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Mycobacteria and Autophagy: Many Questions and Few Answers

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Abstract

Tuberculosis (TB) is an ancient disease caused by *Mycobacterium tuberculosis* (*Mtb*). TB is one of the world's deadliest diseases, with one-third of infected individuals falling ill each year especially in many developing countries. Upon invading host cells, such as macrophages, *Mtb* can replicate in infected cells by arresting phagosome maturation and then potentially escaping into the cytosol. Host cells have a mechanism to control intracellular *Mtb* by inducing autophagy, which is an elaborate cellular process to target intracellular pathogens for degradation in infected cells. However, some factors of *Mtb* are involved in defense against killing by autophagy. Thus, this review highlights the recent advances in the interactions between autophagy and *Mtb*.

Introduction

Tuberculosis (TB), an infectious bacterial disease, is caused by *Mycobacterium tuberculosis* (*Mtb*). It is transmitted mainly via droplets from people showing active respiratory disease to other people. Most infections with *Mtb* usually do not cause any symptoms; this is also known as latent tuberculosis, in which the person's immune system acts to "wall off" the bacteria (Saiga et al., 2011). Some latent infections can progress to active disease with severe symptoms, including chronic cough with blood-containing sputum, fever, and weight loss. Over 100 million people have died from tuberculosis in the past 100 years, and 9 million new cases were reported in 2014 (Zumla et al., 2015). It is estimated that 35 million will die from TB between 2000-2020 (Zumla et al., 2015).

During the early stage of infection, macrophages dominate the immune response, because macrophages are the major reservoir of *Mtb*. The survival and multiplication of mycobacteria in macrophages and/or other host cells determine the outcomes of infection. Host cells have their own degradation systems to antagonize invading bacteria. Meanwhile, *Mtb* tries to avoid degradation by host cells. It is clear that *Mtb* can block phagosomal maturation and may escape into the cytosol for survival in macrophages. However, autophagy could target the cytosolic bacteria to lysosomes for degradation under certain conditions through unclear mechanisms. In light of the mysterious mechanism(s) of degradation of *Mtb* by the host during infection, we will focus on the cross-talk between autophagy and *Mtb* in this review.

Autophagy

Autophagy is a highly-conserved process that serves to deliver proteins or whole organelles to lysosomes for degradation. Three major forms, macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), have been identified. The form of autophagy discussed in this review refers to macroautophagy. Autophagy results in the engulfment of cytoplasmic proteins by a double membrane bounded structure, called the autophagosome, which is initiated from membrane sources, including: the endosome/Golgi system, endoplasmic reticulum-mitochondrial contact sites (Chan and Tang, 2013; Hamasaki et al., 2013), the plasma membrane (Ravikumar et al., 2010), and phospholipid precursors (Dupont et al., 2014). Autophagy-related genes (ATG) have been reported to be accountable for its execution, of which the ubiquitin-like conjugates, Atg12-Atg5 and LC3-phosphatidylethanolamine, are required for autophagosome formation. There are several regulators/stimulators of cell autophagy, including mammalian target of rapamycin (mTOR), presence of microbes (Tattoli et al., 2012), the TAB2/3-TAK1-IKK signaling axis (Criollo et al., 2011), events downstream of pattern recognition receptors (PRR) and immune cytokine activation (Lee et al., 2007), transcription factor EB (Settembre et al., 2011), and proteolytic systems via FOXO3a (Masiero et al., 2009). Meanwhile, autophagy activation is under the control of different promoters/inducers, such as the transcription factor, TFE3 (Martina et al., 2014), and drugs or nutritional supplements (Levine et al., 2015). Through autophagy, the host cell combats intracellular pathogens by fusing autosomes with lysosomes to sustain homeostasis. Moreover, it is implicated that autophagy can modulate MHC Class I-mediated antigen cross-presentation (Oliveira and van Hall, 2015). When autophagy is impaired, it may contribute to the pathogenesis of some pulmonary diseases (Ryter and Choi, 2015).

Restriction of intracellular *Mtb* replication by autophagy

Mtb survives in infected host cells by blocking phagosome maturation or escaping from phagosomes to the cytosol; this is attributed to the failure of bacilli to undergo delivery into lysosomes (Figure 1). The purpose of this review is not to provide a comprehensive summary of phagosomal maturation arrest strategies used by *Mtb*, as there are already excellent reviews covering this subject (Simeone et al., 2015; Welin and Lerm, 2012). Instead, this article will

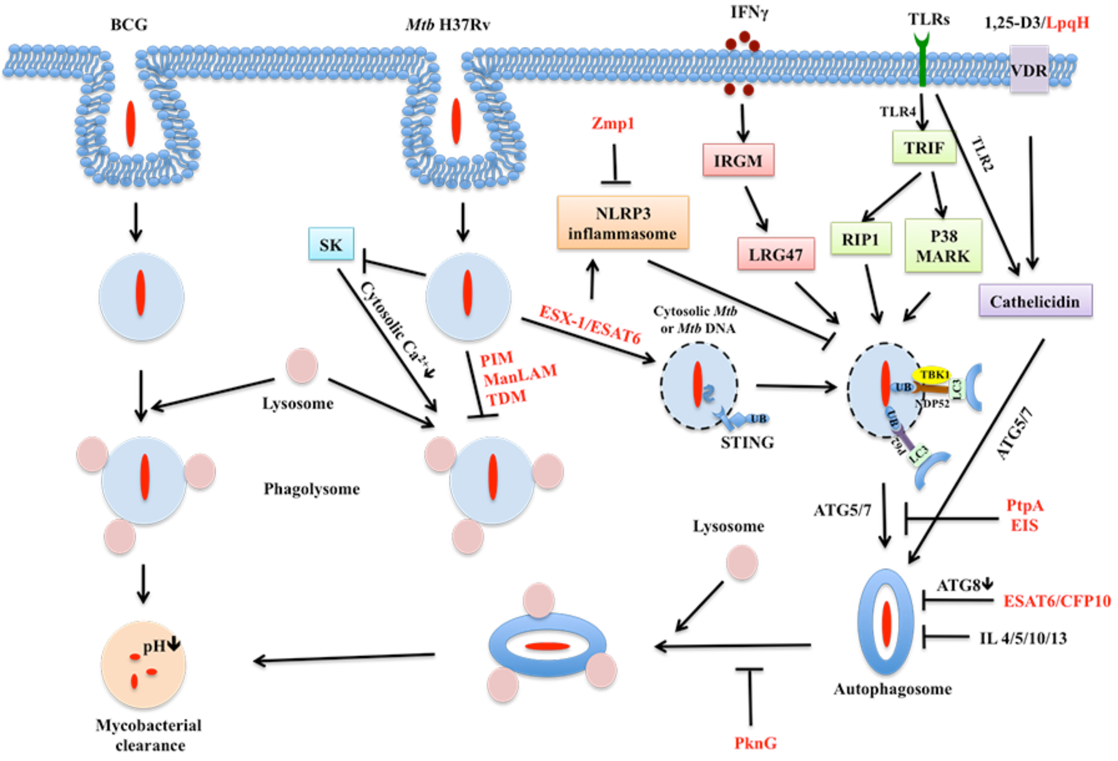

Figure 1. Interaction of *Mtb* with autophagy in host cells.

focus exclusively on the killing mechanisms of autophagy and defense mechanisms against it used by *Mtb*.

Autophagy has been found to target intracellular mycobacteria to lysosomes for degradation, and several components are involved in this process. Human guanosine triphosphatases (GTPase) play pivotal roles in the elimination of intracellular *Mtb* by inducing autophagy and generating the autolysosome in macrophages (Singh et al., 2006). These GTPases regulate vesicular trafficking and protein complex assembly on *Mtb*-containing autophagic vacuoles in macrophages. *Mtb* infection is associated with polymorphisms in immunity-related GTPase 1 (IRGM1), IFN-γ, IFN-γ receptor, TLR8, Vitamin D3 (VDR), and ATP receptor (P2X7R) (Jo, 2013; Saiga et al., 2011; Songane et al., 2012). The aggregation of IFN-γ with GTPase IRG-47 leads to reduced *Mtb* infection in macrophages of mice compared to IRG-47$^{-/-}$ mice (MacMicking et al., 2003). Initiating autophagy by IFN-γ could efficiently suppress intracellular survival of *Mtb*, along with colocalizing *Mtb* and Beclin-1, which boosts mycobacterial phagosome maturation in macrophages (Gutierrez et al., 2004).

Ubiquitin-derived peptides from *Mtb*-infected, macrophage lysosomes play a role in antimicrobial effects in host cells (Alonso et al., 2007). *Mtb* DNA can function as a signal to activate autophagy through the activation of the TBK1 and STING-dependent (stimulator of IFN genes) cytosolic pathways, which flag the bacteria with ubiquitin. TBK1 phosphorylates the autophagic receptor p62 (Pilli et al., 2012), while STING recognizes cyclic GMP-AMP (cGAMP) (Wu et al., 2013) generated by the host DNA-receptor cGAMP synthase, which finally activates the type I IFN pathway via TBK1 signaling (Sun et al., 2013). The ubiquitin-autophagy receptors, p62 and NDP52, recognize the ubiquitin-labelled *Mtb* and transfer them to the autophagosome. STING$^{-/-}$ macrophages were highly susceptible to infection (Ishikawa et al., 2009). In addition, genetic polymorphisms in regulating ubiquitin ligase (PARK2) are associated with increased susceptibility to mycobacterial infections in humans. Ubiquitin aggregates in liver cells, and autophagosome formation is impaired in Atg7$^{-/-}$ mice (Komatsu et al., 2005). Knockout of Atg7 also increased the expression of scavenger receptors on Atg7$^{-/-}$ macrophages, which are more susceptible to *Mtb* infection and intracellular growth (Bonilla et al., 2013). Due to the degradation of mutant α1-antitrypsin Z (α1-ATZ) protein by the ubiquitin-proteasome system, autophagosomes accumulation in Atg5$^{-/-}$ cell after transfection with a plasmid expressing α1-ATZ (Kamimoto et al., 2006), suggesting that the ubiquitin system could regulate *Mtb* in the autophagosome. Knockout of Atg5 in the myeloid lineage also causes the increase of bacillary burden but simultaneously increases damaging inflammation in mice (Castillo et al., 2012). Ubiquitin-derived peptides eradicate *Mtb* after multivesicular body trafficking of ubiquitin to the lysosome (Purdy and Russell, 2007a, b). Moreover, rapamycin (RAP) can enhance autophagy by improving presentation of *Mtb* antigen through antigen-presenting cells (macrophages and the dendritic cells) and strengthen the ability of dendritic cells to prime T cells (Jagannath et al., 2009). It has also been reported that inhaled RAP induces autophagy in lung macrophages *in situ*, with substantial decreases in lung burden of *Mtb* (Gupta et al., 2016). Further, Nordihydroguaiaretic acid (NDGA) and α-mangostin eradicate intracellular bacteria by inducing autophagy in human cells (Guzman-Beltran et al., 2016).

Stimulating *Mtb*-infected cells with different Toll-like receptor (TLR) agonists can decrease the survival of *Mtb*. TLR2 binds with TLR1 or TLR6 to form heterodimers, which is critical for recognition of *Mtb* glycolipids (Kleinnijenhuis et al., 2011). Furthermore, TLR4, TLR9, and possibly TLR8 can also recognize *Mtb* (Kleinnijenhuis et al., 2011). In addition, TLR2/1 activation could increase the expression of the vitamin D receptor to reduce the viability of *Mtb* in monocytes and macrophages, since engagement of TLR2/1 and CD14 by the mycobacterial lipoprotein LpqH could activate autophagy by vitamin D signaling activation (Liu et al., 2006; Shin et al., 2010b). Calcitriol is produced by macrophages treated with calcidiol (25-hyfroxy vitamin D3) through TLR signaling, IFN-γ, and other physiologic stimuli. Low levels of calcidiol and calcitriol in the serum are associated with susceptibility to tuberculosis (Fabri et al., 2011). During the killing of *Mtb* by Vitamin D3, cathelicidin is necessary in mediating autophagy by activation of BECN1 and Atg5 (Yuk et al., 2009). Moreover, the combination of IFN-γ and vitamin D triggers autophagic eradication of *Mtb* in human macrophages (Nnoaham and Clarke, 2008), but not in murine model (Harris et al., 2007).

In human monocytes/macrophages, cell autophagy induced by ATP could trigger lysosome fusion to kill intracellular *Mtb*, which is dependent on Ca^{2+} and the $P2X_7$ receptor (Biswas et al., 2008). Electron microscopy imaging of ATP-treated, BCG-infected monocytes-derived macrophages (MDMs) revealed the presence of the bacteria within autophagosomes characterized by double-membrane, indicating autophagy associated with mycobacterial killing (Biswas et al., 2008).

Non-coding RNAs are also involved in autophagy. Long non-coding RNAs, such as MEG3, were found to be linked with mTOR and PI3K-AKT signaling in regulating autophagy of host cells during infection with the vaccine strain, *M. bovis* Bacille Calmette-Guérin (BCG). IFN-γ-induced autophagy in infected macrophages resulted in sustained MEG3 down-regulation, and knockdown of MEG3 in macrophages lead to induction of autophagy and enhanced eradication of intracellular BCG (Pawar et al., 2016). MiR-155, the most highly upregulated miRNA in *Mtb*-infected bone marrow-derived macrophages (BMDMs), is essential for *Mtb* survival and simultaneously destructive for the innate immune response. It is of interest that BCG could induce miR-155 to trigger the apoptosis of infected macrophages, which is necessary for strong protective immunity in the host. With deletion of miR-155, the apoptosis of infected macrophages was largely compromised (Ghorpade et al., 2012; Kumar et al., 2012).

Mycobacteria can block autophagosome maturation to create a replicate niche

Mycobacteria could interfere the defense of host cells through many factors (Table 1). *Mtb* virulent strains impair autophagy at the level of autophagosome-lysosome fusion that is ESX-1-dependent in dendritic cells (Romagnoli et al., 2012). The ability to inhibit autophagy was fully restored in recombinant BCG and *Mtb* H37Ra strains expressing either *ESX-1* or the *PhoP* gene. After infecting host cells, *Mtb* can up-regulate Th2-type cytokines, including interleukin-5 (IL-5), IL-10, and IL-13 (Freeman et al., 2006). *Mtb* can also stimulate peripheral blood mononuclear cells (PBMC) to synthesize IL-4 and IL-13, which is a hallmark of Th2-polarized immunity. In tuberculosis patients, sensitivity of cells to IFN-γ is reduced to interfere with autophagosome formation (Condos et al., 2003). The cytokines of Th1 and Th2 responses exhibit antagonistic effects on the formation of the autophagosome (Harris et al., 2007; Harris et al., 2009); Th1-type cytokines induce the formation of the autophagosome, while Th2-type cytokines inhibit formation. Infection with *Mtb* inhibits the increase in cytosolic Ca^{2+} by restricting the activity of macrophage sphingosine kinase (SK), which results in the inhibition of phagosome maturation (Thompson et al., 2005; Yadav et al., 2006). *Mtb* can also secrete ESAT-6 and CFP-10 protein to inhibit autophagosome formation and survive in macrophages by decreasing ATG8 protein (Zhang et al., 2012).

The *Mtb* enhanced intracellular survival (*eis*) gene overturns macrophage autophagy through the inhibition of reactive oxygen species (ROS) generation (Shin et al., 2010a). Eis possibly interacts with specific autophagy factors or affects upstream signaling regulators that interfere with fusion between phagosomal compartments containing *Mtb* and lysosomes. Deletion of the *Mtb eis* gene could boost accumulation of massive autophagic vacuoles and formation of autophagosomes after infecting macrophages (Shin et al., 2010a). The *Mtb* mannose-capped lipoarabinomannan (ManLAM) could reduce the accumulation of autophagosomes and suppress the level of LC3 in phagosomal membranes in the RAW264.7 cell line (Shui et al., 2011). Further, Eis was reported to inhibit macrophage autophagy in the phorbol myristate acetate (PMA)-treated, human, THP-1 cell line and in murine macrophages through the up-regulation of IL-10 due to an increase in acetylation of histone H3 by the activation of the PI3K/Akt/mTOR/p70S6K pathway (Duan et al., 2016).

IL-1β also plays an important role in macrophages by eradicating *Mtb* in host cells (Mayer-Barber et al., 2011). Deficiency of autophagosome forming-related protein could elevate endotoxin-induced IL-1β levels (Saitoh et al., 2008). On the contrary, induction of autophagy inhibits IL-1β secretion by degradation of pro-IL-1β (Harris et al., 2011). IL-1 receptor-deficient mice are more susceptible to *Mtb* infecton (Fremond et al., 2007). *Mtb*-infected, IL-1$\beta^{-/-}$ mice showed increased mortality and bacterial burden by a mechanism

Table 1 Known modulatory effects of different factors on autophagy

Factors	Functions	References
Vitamin D3	Trigger the formation of autophagosomes and autophagolysosomes to eliminate *Mtb* via cathelicidin	Yuk et al., 2009
Ubiquitin derived Peptide	Contribute to kill *Mtb* in the autophagolysosome	Alonso et al., 2007
mTOR	Lipid component of *Mycobacteria* induce mTOR activity	Zullo et al., 2012
INF-γ	Induce autophagy to eliminate *Mtb*	Songane et al., 2012; Condos et al., 2003
IL-1β	Induced by *Mtb* and inhibition *Mtb* by Vitamin D3 need IL-1β receptor 1	Mayer-Barber et al., 2011; Kleinnijenhuis et al., 2011
Rab GTPase	*Mtb* recruits GTPase on its phagosome and prevent phagolysosome biogenesis	Lopez de Armentia et al., 2016
ATP	Trigger autophagy to kill intracellular *Mtb*	Biswas et al., 2008
Rapamycin	Improve autophagy by presenting more *Mtb* antigen and strengthen the ability of dendritic cells to prime T cells	Jagannath et al., 2009
T helper2 cytokines (IL-4, 5, 10, 13)	Inhibit autophagic *Mtb* phagolysosome maturation and limination of *Mtb* by autophagy	Harris J et al., 2007
Eis	*Eis*-deletion *Mtb* increased accumulation of massive autophagic vacuoles and formation of autophagosomes	Shin, D.M et al., 2010
miR-155	*Mtb* infection upregulate miR-155 to modulate cell apoptosis	Ghorpade et al., 2012; Kumar et al., 2012
miR-30A	*Mtb* infection upregulate miR-30A to escape from intracellular elimination	Chen et al., 2015
MiR-33	Inhibition of miR-33 enhance killing *Mtb* by upregulate autophagy	Ouimet et al., 2016
Zn^{2+} metalloprotease (Zmp1)	Zmp1 is required for *Mtb* virulence and inhibition of host cell inflammasome activation	Master et al., 2008
Sphingosine kinase 1 (SK1)	Activation of SK is inhibited by *Mtb* and increase of SK activity is associated with phagocytosis	Thompson et al., 2005; Yadav et al., 2006
Bfl-1/A1	Negtively regulate autophagy in *Mtb* infected host cells	Kathania et al., 2011
ESAT6/CFP-10	Inhibition of autophagosome formation and allow *Mtb* to survive in host cell	Zhang et al., 2012
PtpA	Secreted by *Mtb* and inhibit phagosome-lysosome fusion by dephosphorylating host cell VPS33B to persistence intracellularly.	Bach et al., 2008
TAB2/3	Interact with beclin 1 and inhibit autophagy, dissciate with beclin 1 induce autophagy	Criollo et al., 2011
PIM	Stimulate fusion between phagosomes and early endosomes	Vergne et al., 2004
ManLAM	Inhibit accumulation of autophagic vacuoles in host cell	Shui et al., 2011

that does not require TLR signaling or caspase-1 (Mayer-Barber et al., 2010). The deficiency of Zmp1 (Zn^{2+} metalloprotease) in *Mtb* could attenuate *Mtb* virulence and induce IL-1β during *Mtb* infection (Master et al., 2008).

It has been reported that *Mtb* can upregulate miR-30A to escape intracellular elimination in macrophages (Chen et al., 2015). MiRNA downregulates Beclin and ATG5 expression, and inhibits autophagy (Zou et al., 2012). Exogenous and overexpression of miR-30A could prevent abolition of intracellular *Mtb* by inhibiting autophagy. Another study reported that *Mtb* regulates miR-155 through an ESAT6-dependent manner to overcome its elimination and promote infection in macrophages (Kumar et al., 2012). *Mtb* also induces miR-33 and its passenger strand to inhibit integrated pathways involved in autophagy and reprogram host lipid metabolism to enable intracellular survival (Ouimet et al., 2016). *Mtb* blocks the autophagic machinery by blocking phagosome maturation through secretion of the macromolecules, PtpA and SapM. PtpA is crucial for *Mtb* pathogenicity within the macrophage (Bach et al., 2008). *Mtb* also utilizes Rab GTPases, which regulate phagosomal maturation to escape autophagy (Lopez de Armentia et al., 2016). Rab GTPases interferes with late endosome/lysosome vesicular interactions, leading to arrested autophagy (Lopez de Armentia et al., 2016). *Mtb* H37Rv limits autophagy by upregulating the expression of host anti-autophagic factor, Bfl-1/A1 (Kathania et al., 2011). Down-regulation of Bfl-1/A1 by siRNA prompted autophagy and suppressed bacterial growth, confirming the role of Bfl-1/A1in helping bacteria to outmaneuver host defenses. *Mtb* products, like the PI3P phosphatase, SapM, glycosylated phosphatidyl-inositol-mimic, LAM, and phosphatidylinositol mannoside (PIM) were reported to suppress PI3K signaling to offset autophagy (Ramachandra et al., 2005).

Conclusion

Autophagy is an efficient way to clear intracellular pathogens, including *Mtb*, in eukaryotic cells. Although autophagy-based therapies have clear potential as a *Mtb* treatment strategy, the knowledge of how autophagy kills *Mtb in vivo* is still far from complete. In addition, how *Mtb* escape elimination by autophagy is poorly understood. Several questions remain: (1) How does *Mtb* escape lysosomal delivery inside of infected host cells; (2) Which factors of *Mtb* are involved in escaping degradation by autophagy in infected cells; (3) Will therapies based on boosting host cell autophagy be able to eradicate *Mtb* infection?

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Disclosure statement

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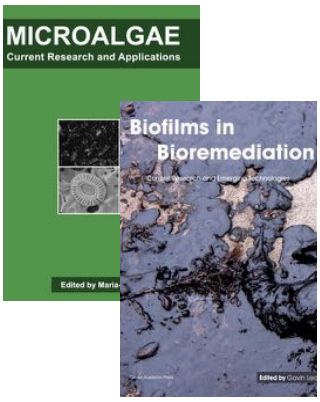

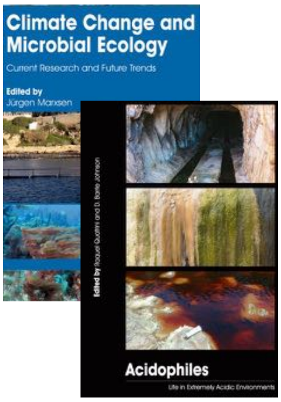

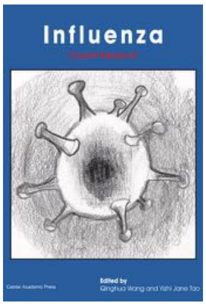

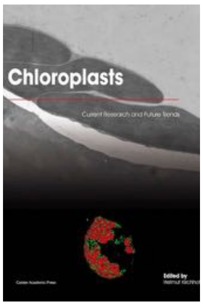

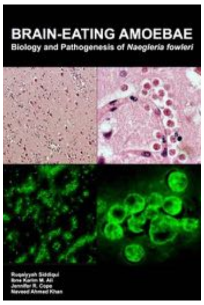

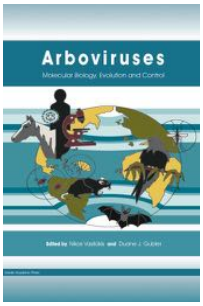

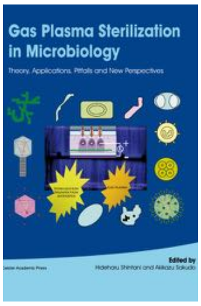

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