study did not demonstrate a mitophagic role for DJ-1 during sepsis, a higher circulating DJ-1 level may suppress host response to sepsis (Amatullah et al., 2017).

Several viruses and microbes induce mitochondrial fission, which can promote mitophagy during infection. The influenza A viral protein PB1-F2 induces mitochondrial fragmentation, which attenuates retinoic acid-inducible gene I (RIG-I) signaling activation and impairs the NLRP3 inflammasome pathway (Yoshizumi et al., 2014). RIG-I like receptors (RLRs) function as cytoplasmic sensors of PAMPs within viral RNA to initiate and modulate antiviral immunity. Therefore, mitochondrial stress in response to pathogens and danger signals induces mitophagy through the PINK1/Parkin pathway (Zhang et al., 2017).

Pathogen infection has been reported to inhibit the ability of PINK1/Parkin to modulate antiviral responses. Viral infection inhibits PINK1, which mediates RLR signaling, by interacting with TNF receptor-associated factor (TRAF) 3 and inhibiting its degradation (Zhou et al., 2019b). Although these data suggest a key role for PINK1 in RLR immunity, the role of mitophagy in RLR signaling requires further elucidation. Notably, PINK1 deficiency disrupted the control of inflammation (Sliter et al., 2018). Following exhaustive exercise, *Parkin*$^{-/-}$ and *pink1*$^{-/-}$ mice exhibited excessive inflammation, which was completely abrogated by the loss of STING, a key regulator of the type I IFN response after sensing cytosolic DNA (Sliter et al., 2018). Thus, the orchestration of mitophagy mediated by PINK1 and Parkin promotes host innate defense and inhibits pathologic inflammation during infection. Interestingly, *pink1*$^{-/-}$ mice developed autoimmunity, mitochondria-specific CD8+ T cell responses, and motor impairment during intestinal bacterial infection (Matheoud et al., 2019). However, the mechanism by which PINK1/Parkin-mediated mitophagy finely adjusts the inflammatory response is unknown.

Signaling mediators in innate immunity connected with mitophagy

Several kinases are involved in innate immunity function in mitophagy, such as TBK1, which induces the antiviral innate immune response by activating the synthesis of IFN regulatory factor (IRF)-3 and type I IFN (Zhao and Zhao, 2019). Ubiquitination of mitochondrial fragments, which is an early step of mitophagy, is mediated by the autophosphorylation of TBK1 (Zachari et al., 2019). In addition, TBK1 is involved in xenophagy; for example, it promotes the xenophagic clearance of *Salmonella* infection (Weidberg and Elazar, 2011). Importantly, the interaction of TBK1 with, and the phosphorylation of, OPTN is essential for promoting the binding of OPTN to Ub chains, which promotes mitophagy (Richter et al., 2016). Several viral components and TBK1-spliced isoforms negatively regulate RIG-I-dependent antiviral signaling (Dalrymple et al., 2015; Hu et al., 2018), suggesting that TBK1-mediated innate immune signaling is finely tuned by various pathogens and by TBK1 itself. The results of these studies suggest that several players in innate immunity and xenophagy participate in the activation of mitophagy during infection. Thus, future studies should focus on how TBK1 and its partners protect against and drive the pathogenesis of infectious diseases.

Mitogen-activated protein kinase is a key mediator of innate immune signaling and is targeted by various pathogens (McGuire and Arthur, 2015). Notably, Jnk2-deficient mice exhibit defective mitophagy, excessive tissue damage and inflammasome activation, and increased susceptibility to sepsis (Zhang et al., 2015), suggesting that Jnk2-mediated mitophagy is critical for controlling pathologic inflammation (Zhang

et al., 2015). MAP kinase kinase 3 (MKK3) deficiency protects against sepsis by inhibiting mitochondrial injury and ROS production (Mannam et al., 2014). MKK3 is associated with decreased mitochondrial biogenesis and mitophagy, an effect mediated by sirtuin 1 (Sirt1), PINK1, and Parkin, suggesting a role for MKK3 in mitochondrial quality control (Mannam et al., 2014). MKK3 has also been reported to increase susceptibility to septic injury, again suggesting a role in mitochondrial quality control (Srivastava et al., 2015). As such, the mechanisms underlying regulation by MKK3 of mitophagy and mitochondrial biogenesis should be investigated. In particular, the regulatory effect of mitophagy activation by a variety of factors on innate immune signaling pathways is unclear.

Roles of mitophagy receptors during infection and inflammation

NIX is a mitophagy receptor (Ney, 2015) that binds to viral IFN regulatory factor 1 (vIRF-1) of human herpesvirus 8 (HHV-8), an oncogenic virus (Vo et al., 2019). The interaction between vIRF-1 and NIX leads to the activation of mitophagy to promote mitochondrial homeostasis during viral infection (Vo et al., 2019). In addition, several autophagy cargo receptors play crucial roles in the xenophagy and mitophagy pathways (Deng et al., 2017). NDP52 and OPTN are involved in the early step of PINK1-dependent mitophagy (Lazarou et al., 2015). Whether these autophagy receptors simultaneously participate in xenophagy and mitophagy during infection is unknown. In addition, many issues remain to be resolved; for example, how mitophagy affects xenophagy, and vice versa, and the role of cargo receptors in the overall control of infection. Recent studies revealed the functions of NDP52 and p62 in the regulation of infection by coxsackievirus B3 and mycobacteria (Mohamud et al., 2019; Zhang et al., 2019a). Although both receptors are involved in selective autophagy against the virus, NDP52, but not p62, exerts a proviral role by degrading autophagy-mediated mitochondrial antiviral-signaling protein (MAVS), which regulates the activation of NF-κB and IRF3 in response to viral infection to inhibit type I IFN signaling (Mohamud et al., 2019). Coxsackievirus B can escape from infected host cells by inducing mitochondrial fragmentation and the generation of mitochondrion-containing autophagosomes to promote viral dissemination (Shi et al., 2013; Sin et al., 2017). In this context, the blockade of mitophagy was found to reduce the viral load in infected cells (Sin et al., 2017). Thus, it is possible that NDP52 at the early stage of mitophagy promotes proviral responses during coxsackievirus B3 infection. A recent study of the function of RNF34, a cytosolic E3 Ub ligase, reported that NDP52 participates in the autophagic degradation of MAVS to regulate the innate immune response and mitochondrial homeostasis following RIG-I stimulation (He et al., 2019).

Upon RNA virus infection, p62 is involved in selective autophagy-mediated RIG-I degradation, which is activated and inhibited by leucine-rich repeat containing protein 25 (LRRC25) (Du et al., 2018) and LRRC59 (Xian et al., 2019), respectively. In addition, OPTN related to the clearance of *Salmonella* infection, suppresses the inflammatory response in the intestine (Tschurtschenthaler and Adolph, 2018) and increases susceptibility to *Citrobacter* colitis and *Escherichia coli* peritonitis (Chew et al., 2015). Under stress conditions such as infection, mitophagy receptors may orchestrate host defense, mitochondrial quality control, inflammation, and redox homeostasis by targeting key innate immune signaling factors.

New mitophagy receptors implicated in the control of mitochondrial dysfunction in various infectious and inflammatory conditions have been identified. A recent study reported that *Listeria monocytogenes* infection induced mitophagy in macrophages through a new mitophagic receptor, NOD-like receptor X1 (NLRX1), which contains an LIR motif for association with LC3 (Zhang et al., 2019b). Notably, NLRX1 deficiency resulted in increased mouse survival and bacterial control, suggesting that *L. monocytogenes* manipulates a host-cell homeostatic pathway to promote its survival (Zhang et al., 2019b). Disrupted-in-schizophrenia-1 (DISC1), which contains a LIR motif (^{210}FSFI^{213}), is a mitophagy receptor that inhibits amyloid β-induced neuro-inflammatory pathology in mice with Alzheimer disease (Wang et al., 2019b). In addition to mitophagy receptors, several factors that regulate mitophagy have been reported. Progranulin (PGRN), a secreted glycoprotein, reportedly regulates mitochondrial homeostasis by enhancing mitophagy and mitochondrial biogenesis via the Sirt1-PGC1α/FoxO1 signaling pathway (Zhou et al., 2019a). *PGRN* deficiency is related to mitochondrial damage and podocyte injury in mice and patients with diabetic nephropathy (Zhou et al., 2019a). Nonetheless, the roles of these receptors in the regulation of infection are unclear.

Tetherin is reportedly involved in both mitophagy and autophagy. Tetherin restricts human immunodeficiency virus (HIV) and hepatitis C virus (HCV) virions and reportedly regulates the initiation of autophagy and mitophagy (Jin et al., 2017b; Zou et al., 2015). The interaction of tetherin with the autophagy/mitophagy suppressor leucine-rich pentatricopeptide repeat-containing protein (LRPPRC) prevents the formation of a ternary complex of the latter with BECN1/Beclin 1 and Bcl-2, thereby allowing BECN1 to bind to PI3KCIII (class III PI3K) to activate autophagy (Zou et al., 2015). Interestingly, tetherin plays a role in the autophagic degradation of both mitochondria and infecting viruses (Table 1) (Zou et al., 2015).

REGULATION OF MITOPHAGY BY PATHOGENS

HCV and hepatitis B virus (HBV)

HCV and HBV regulate mitophagy. HCV induces mitophagy via the Parkin pathway to attenuate host cell apoptosis during infection (Kim et al., 2013b; 2014). Parkin levels are elevated in the liver tissues of patients with chronic HCV (Kim et al., 2013b). Silencing PINK1/Parkin inhibits HCV replication, suggesting that mitophagy plays a role in the liver during HCV infection (Kim et al., 2013b). In addition, HCV infection increases the expression and phosphorylation of Drp1, promoting mitochondrial translocation and mitophagy (Kim et al., 2014). Drp1-mediated mitophagy activation inhibits host-cell apoptotic signaling to favor persistent HCV infection (Kim et al., 2014). The HCV non-structural protein 5A activates mitophagy by promoting ROS generation (Jassey et al., 2019). These studies support a role for mitophagy in the pathogenesis of HCV infection. However, control of mi-

Table 1. Role of mitophagy regulator in infection and immunity

Regulator	Role	References
PINK1/PARKIN	Impaired PINK1-PARKIN pathway contributes to septic death by increasing sensitivity for polymicrobial sepsis-induced organ failure PARKIN-deficiency exhibits impaired recovery of cardiac contractility and constant degradation of mitochondria	(Kang et al., 2016; Piquereau et al., 2013)
DJ-1	DJ-1 impairs optimal ROS production for bacterial killing with important implications for host survival in sepsis	(Amatullah et al., 2017)
TBK1	TBK1 promotes autophagic clearance of the bacterium *Salmonella enterica* via direct phosphorylation of OPTN	(Weidberg and Elazar, 2011)
Jnk2	Loss of Jnk2 defects mitophagy but activates inflammasomes and increases mortality in sepsis	(Zhang et al., 2015)
MKK3	Loss of MKK3 promotes mitophagy and leads decreased inflammatory response in LPS-stimulated cells	(Srivastava et al., 2015)
NIX	NIX increases mitophagy to promote mitochondrial homeostasis by inhibiting HHV-8 productive replication during viral infection	(Vo et al., 2019)
NDP52	NDP52 induces RNF34-mediated autophagic degradation of MAVS, which regulates the innate immune response	(He et al., 2019; Mohamud et al., 2019)
p62	p62 reduces the *Mycobacterium marinum* infection burden. p62 is impaired by cleavage of a viral protease 2A of in coxsackievirus B3 infected cells	(Shi et al., 2013; Zhang et al., 2019a)
OPTN	OPTN controls the clearance of *Salmonella* infection and confers protection against bacterial infection in mice and zebrafish	(Chew et al, 2015; Tschurtschenthaler and Adolph, 2018)
LRRC25/LRRC59	LRRC25 binds to ISG15-associated RIG-I to mediate RIG-I degradation via selective autophagy	(Du et al., 2018; Xian et al., 2019)
DISC1	DISC1 enhances mitophagy and rescues synaptic loss and Aβ plaque accumulation in inflammatory Alzheimer's disease model	(Wang et al., 2019b)
BST2 (Tetherin)	BST2, a ligand of ILT7 receptor interacts with the autophagy suppressor LRPPRC and accelerates MAVS degradation by mitophagy	(Jin et al., 2017b; Zou et al., 2015)

tophagy is reportedly required to ameliorate HCV-induced injury. The HCV core protein interacts with Parkin to inhibit mitophagic degradation by suppressing Parkin translocation to mitochondria, thereby amplifying HCV-induced mitochondrial injury (Hara et al., 2014). In addition, the ginsenoside Rg3 modulates the effect of HCV on mitochondrial dynamics, rescuing HCV-induced mitophagy and aberrant mitochondrial fission and inhibiting HCV propagation (Kim et al., 2017).

Alteration of mitochondrial dynamics by HBV x protein may lead to persistent HBV infection (Kim et al., 2013a). HBV induces mitochondrial fission and mitophagy by promoting the mitochondrial translocation of Drp1 (Kim et al., 2013a). Mechanistically, HBV upregulates the expression of Parkin and its recruitment to the mitochondria, where it facilitates the ubiquitination and degradation of Mfn2, a mitochondrial fusion protein in the OMM (Kim et al., 2013a). Therefore, it is speculated that the alteration of mitochondrial dynamics is associated with the pathogenesis of infection with diverse viruses. With this in mind, the ability of viruses to modulate mitochondrial dynamics and mitophagy is discussed below.

Other viruses

A variety of pathogens and their products modulate mitophagy to favor their replication in host cells. The matrix (M) protein of human parainfluenza virus type 3 activates mitophagy by interacting with the Tu translation elongation factor mitochondrial (TUFM) pathway, but not the PINK1/Parkin pathway (Ding et al., 2017). M protein-mediated mitophagy inhibits the antiviral type I IFN response (Ding et al., 2017). The vIRF-1 of HHV-8 interacts with the mitophagy receptor NIX to activate mitophagy for HHV-8 lytic replication (Vo et al., 2019). In addition, attenuated measles virus of the Edmonston strain (MV-Edm) triggers the p62-mediated mitophagy pathway to inhibit MAVS and attenuate the RLR-induced antiviral innate immune response (Xia et al., 2014a). Thus, activation of mitophagy contributes to measles virus replication by inhibiting host RLR signaling (Xia et al., 2014a).

The porcine reproductive and respiratory syndrome virus (PRRSV) activates mitochondrial fission and mitophagy by promoting Drp1 expression and translocation to mitochondria (Li et al., 2016). PRRSV infection also induces PINK1 and Parkin expression, thus activating mitophagy and blocking proapoptotic signaling (Li et al., 2016). Transmissible gastroenteritis virus (TGEV) infection induced mitophagy to promote cell survival by inhibiting oxidative stress and apoptosis in porcine epithelial cells (IPEC-J2) (Zhu et al., 2016). TGEV-induced DJ-1 inhibits oxidative stress induced by viral infection (Zhu et al., 2016). These data suggest that viruses use multiple strategies to modulate mitochondrial dynamics and mitophagy to facilitate their replication.

Interestingly, the glycoprotein and nucleocapsid protein of the Hantann virus modulate mitophagy and autophagy, respectively (Wang et al., 2019a). The glycoprotein of the Hantann virus can induce mitophagy, thereby abrogating the type

I IFN response by degrading MAVS; by contrast, the nucleocapsid protein interacts with host SNAP29 to inhibit autophagosome-lysosome fusion (Wang et al., 2019a). The classical swine fever virus infection results in mitochondrial fission and activation of mitophagy to suppress host cell apoptosis, thus enhancing host cell survival and its intracellular persistence during infection (Gou et al., 2017). In addition, the Newcastle disease virus (NDV) induces autophagy, promoting its replication by inhibiting the apoptosis of non-small cell lung cancer cells (NSCLCs). NDV also contributes to p62-mediated mitophagy, which inhibits cytochrome c release and intrinsic proapoptotic signaling (Meng et al., 2014). Also, MV-Edm induces autophagy and p62-mediated mitophagy, thereby blocking proapoptotic signaling in NSCLCs (Xia et al., 2014b). The sustained viral replication resulted in necrotic cell death, suggesting that mitophagy activation plays a role in the switch from apoptotic to necrotic cell death (Table 2) (Xia et al., 2014b). These data indicate that numerous viral/bacterial effectors suppress or promote host mitophagy, autophagy, and apoptosis during infection. In summary, the degree of mitophagy in a given context determines the effect on host defense and viral replication.

Regulation of mitophagy by fungi

Mitophagy activation is important in the longevity of *Candida glabrata*, thus affecting pathogenesis during opportunistic infection (Nagi et al., 2016). A mitophagy-deficient mutant of *C. glabrata* exhibited increased susceptibility under iron-deficient conditions, and decreased longevity and pathogenesis in a model of disseminated infection (Nagi et al., 2016). These data suggest that mitophagy activation is not only important in mammalian host cells but also influences the survival of the pathogen itself.

MITOPHAGY AND THE INFLAMMASOME DURING INFECTION

A number of pathogen products modulate the balance between mitophagy and inflammasome activation (Fig. 2). HIV type-1 (HIV-1) single-stranded RNA (ssRNA) activates the NLRP3 inflammasome in human primary microglia to promote neurotoxicity and neurodegeneration by increasing ROS generation. HIV ssRNA inhibits autophagy/mitophagy, negatively regulating the NLRP3 inflammasome and promoting the release of proinflammatory and neurotoxic cytokines by microglia (Rawat et al., 2019). Moreover, mitophagy activation counteracts the mitochondrial injury and cell death caused by HIV-1 infection in astrocytes (Ojeda et al., 2018). The HIV components gp120 and Tat impair mitophagic flux, thereby promoting mitochondrial damage and altering mitochondrial dynamics (Teodorof-Diedrich and Spector, 2018). These responses may cause neuronal degeneration and neurodegenerative disorders related to HIV infection (Teodorof-Diedrich and Spector, 2018). Furthermore, *Pseudomonas aeruginosa* activates the NLRC4 inflammasome via its type III secretion apparatus (T3SS) (Jabir et al., 2015). Mitochondrial damage induced by *P. aeruginosa* T3SS leads to increased ROS production and release of mitochondrial DNA (mtDNA), triggering NLRC4 inflammasome activation (Jabir et al., 2015). Autophagy activation inhibits NLRC4

Table 2. Interplay between pathogen pathogenesis and mitophagy

Viruses	Mitophagy	Pathway	Outcome	References
HCV	↑	Parkin-dependent	Apoptosis↓	(Kim et al., 2013b)
HCV	↑	Increased the expression and phosphorylation of Drp1	Apoptotic signaling↓	(Kim et al., 2014)
HCV NS5A	↑	ROS production	Interferon response↓	(Jassey et al., 2019)
HCV core protein	↓	Suppression of Parkin translocation to the mitochondria	HCV-induced mitochondrial injury↑	(Hara et al., 2014)
HBV	↑	Upregulated the expression of Parkin	Apoptosis↓	(Kim et al., 2013a)
Matrix protein (M) of HPIV3	↑	Interaction with TUFM and LC3	Type I interferon response↓	(Ding et al., 2017)
vIRF-1 of HHV-8	↑	Interaction with NIX	HHV-8 productive replication↓	(Vo et al., 2019)
MV-Edm	↑	p62-mediated	RLR-induced innate immune responses↓	(Xia et al., 2014a)
PRRSV	↑	Increased the expression of Drp1, PINK1 and Parkin	Apoptotic signaling↓	(Li et al., 2016)
TGEV	↑	Induction of DJ-1	Oxidative stress and apoptosis↓	(Zhu et al., 2016)
Glycoprotein (Gn) of Hantann virus	↑	Interaction with TUFM	Type I interferon response↓	(Wang et al., 2019a)
CSFV	↑	Activation of PINK1-Parkin pathway	Apoptosis↓	(Gou et al., 2017)
NDV	↑	p62-mediated	Instrinsic pro-apoptotic signaling↓	(Meng et al., 2014)
MV-Edm	↑	p62-mediated	Pro-apoptotic signaling↓	(Xia et al., 2014b)

HCV, hepatitis C virus; NS5A, non-structural protein 5A; HBV, hepatitis B virus; HPIV3, human parainfluenza virus type 3; TUFM, Tu translation elongation factor mitochondrial; vIRF-1, viral interferon regulatory factor 1; HHV-8, human herpesvirus 8; MV-Edm, measles virus of the Edmonston strain; MAVS, mitochondrion-tethered mitochondrial antiviral signaling protein; PRRSV, porcine reproductive and respiratory syndrome virus; TGEV, transmissible gastroenteritis virus; CSFV, classical swine fever virus; NDV, Newcastle disease virus; MV-Edm, measles virus vaccine strain Edmonston B.

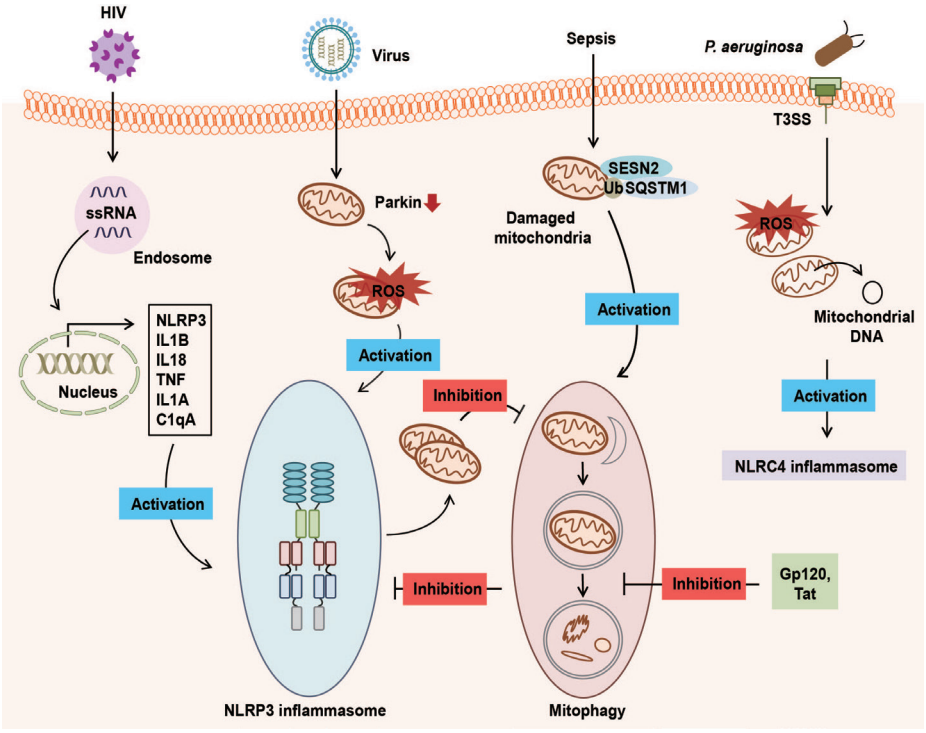

Fig. 2. Schematic overview of the balance between mitophagy and inflammasome activation. It is critical to maintain the balance between mitophagy and inflammasome complex activation to promote host defense while controlling excessive pathological inflammation during infection. Among pathogen products, HIV ssRNA, gp120, and Tat can activate the NLRP3 inflammasome through inhibition of mitophagy and mitochondrial damage. In addition, *Pseudomonas aeruginosa* activates the NLRC4 inflammasome through increased ROS production and release of mtDNA. Mechanistically, SESN2 and Parkin participate in the suppression of NLRP3 inflammasome activation through mitophagy induction. Several pathogens including HCV can also increase mitochondrial ROS production, resulting in pathological responses during infection and inflammation. In a sepsis model, mitophagy activation to control mitochondrial ROS was found to be related to enhanced host defense.

activation during *P. aeruginosa* infection (Jabir et al., 2014), and autophagy-mediated removal of damaged mitochondria downregulated NLRC4 inflammasome activation (Jabir et al., 2015). The mitophagy pathway regulates excessive inflammatory responses via inflammasome activation mediated by several viruses and *P. aeruginosa* infection (Fig. 2). However, the mitophagic regulation of inflammasome activation during infection with other bacteria and fungi is not well addressed.

The regulators responsible for maintaining the balance between mitophagy and inflammasome activation remain to be identified. During sepsis, stress-inducible protein sesterin 2 (SESN2) suppresses NLRP3 inflammasome activation and host protection by inducing mitophagy via the p62-dependent pathway (Kim et al., 2016). In addition, the loss of Parkin, a key player in mitophagy, improves the host antiviral immune response by activating the NLRP3 inflammasome, suggesting that mitophagy activation is critical for the regulation of antiviral immunity (Li et al., 2019). However, whether *Parkin* deficiency is beneficial in chronic viral infection needs to be investigated because a prolonged inflammatory response may lead to host immune exhaustion and immune evasion (Fig. 2) (Snell et al., 2017). Future studies should identify the key regulators of the functional crosstalk between mitophagy and inflammasome activation during infection and inflammation. In the next section, we briefly discuss the role of mitochondrial ROS in linking mitophagy and inflammation during infection.

MITOCHONDRIAL ROS: A LINK BETWEEN MITOPHAGY AND THE INFLAMMASOME

As stated above, mitophagy and macroautophagy are required for mitochondrial quality control and play a physiological role in mitochondria (Pickles et al., 2018). Mitochondrial ROS production, which is accompanied by hydroxyl radical generation during iron metabolism, plays a detrimental role in the pathogenesis of chronic hepatitis and the progression of hepatocellular carcinoma induced by HCV infection (Hino et al., 2019). Group A *Streptococcus* infection triggers mitochondrial ROS generation, leading to streptolysin S-mediated mitochondrial damage and macrophage death (Tsao et al., 2019). In a sepsis model, mesenchymal stromal cells played a crucial role in mitophagy and the inhibition of mitochondrial ROS, thus restricting NLRP3 inflammasome activation and enhancing host defense against sepsis (Li et al., 2018). The mtDNA that had escaped from autophagy induced a TLR9-mediated inflammatory response in cardiomyocytes, which led to myocarditis and dilated cardiomyopathy (Oka et

al., 2012). During septic shock or inflammatory injury, mitochondria are the major organelles producing DAMP signals; for example, release of mtDNA and peptides into the circulatory system induced cell damage and endothelial permeability (Sun et al., 2013), suggesting that mitochondrial ROS and DAMPs are key factors in the inflammatory response. Future studies should focus on characterizing the functions of mitochondrial ROS during infection with various viruses.

Several lines of evidence suggest that controlling mitochondrial ROS modulates the pathogenesis of various infectious diseases. During influenza virus A infection, pharmacologic inhibition of mitochondrial ROS by a chemical inhibitor attenuated innate immune inflammation and ameliorated viral pathogenesis (To et al., 2019), suggesting that excessive mitochondrial ROS plays a role in viral infection. However, scavenging of mitochondrial ROS reportedly failed to exert a long-term beneficial effect on sepsis (Rademann et al., 2017). In support of the therapeutic potential of mitochondrial ROS for viral infections, treatment with docosahexaenoic acid induced proteasome-mediated degradation of oncogenic human papillomavirus E6/E7 proteins and apoptosis of cancer cells by promoting the production of mitochondrial ROS (Jing et al., 2014). An understanding of how mitochondrial ROS modulate the balance between host defense and pathologic inflammation will facilitate the development of targeted treatments for a variety of infections and inflammatory responses.

CONCLUSION

Recent efforts have provided much information on how autophagy modulates innate host defenses during infection. Invading pathogens alter mitochondrial homeostasis in innate immune cells and trigger the mitophagy pathway, which affects host innate defense and inflammatory response. Also, critical regulators of mitophagy, including cargo receptors, affect the host antimicrobial response to a variety of infections. In addition, several signaling mediators, such as TBK1, Jnk2, and MKK3, participate in the regulation of mitochondrial homeostasis and mitophagy during infection. Moreover, numerous pathogens, including HCV and HBV, modulate mitophagy to benefit their survival. Mitophagy activation during infection is required for maintaining a balance with inflammasome activation and preventing excessive inflammatory responses during infection. Mitochondrial ROS serves as a link between mitophagy and the inflammasome; however, the regulation of the relationship between mitophagy and the inflammasome remains unclear. Therefore, further studies should seek to identify key regulators of the connection between mitophagy and the innate immune response to infection and to understand the impact of mitophagy on infection and inflammation. It remains to be investigated whether autophagy receptors are involved in the activation of both xenophagy and mitophagy during infection. Also, how a mitophagy receptor regulates the innate immune system in the context of other biological responses is unknown. Answering these questions will shed light on the regulatory mechanisms of innate immunity and inflammation during infection. In addition, a more detailed understanding of how mitophagy coordinates the effector responses of innate immune cells will facilitate the development of novel therapeutic approaches to diverse infectious diseases.

Disclosure

The authors have no potential conflicts of interest to disclose.

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REFERENCES

Amatullah, H., Shan, Y., Beauchamp, B.L., Gali, P.L., Gupta, S., Maron-Gutierrez, T., Speck, E.R., Fox-Robichaud, A.E., Tsang, J.L., Mei, S.H., et al. (2017). DJ-1/PARK7 impairs bacterial clearance in sepsis. Am. J. Respir. Crit. Care Med. *195*, 889-905.

Asrat, S., de Jesus, D.A., Hempstead, A.D., Ramabhadran, V., and Isberg, R.R. (2014). Bacterial pathogen manipulation of host membrane trafficking. Annu. Rev. Cell Dev. Biol. *30*, 79-109.

Bento, C.F., Empadinhas, N., and Mendes, V. (2015). Autophagy in the fight against tuberculosis. DNA Cell Biol. *34*, 228-242.

Bingol, B., Tea, J.S., Phu, L., Reichelt, M., Bakalarski, C.E., Song, Q., Foreman, O., Kirkpatrick, D.S., and Sheng, M. (2014). The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature *510*, 370-375.

Burman, J.L., Pickles, S., Wang, C., Sekine, S., Vargas, J.N.S., Zhang, Z., Youle, A.M., Nezich, C.L., Wu, X., Hammer, J.A., et al. (2017). Mitochondrial fission facilitates the selective mitophagy of protein aggregates. J. Cell Biol. *216*, 3231-3247.

Chen, G., Han, Z., Feng, D., Chen, Y., Chen, L., Wu, H., Huang, L., Zhou, C., Cai, X., Fu, C., et al. (2014). A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy. Mol. Cell *54*, 362-377.

Chew, T.S., O'Shea, N.R., Sewell, G.W., Oehlers, S.H., Mulvey, C.M., Crosier, P.S., Godovac-Zimmermann, J., Bloom, S.L., Smith, A.M., and Segal, A.W. (2015). Optineurin deficiency in mice contributes to impaired cytokine secretion and neutrophil recruitment in bacteria-driven colitis. Dis. Model. Mech. *8*, 817-829.

Cho, D.H., Nakamura, T., and Lipton, S.A. (2010). Mitochondrial dynamics in cell death and neurodegeneration. Cell. Mol. Life Sci. *67*, 3435-3447.

Choi, Y.B., Shembade, N., Parvatiyar, K., Balachandran, S., and Harhaj, E.W. (2017). TAX1BP1 restrains virus-induced apoptosis by facilitating itch-mediated degradation of the mitochondrial adaptor MAVS. Mol. Cell. Biol. *37*, e00422-16.

Cloonan, S.M. and Choi, A.M. (2013). Mitochondria: sensors and mediators of innate immune receptor signaling. Curr. Opin. Microbiol. *16*, 327-338.

Colonne, P.M., Winchell, C.G. and Voth, D.E. (2016). Hijacking host cell highways: Manipulation of the host actin cytoskeleton by obligate intracellular bacterial pathogens. Front. Cell. Infect. Microbiol. *6*, 107.

Cui, J., Chen, Y., Wang, H.Y., and Wang, R.F. (2014). Mechanisms and pathways of innate immune activation and regulation in health and cancer. Hum. Vaccin. Immunother. *10*, 3270-3285.

Dalrymple, N.A., Cimica, V., and Mackow, E.R. (2015). Dengue virus NS proteins inhibit RIG-I/MAVS signaling by blocking TBK1/IRF3 phosphorylation: Dengue virus serotype 1 NS4A is a unique interferon-regulating virulence determinant. mBio *6*, e00553-15.

Deng, Z., Purtell, K., Lachance, V., Wold, M.S., Chen, S., and Yue, Z. (2017). Autophagy receptors and neurodegenerative diseases. Trends Cell Biol. *27*, 491-504.

Ding, B., Zhang, L., Li, Z., Zhong, Y., Tang, Q., Qin, Y., and Chen, M. (2017). The matrix protein of human parainfluenza virus type 3 induces mitophagy that suppresses interferon responses. Cell Host Microbe *21*, 538-547.e4.

Dromparis, P. and Michelakis, E.D. (2013). Mitochondria in vascular health and disease. Annu. Rev. Physiol. *75*, 95-126.

Du, Y., Duan, T., Feng, Y., Liu, Q., Lin, M., Cui, J., and Wang, R.F. (2018). LRRC25 inhibits type I IFN signaling by targeting ISG15-associated RIG-I for autophagic degradation. EMBO J. *37*, 351-366.

Gegg, M.E., Cooper, J.M., Chau, K.Y., Rojo, M., Schapira, A.H., and Taanman, J.W. (2010). Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Hum. Mol. Genet. *19*, 4861-4870.

Geisler, S., Holmstrom, K.M., Skujat, D., Fiesel, F.C., Rothfuss, O.C., Kahle, P.J., and Springer, W. (2010). PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat. Cell Biol. *12*, 119-131.

Gkikas, I., Palikaras, K., and Tavernarakis, N. (2018). The role of mitophagy in innate immunity. Front. Immunol. *9*, 1283.

Gomes, L.C. and Scorrano, L. (2013). Mitochondrial morphology in mitophagy and macroautophagy. Biochim. Biophys. Acta *1833*, 205-212.

Gou, H., Zhao, M., Xu, H., Yuan, J., He, W., Zhu, M., Ding, H., Yi, L., and 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., et al. (2014). Hepatitis C virus core protein suppresses mitophagy by interacting with parkin in the context of mitochondrial depolarization. Am. J. Pathol. *184*, 3026-3039.

Hawn, T.R., Shah, J.A., and Kalman, D. (2015). New tricks for old dogs: countering antibiotic resistance in tuberculosis with host-directed therapeutics. Immunol. Rev. *264*, 344-362.

He, X., Zhu, Y., Zhang, Y., Geng, Y., Gong, J., Geng, J., Zhang, P., Zhang, X., Liu, N., Peng, Y., et al. (2019). RNF34 functions in immunity and selective mitophagy by targeting MAVS for autophagic degradation. EMBO J. *38*, e100978.

Heo, J.M., Ordureau, A., Paulo, J.A., Rinehart, J., and 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.

Hino, K., Nishina, S., Sasaki, K., and Hara, Y. (2019). Mitochondrial damage and iron metabolic dysregulation in hepatitis C virus infection. Free Radic. Biol. Med. *133*, 193-199.

Hirota, Y., Tamashita, S., Kurihara, Y., Jin, X., Aihara, M., Saigusa, T., Kang, D., and Kanki, T. (2015). Mitophagy is primarily due to alterative autophagy and requires the MAPK1 and MAPK14 signaling pathways. Autophagy *11*, 332-343.

Hollville, E., Carroll, R.G., Cullen, S.P., and Martin, S.J. (2014). Bcl-2 family proteins participate in mitochondrial quality control by regulating Parkin/PINK1-dependent mitophagy. Mol. Cell *55*, 451-466.

Hu, Y.W., Zhang, J., Wu, X.M., Cao, L., Nie, P., and Chang, M.X. (2018). TANK-Binding Kinase 1 (TBK1) isoforms negatively regulate type I interferon induction by inhibiting TBK1-IRF3 interaction and IRF3 phosphorylation. Front. Immunol. *9*, 84.

Ishii, K.J., Koyama, S., Nakagawa, A., Coban, C., and Akira, S. (2008). Host innate immune receptors and beyond: making sense of microbial infections. Cell Host Microbe *3*, 352-363.

Jabir, M.S., Hopkins, L., Ritchie, N.D., Ullah, I., Bayes, H.K., Li, D., Tourlomousis, P., Lupton, A., Puleston, D., Simon, A.K., et al. (2015). Mitochondrial damage contributes to *Pseudomonas aeruginosa* activation of the inflammasome and is downregulated by autophagy. Autophagy *11*, 166-182.

Jabir, M.S., Ritchie, N.D., Li, D., Bayes, H.K., Tourlomousis, P., Puleston, D., Lupton, A., Hopkins, L., Simon, A.K., Bryant, C., et al. (2014). Caspase-1 cleavage of the TLR adaptor TRIF inhibits autophagy and beta-interferon production during *Pseudomonas aeruginosa* infection. Cell Host Microbe *15*, 214-227.

Jassey, A., Liu, C.H., Changou, C.A., Richardson, C.D., Hsu, H.Y., and Lin, L.T. (2019). Hepatitis C virus non-structural protein 5A (NS5A) disrupts mitochondrial dynamics and induces mitophagy. Cells *8*, E290.

Jin, H.S., Suh, H.W., Kim, S.J., and Jo, E.K. (2017a). Mitochondrial control of innate immunity and inflammation. Immune Netw. *17*, 77-88.

Jin, S., Tian, S., Luo, M., Xie, W., Liu, T., Duan, T., Wu, Y., and Cui, J. (2017b). Tetherin suppresses type I interferon signaling by targeting MAVS for NDP52-mediated selective autophagic degradation in human cells. Mol. Cell *68*, 308-322.e4.

Jin, S.M., Lazarou, M., Wang, C., Kane, L.A., Narendra, D.P., and Youle, R.J. (2010). Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. J. Cell Biol. *191*, 933-942.

Jing, K., Shin, S., Jeong, S., Kim, S., Song, K.S., Park, J.H., Heo, J.Y., Seo, K.S., Park, S.K., Kweon, G.R., et al. (2014). Docosahexaenoic acid induces the degradation of HPV E6/E7 oncoproteins by activating the ubiquitin-proteasome system. Cell Death Dis. *5*, e1524.

Kang, R., Zeng, L., Xie, Y., Yan, Z., Zhou, B., Cao, L., Klionsky, D.J., Tracey, K.J., Li, J., Wang, H., et al. (2016). A novel PINK1- and PARK2-dependent protective neuroimmune pathway in lethal sepsis. Autophagy *12*, 2374-2385.

Kawai, T. and Akira, S. (2011). Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity *34*, 637-650.

Kim, M.J., Bae, S.H., Ryu, J.C., Kwon, Y., Oh, J.H., Kwon, J., Moon, J.S., Kim, K., Miyawaki, A., Lee, M.G., et al. (2016). SESN2/sestrin2 suppresses sepsis by inducing mitophagy and inhibiting NLRP3 activation in macrophages. Autophagy *12*, 1272-1291.

Kim, S.J., Jang, J.Y., Kim, E.J., Cho, E.K., Ahn, D.G., Kim, C., Park, H.S., Jeong, S.W., Lee, S.H., Kim, S.G., et al. (2017). Ginsenoside Rg3 restores hepatitis C virus-induced aberrant mitochondrial dynamics and inhibits virus propagation. Hepatology *66*, 758-771.

Kim, S.J., Khan, M., Quan, J., Till, A., Subramani, S., and 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., and 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., and 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.

Klein, C. and Westenberger, A. (2012). Genetics of Parkinson's disease. Cold Spring Harb. Perspect. Med. *2*, a008888.

Krakauer, T. (2019). Inflammasomes, autophagy, and cell death: the trinity of innate host defense against intracellular bacteria. Mediators Inflamm.

2019, 2471215.

Kurose, I., Miura, S., Fukumura, D., Yonei, Y., Saito, H., Tada, S., Suematsu, M., and Tsuchiya, M. (1993). Nitric oxide mediates Kupffer cell-induced reduction of mitochondrial energization in hepatoma cells: a comparison with oxidative burst. Cancer Res. *53*, 2676-2682.

Lazarou, M., Sliter, D.A., Kane, L.A., Sarraf, S.A., Wang, C., Burman, J.L., Sideris, D.P., Fogel, A.I., and Youle, R.J. (2015). The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature *524*, 309-314.

Li, J., Ma, C., Long, F., Yang, D., Liu, X., Hu, Y., Wu, C., Wang, B., Wang, M., Chen, Y., et al. (2019). Parkin impairs antiviral immunity by suppressing the mitochondrial reactive oxygen species-Nlrp3 axis and antiviral inflammation. iScience *16*, 468-484.

Li, S., Wang, J., Zhou, A., Khan, F.A., Hu, L., and Zhang, S. (2016). Porcine reproductive and respiratory syndrome virus triggers mitochondrial fission and mitophagy to attenuate apoptosis. Oncotarget *7*, 56002-56012.

Li, S., Wu, H., Han, D., Ma, S., Fan, W., Wang, Y., Zhang, R., Fan, M., Huang, Y., Fu, X., et al. (2018). A novel mechanism of mesenchymal stromal cell-mediated protection against sepsis: restricting inflammasome activation in macrophages by increasing mitophagy and decreasing mitochondrial ROS. Oxid. Med. Cell. Longev. *2018*, 3537609.

Liu, L., Feng, D., Chen, G., Chen, M., Zheng, Q., Song, P., Ma, Q., Zhu, C., Wang, R., Qi, W., et al. (2012a). Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat. Cell Biol. *14*, 177-185.

Liu, S., Sawada, T., Lee, S., Yu, W., Silverio, G., Alapatt, P., Millan, I., Shen, A., Saxton, W., Kanao, T., et al. (2012b). Parkinson's disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria. PLoS Genet. *8*, e1002537.

Mannam, P., Shinn, A.S., Srivastava, A., Neamu, R.F., Walker, W.E., Bohanon, M., Merkel, J., Kang, M.J., Dela Cruz, C.S., Ahasic, A.M., et al. (2014). MKK3 regulates mitochondrial biogenesis and mitophagy in sepsis-induced lung injury. Am. J. Physiol. Lung Cell. Mol. Physiol. *306*, L604-L619.

Martinon, F., Mayor, A., and Tschopp, J. (2009). The inflammasomes: guardians of the body. Annu. Rev. Immunol. *27*, 229-265.

Matheoud, D., Cannon, T., Voisin, A., Penttinen, A.M., Ramet, L., Fahmy, A.M., Ducrot, C., Laplante, A., Bourque, M.J., Zhu, L., et al. (2019). Intestinal infection triggers Parkinson's disease-like symptoms in Pink1(-/-) mice. Nature *571*, 565-569.

McGuire, V.A. and Arthur, J.S. (2015). Subverting toll-like receptor signaling by bacterial pathogens. Front. Immunol. *6*, 607.

Meng, G., Xia, M., Wang, D., Chen, A., Wang, Y., Wang, H., Yu, D., and Wei, J. (2014). Mitophagy promotes replication of oncolytic Newcastle disease virus by blocking intrinsic apoptosis in lung cancer cells. Oncotarget *5*, 6365-6374.

Mohamud, Y., Qu, J., Xue, Y.C., Liu, H., Deng, H., and Luo, H. (2019). CALCOCO2/NDP52 and SQSTM1/p62 differentially regulate coxsackievirus B3 propagation. Cell Death Differ. *26*, 1062-1076.

Mohanty, A., Tiwari-Pandey, R., and Pandey, N.R. (2019). Mitochondria: the indispensable players in innate immunity and guardians of the inflammatory response. J. Cell Commun. Signal. *13*, 303-318.

Montava-Garriga, L. and Ganley, I.G. (2020). Outstanding questions in mitophagy: what we do and do not know. J. Mol. Biol. *432*, 206-230.

Murray, P.J. and Wynn, T.A. (2011). Protective and pathogenic functions of macrophage subsets. Nat. Rev. Immunol. *11*, 723-737.

Nagi, M., Tanabe, K., Nakayama, H., Ueno, K., Yamagoe, S., Umeyama, T., Ohno, H., and Miyazaki, Y. (2016). Iron-depletion promotes mitophagy to maintain mitochondrial integrity in pathogenic yeast *Candida glabrata*. Autophagy *12*, 1259-1271.

Narendra, D., Tanaka, A., Suen, D.F., and 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., and Youle, R.J. (2010). PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol. *8*, e1000298.

Ney, P.A. (2015). Mitochondrial autophagy: origins, significance, and role of BNIP3 and NIX. Biochim. Biophys. Acta *1853*, 2775-2783.

Niller, H.H., Masa, R., Venkei, A., Meszaros, S., and Minarovits, J. (2017). Pathogenic mechanisms of intracellular bacteria. Curr. Opin. Infect. Dis. *30*, 309-315.

Novak, I., Kirkin, V., McEwan, D.G., Zhang, J., Wild, P., Rozenknop, A., Rogov, V., Lohr, F., Popovic, D., Occhipinti, A., et al. (2010). Nix is a selective autophagy receptor for mitochondrial clearance. EMBO Rep. *11*, 45-51.

Ogawa, M., Mimuro, H., Yoshikawa, Y., Ashida, H., and Sasakawa, C. (2011). Manipulation of autophagy by bacteria for their own benefit. Microbiol. Immunol. *55*, 459-471.

Ojeda, D.S., Grasso, D., Urquiza, J., Till, A., Vaccaro, M.I., and Quarleri, J. (2018). Cell death is counteracted by mitophagy in HIV-productively infected astrocytes but is promoted by inflammasome activation among non-productively infected cells. Front. Immunol. *9*, 2633.

Oka, T., Hikoso, S., Yamaguchi, O., Taneike, M., Takeda, T., Tamai, T., Oyabu, J., Murakawa, T., Nakayama, H., Nishida, K., et al. (2012). Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure. Nature *485*, 251-255.

Paik, S., Kim, J.K., Chung, C., and Jo, E.K. (2018). Autophagy: a new strategy for host-directed therapy of tuberculosis. Virulence *10*, 1-12.

Pareja, M.E. and Colombo, M.I. (2013). Autophagic clearance of bacterial pathogens: molecular recognition of intracellular microorganisms. Front. Cell. Infect. Microbiol. *3*, 54.

Pickles, S., Vigie, P., and Youle, R.J. (2018). Mitophagy and quality control mechanisms in mitochondrial maintenance. Curr. Biol. *28*, R170-R185.

Pilli, M., Arko-Mensah, J., Ponpuak, M., Roberts, E., Master, S., Mandell, M.A., Dupont, N., Ornatowski, W., Jiang, S., Bradfute, S.B., et al. (2012). TBK-1 promotes autophagy-mediated antimicrobial defense by controlling autophagosome maturation. Immunity *37*, 223-234.

Piquereau, J., Godin, R., Deschenes, S., Bessi, V.L., Mofarrahi, M., Hussain, S.N., and Burelle, Y. (2013). Protective role of PARK2/Parkin in sepsis-induced cardiac contractile and mitochondrial dysfunction. Autophagy *9*, 1837-1851.

Quinsay, M.N., Thomas, R.L., Lee, Y., and Gustafsson, A.B. (2010). Bnip3-mediated mitochondrial autophagy is independent of the mitochondrial permeability transition pore. Autophagy *6*, 855-862.

Rademann, P., Weidinger, A., Drechsler, S., Meszaros, A., Zipperle, J., Jafarmadar, M., Dumitrescu, S., Hacobian, A., Ungelenk, L., Rostel, F., et al. (2017). Mitochondria-targeted antioxidants SkQ1 and MitoTEMPO failed to exert a long-term beneficial effect in murine polymicrobial sepsis. Oxid. Med. Cell. Longev. *2017*, 6412682.

Randow, F. and Munz, C. (2012). Autophagy in the regulation of pathogen replication and adaptive immunity. Trends Immunol. *33*, 475-487.

Rawat, P., Teodorof-Diedrich, C., and Spector, S.A. (2019). Human immunodeficiency virus Type-1 single-stranded RNA activates the NLRP3 inflammasome and impairs autophagic clearance of damaged mitochondria in human microglia. Glia *67*, 802-824.

Richter, B., Sliter, D.A., Herhaus, L., Stolz, A., Wang, C., Beli, P., Zaffagnini, G., Wild, P., Martens, S., Wagner, S.A., et al. (2016). Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria. Proc. Natl. Acad. Sci. U. S. A. *113*, 4039-4044.

Schulze-Osthoff, K., Bakker, A.C., Vanhaesebroeck, B., Beyaert, R., Jacob, W.A., and Fiers, W. (1992). Cytotoxic activity of tumor necrosis factor is mediated by early damage of mitochondrial functions. Evidence for the involvement of mitochondrial radical generation. J. Biol. Chem. *267*, 5317-5323.

Shi, G. and McQuibban, G.A. (2017). The mitochondrial rhomboid protease PARL is regulated by PDK2 to integrate mitochondrial quality control and metabolism. Cell Rep. *18*, 1458-1472.

Shi, J., Wong, J., Piesik, P., Fung, G., Zhang, J., Jagdeo, J., Li, X., Jan, E., and Luo, H. (2013). Cleavage of sequestosome 1/p62 by an enteroviral protease results in disrupted selective autophagy and impaired NFKB signaling. Autophagy *9*, 1591-1603.

Silva, M.T. (2011). Macrophage phagocytosis of neutrophils at inflammatory/infectious foci: a cooperative mechanism in the control of infection and infectious inflammation. J. Leukoc. Biol. *89*, 675-683.

Sin, J., McIntyre, L., Stotland, A., Feuer, R., and Gottlieb, R.A. (2017). Coxsackievirus B escapes the infected cell in ejected mitophagosomes. J. Virol. *91*, e01347-17.

Sliter, D.A., Martinez, J., Hao, L., Chen, X., Sun, N., Fischer, T.D., Burman, J.L., Li, Y., Zhang, Z., Narendra, D.P., et al. (2018). Parkin and PINK1 mitigate STING-induced inflammation. Nature *561*, 258-262.

Snell, L.M., McGaha, T.L., and Brooks, D.G. (2017). Type I interferon in chronic virus infection and cancer. Trends Immunol. *38*, 542-557.

Sorbara, M.T. and Girardin, S.E. (2015). Emerging themes in bacterial autophagy. Curr. Opin. Microbiol. *23*, 163-170.

Srivastava, A., McGinniss, J., Wong, Y., Shinn, A.S., Lam, T.T., Lee, P.J., and Mannam, P. (2015). MKK3 deletion improves mitochondrial quality. Free Radic. Biol. Med. *87*, 373-384.

Sumpter, R., Jr. and Levine, B. (2010). Autophagy and innate immunity: triggering, targeting and tuning. Semin. Cell Dev. Biol. *21*, 699-711.

Sun, S., Sursal, T., Adibnia, Y., Zhao, C., Zheng, Y., Li, H., Otterbein, L.E., Hauser, C.J., and Itagaki, K. (2013). Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways. PLoS One *8*, e59989.

Tal, M.C. and Iwasaki, A. (2011). Mitoxosome: a mitochondrial platform for cross-talk between cellular stress and antiviral signaling. Immunol. Rev. *243*, 215-234.

Tang, D., Kang, R., Coyne, C.B., Zeh, H.J., and Lotze, M.T. (2012). PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunol. Rev. *249*, 158-175.

Taylor, D.E., Ghio, A.J., and Piantadosi, C.A. (1995). Reactive oxygen species produced by liver mitochondria of rats in sepsis. Arch. Biochem. Biophys. *316*, 70-76.

Teodorof-Diedrich, C. and Spector, S.A. (2018). Human immunodeficiency virus type 1 gp120 and Tat induce mitochondrial fragmentation and incomplete mitophagy in human neurons. J. Virol. *92*, e00993-18.

To, E.E., Erlich, J.R., Liong, F., Luong, R., Liong, S., Esaq, F., Oseghale, O., Anthony, D., McQualter, J., Bozinovski, S., et al. (2019). Mitochondrial reactive oxygen species contribute to pathological inflammation during influenza A virus infection in mice. Antioxid. Redox Signal. 2019 Jul 12 [Epub]. doi: 10.1089/ars.2019.7727.

Tsao, N., Kuo, C.F., Cheng, M.H., Lin, W.C., Lin, C.F., and Lin, Y.S. (2019). Streptolysin S induces mitochondrial damage and macrophage death through inhibiting degradation of glycogen synthase kinase-3beta in *Streptococcus pyogenes* infection. Sci. Rep. *9*, 5371.

Tschurtschenthaler, M. and Adolph, T.E. (2018). The selective autophagy receptor Optineurin in Crohn's disease. Front. Immunol. *9*, 766.

Vo, M.T., Smith, B.J., Nicholas, J., and Choi, Y.B. (2019). Activation of NIX-mediated mitophagy by an interferon regulatory factor homologue of human herpesvirus. Nat. Commun. *10*, 3203.

Wang, K., Ma, H., Liu, H., Ye, W., Li, Z., Cheng, L., Zhang, L., Lei, Y., Shen, L., and Zhang, F. (2019a). The glycoprotein and nucleocapsid protein of Hantaviruses manipulate autophagy flux to restrain host innate immune responses. Cell Rep. *27*, 2075-2091.e5.

Wang, Y., Serricchio, M., Jauregui, M., Shanbhag, R., Stoltz, T., Di Paolo, C.T., Kim, P.K., and McQuibban, G.A. (2015). Deubiquitinating enzymes regulate PARK2-mediated mitophagy. Autophagy *11*, 595-606.

Wang, Z.T., Lu, M.H., Zhang, Y., Ji, W.L., Lei, L., Wang, W., Fang, L.P., Wang, L.W., Yu, F., Wang, J., et al. (2019b). Disrupted-in-schizophrenia-1 protects synaptic plasticity in a transgenic mouse model of Alzheimer's disease as a mitophagy receptor. Aging Cell *18*, e12860.

Wei, Y., Chiang, W.C., Sumpter, R., Jr., Mishra, P., and Levine, B. (2017). Prohibitin 2 is an inner mitochondrial membrane mitophagy receptor. Cell *168*, 224-238.e10.

Weidberg, H. and Elazar, Z. (2011). TBK1 mediates crosstalk between the innate immune response and autophagy. Sci. Signal. *4*, pe39.

Wong, Y.C. and Holzbaur, E.L. (2014). Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proc. Natl. Acad. Sci. U. S. A. *111*, E4439-E4448.

Wu, W., Tian, W., Hu, Z., Chen, G., Huang, L., Li, W., Zhang, X., Xue, P., Zhou, C., Liu, L., et al. (2014). ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. EMBO Rep. *15*, 566-575.

Xia, M., Gonzalez, P., Li, C., Meng, G., Jiang, A., Wang, H., Gao, Q., Debatin, K.M., Beltinger, C., and 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., and Wei, J. (2014b). Mitophagy switches cell death from apoptosis to necrosis in NSCLC cells treated with oncolytic measles virus. Oncotarget *5*, 3907-3918.

Xian, H., Yang, S., Jin, S., Zhang, Y. and Cui, J. (2019). LRRC59 modulates type I interferon signaling by restraining the SQSTM1/p62-mediated autophagic degradation of pattern recognition receptor DDX58/RIG-I. Autophagy 2019 May 22 [Epub]. doi: 10.1080/15548627.2019.1615303.

Xu, Y., Shen, J., and Ran, Z. (2019). Emerging views of mitophagy in immunity and autoimmune diseases. Autophagy *16*, 3-17.

Yoo, S.M. and Jung, Y.K. (2018). A molecular approach to mitophagy and mitochondrial dynamics. Mol. Cells *41*, 18-26.

Yoshizumi, T., Ichinohe, T., Sasaki, O., Otera, H., Kawabata, S., Mihara, K., and 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. and van der Bliek, A.M. (2012). Mitochondrial fission, fusion, and stress. Science *337*, 1062-1065.

Zachari, M., Gudmundsson, S.R., Li, Z., Manifava, M., Shah, R., Smith, M., Stronge, J., Karanasios, E., Piunti, C., Kishi-Itakura, C., et al. (2019). Selective autophagy of mitochondria on a ubiquitin-endoplasmic-reticulum platform. Dev. Cell *50*, 627-643.e5.

Zhang, Q., Kuang, H., Chen, C., Yan, J., Do-Umehara, H.C., Liu, X.Y., Dada, L., Ridge, K.M., Chandel, N.S., and Liu, J. (2015). The kinase Jnk2 promotes stress-induced mitophagy by targeting the small mitochondrial form of the tumor suppressor ARF for degradation. Nat. Immunol. *16*, 458-466.

Zhang, R., Varela, M., Vallentgoed, W., Forn-Cuni, G., van der Vaart, M., and Meijer, A.H. (2019a). The selective autophagy receptors Optineurin and p62 are both required for zebrafish host resistance to mycobacterial infection. PLoS Pathog. *15*, e1007329.

Zhang, X., Yuan, D., Sun, Q., Xu, L., Lee, E., Lewis, A.J., Zuckerbraun, B.S., and Rosengart, M.R. (2017). Calcium/calmodulin-dependent protein kinase regulates the PINK1/Parkin and DJ-1 pathways of mitophagy during sepsis. FASEB J. *31*, 4382-4395.

Zhang, Y., Yao, Y., Qiu, X., Wang, G., Hu, Z., Chen, S., Wu, Z., Yuan, N., Gao, H., Wang, J., et al. (2019b). Listeria hijacks host mitophagy through a novel mitophagy receptor to evade killing. Nat. Immunol. *20*, 433-446.

Zhao, C. and Zhao, W. (2019). TANK-binding kinase 1 as a novel therapeutic target for viral diseases. Expert Opin. Ther. Targets *23*, 437-446.

Zhou, D., Zhou, M., Wang, Z., Fu, Y., Jia, M., Wang, X., Liu, M., Zhang, Y., Sun,

Y., Lu, Y., et al. (2019a). PGRN acts as a novel regulator of mitochondrial homeostasis by facilitating mitophagy and mitochondrial biogenesis to prevent podocyte injury in diabetic nephropathy. Cell Death Dis. *10*, 524.

Zhou, J., Yang, R., Zhang, Z., Liu, Q., Zhang, Y., Wang, Q., and Yuan, H. (2019b). Mitochondrial protein PINK1 positively regulates RLR signaling. Front. Immunol. *10*, 1069.

Zhu, L., Mou, C., Yang, X., Lin, J., and Yang, Q. (2016). Mitophagy in TGEV infection counteracts oxidative stress and apoptosis. Oncotarget *7*, 27122-27141.

Zou, J., Li, W., Misra, A., Yue, F., Song, K., Chen, Q., Guo, G., Yi, J., Kimata, J.T., and Liu, L. (2015). The viral restriction factor tetherin prevents leucine-rich pentatricopeptide repeat-containing protein (LRPPRC) from association with beclin 1 and B-cell CLL/lymphoma 2 (Bcl-2) and enhances autophagy and mitophagy. J. Biol. Chem. *290*, 7269-7279.