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Review Article

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Host-Pathogen Dialogues in Autophagy, Apoptosis, and Necrosis during Mycobacterial Infection

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
ATPase, adenosine triphosphatase; c-GAS, cyclic GMP-AMP synthase; CISH, cytokine-inducible SH2-containing protein; COX,

ABSTRACT

Mycobacterium tuberculosis (Mtb) is an etiologic pathogen of human tuberculosis (TB), a serious infectious disease with high morbidity and mortality. In addition, the threat of drug resistance in anti-TB therapy is of global concern. Despite this, it remains urgent to research for understanding the molecular nature of dynamic interactions between host and pathogens during TB infection. While Mtb evasion from phagolysosomal acidification is a well-known virulence mechanism, the molecular events to promote intracellular parasitism remains elusive. To combat intracellular Mtb infection, several defensive processes, including autophagy and apoptosis, are activated. In addition, Mtb-ingested phagocytes trigger inflammation, and undergo necrotic cell death, potentially harmful responses in case of uncontrolled pathological condition. In this review, we focus on Mtb evasion from phagosomal acidification, and Mtb interaction with host autophagy, apoptosis, and necrosis. Elucidation of the molecular dialogue will shed light on Mtb pathogenesis, host defense, and development of new paradigms of therapeutics.

Keywords: Tuberculosis; Host-pathogen interactions; Autophagy; Apoptosis; Necrosis

INTRODUCTION

There is a need for new therapeutics for tuberculosis (TB), the leading cause of death by a single infectious agent worldwide. Although much effort has been focused on controlling TB, multidrug- and extensively drug-resistant TB threaten human health globally. In addition, approximately 25% of people are estimated to have latent TB, and so are at risk of active TB (World Health Organization, Global Tuberculosis Report 2018).

Mycobacterium tuberculosis (Mtb) is the major pathogen of human TB and can escape from host immunity and phagolysosomal fusion, surviving in phagosomes (1). Mtb cell-wall lipid components are coordinately expressed during different stages of infection (2). Mtb infection triggers intracellular signaling pathways, enhancing the inflammatory cytokine/chemokine responses that are crucial for controlling Mtb replication and the immunopathologic response (3). The host-Mtb interaction alters the host immune response and triggers cell

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cyclooxygenase; ER, endoplasmic reticulum; ESAT-6, 6-kDa early secretory antigenic target; ESX, early secretory antigenic target protein family secretion; LAP, LC3-associated phagocytosis; Mtb, Mycobacterium tuberculosis; NET, neutrophil extracellular trap; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; TB, tuberculosis; TDM, trehalose 6,6′-dimycolate; Ub, ubiquitin; V-ATPase, vacuolar adenosine triphosphatase; WASH, Wiskott-Aldrich syndrome protein and SCAR homolog.

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death (4,5). The virulence factors of Mtb manipulate host immune, inflammatory, and cell death responses to facilitate intracellular growth (4).

Host protective immunity involves the control of inflammation and cell death, as well as the induction of antimicrobial factors (6). Autophagy is a cell-autonomous defense mechanism against a variety of stresses, including intracellular pathogens (7,8). Xenophagy is activated to target cytosolic Mtb for lysosomal delivery and degradation (9). However, Mtb evades xenophagy and LC3-associated phagocytosis via its virulence effectors and by modulating host factors (10). Mtb and its components regulate host cell death—*i.e.*, apoptosis and necrosis, during infection (11,12). Generally, apoptosis is beneficial, whereas necrosis is detrimental, depending on the context. Mtb causes cell death by apoptosis and necrosis, contributing to the outcomes of infection.

This review provides insight into how Mtb manipulates host-cell autophagy, apoptosis, and necrosis. An appreciation of the host-Mtb interaction will enable the development of novel therapeutics and identification of the factors implicated in progression to active TB.

HOST REACTION TO Mtb INFECTION

Mtb is an obligate aerobic mycobacterium with a unique cell-wall structure and is capable of surviving within an immunocompetent host (13). As a primarily airborne disease, TB is transmitted person-to-person by aerosolized droplets containing Mtb (13,14). Mtb travels through the respiratory tract to the alveoli, where it is phagocytosed by alveolar macrophages, monocytes, and dendritic cells (14,15). Once phagocytosed, Mtb replicates within the macrophages, resulting in a robust inflammatory response followed by T-cell activation and recruitment of mononuclear cells and lymphocytes from neighboring blood vessels, forming granulomatous lesions (14,16,17). In this environment, macrophages differentiate into foamy macrophages filled with lipid droplets, multinucleate giant cells, and epithelial macrophages. Over time, the granuloma acquires a more organized structure with the formation of a fibrous sheath of extracellular matrix (17). Although most granulomas comprise a balance between Mtb and host-derived immune cells, under certain conditions, these structures progress into a more pathologic state characterized by diminished vascularization, increased necrosis, proliferation of foamy macrophages, and accumulation of caseous and hypoxic portions in the center (17). Rupture of these granulomas releases infectious bacilli into the airway (17,18). Our understanding of the granulomatous response to mycobacteria is in its infancy, and the mechanisms underlying the formation of protective and destructive granulomas are unclear.

The cell wall of Mtb is composed primarily of mycolic acids, which contribute to its acid resistance, along with smaller proportions of other lipids, including mannosyl-phosphatidyl-*myo*-inositol-based glycolipids, lipomannan, and lipoarabinomannan (19,20). To transport proteins across the cell wall, Mtb uses the 6-kDa early secretory antigenic target (ESAT-6) protein family secretion (ESX) system, which is encoded by the *esx-1* locus. ESAT-6 (EsxA) is a key virulence factor (21). Upon infection with Mtb, phagocytes, particularly macrophages, respond to pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs), such as TLRs, C-type lectin receptors (*e.g.*, Dectin-1), and Fc receptors (22-24). Recognition of Mtb PAMPs by PRRs triggers an intracellular signaling cascade resulting in activation of the NF-κB and mitogen-activated protein kinase pathways. This induces the production of proinflammatory cytokines and other antimicrobial effector molecules (24).

The mechanisms by which innate immune signaling activates inflammatory and effector pathways during mycobacterial infection are reviewed elsewhere (24-27). The details of the innate immune pathways subverted by virulent Mtb are beyond the scope of this review. To successfully respond to Mtb infection, it is important to minimize immune-related damage while maintaining the host's ability to mount a protective immune response.

Mtb ESCAPE FROM PHAGOLYSOSOMAL FUSION

Mtb has evolved multiple strategies to evade host immunity and overcome macrophage defenses. Mtb survives within macrophages primarily by blocking phagosomal maturation (28,29). Mtb phagosomal vacuoles do not acquire vesicular proton-adenosine triphosphatase (ATPase) (30). The ESAT-6-CFP-10 secretion system is implicated in the blockade of phagolysosomal fusion, contributing to intracellular survival of Mtb (31). In addition, the function of Mtb *Rv3671c*, which encodes a membrane-associated protein, is related to acid resistance and virulence; it also maintains intrabacterial pH (32). Furthermore, the most abundant Mtb lipid component, trehalose 6,6′-dimycolate (TDM), inhibits phagosomal acidification and promotes virulence (33). Notably, injection of TDM emulsion into mice resulted in a similar immunopathology in the lung as that observed in mice infected with Mtb (34). By interacting with the Mincle receptor, TDM inhibits phagosome maturation, contributing to TDM-induced virulence (35). Also, Mtb-derived TDM has been shown to induce severe tissue disruption, vascular occlusion, cell damage, and inflammation (36).

Phagosomal maturation by fusion with lysosomes depends on vacuolar ATPase (V-ATPase), which acidifies the phagosomal lumen by hydrolyzing ATP (37,38). Mtb inhibits host V-ATPase via mechanisms involving the mycobacterial phosphatase PtpA (39). As a secreted protein, PtpA interacts with V-ATPase to promote Mtb survival and pathogenicity (39). PtpA promotes escape from *Mycobacterium*-containing vacuoles by inhibiting the recruitment of V-ATPase (40). The Mtb SecA2 accessory system is required for arrest of phagosome maturation and the intracellular growth of Mtb (41). In addition, the phosphatase SapM and the kinase PknG, which are exported by SecA2, block Mtb delivery to autophagolysosomes (42).

Host factors are required for arresting phagosome acidification during Mtb infection. Mtb-induced STAT5-mediated expression of cytokine-inducible SH2-containing protein (CISH) promotes intracellular Mtb replication by inducing the degradation of V-ATPase catalytic subunit A (43). By contrast, disruption of Wiskott-Aldrich syndrome protein and SCAR homolog (WASH), a host actin nucleation-promoting factor, contributes to the accumulation of V-ATPase around the phagosomal vacuole by generating and associating with F-actin on the mycobacterial vacuole (44). Pathogenic mycobacteria subvert actin polymerization to escape phagosomal acidification. Cytokines are implicated in phagolysosomal acidification. For example, IL-12 exerted a positive, and IL-27 a negative, effect on phagosomal acquisition of V-ATPase and cathepsin D activity (**Table 1**) (45). Although arrest of phagosome maturation is a key virulence mechanism of Mtb, the effectors and their functions *in vivo* are unknown. Identification of the effectors that promote Mtb escape from phagolysosomal fusion will promote the development of therapeutics for TB.

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Table 1. Mtb strategies for escaping phagolysosomal fusion

Effectors/factors	Strategy	Ref.
Mtb effectors		
ESAT-6-CFP-10	Inhibition of phagolysosomal fusion	(31)
Rv3671c	Maintenance of intrabacterial pH	(32)
TDM	Inhibition of phagosomal acidification and promotion of virulence	(33)
PtpA	Interaction with V-ATPase and inhibition the recruitment of V-ATPase to phagosome	(39)
SapM & PknG	Blockade of Mtb delivery to autophagolysosomes	(42)
Host factors		
CISH	Degradation of V-ATPase catalytic subunit A	(43)
WASH	Accumulation of V-ATPase of phagosomal vacuole to escape phagosomal acidification	(44)
IL-27	Neutralization of lysosomal acidification and cathepsin D activity	(45)

Mtb INTERACTIONS WITH HOST AUTOPHAGY

Autophagy is an intrinsic catabolic process of lysosomal degradation of damaged organelles or intracellular protein aggregates (46). There are three major types of autophagy—macro-autophagy, micro-autophagy, and chaperone-mediated autophagy (47). Although initially regarded as a nonspecific bulk degradation process, autophagy is required for selective degradation of protein aggregates, damaged mitochondria, and intracellular pathogens (48,49). Importantly, selective autophagy is mediated by autophagy receptors that recognize signals and bind to LC3/GABARAP proteins on the autophagosome membrane. Selective autophagy operates via ubiquitin (Ub)-dependent or -independent pathways (49-51). As an antibacterial defense, xenophagy of intracellular pathogens has been reported for Mtb and *Salmonella typhimurium* (2).

Mtb interactions with xenophagy

Direct contact between Mtb and the cytosol induces xenophagy, which promotes clearance of pathogens (52-54). The ESX-1 secretion system of Mtb facilitates phagosomal permeabilization, thus activating Ub-mediated, STING-dependent xenophagy and enhancing resistance to Mtb infection (53). The Ub ligases Parkin and Smurf1 are required for Ub-mediated autophagy of Mtb (54,55). The sensing of bacterial DNA by the cytosolic DNA sensor, cyclic GMP-AMP synthase (c-GAS), promotes the production of type I IFN (53), which is related to host susceptibility to chronic TB and impaired control of intracellular mycobacteria in human macrophages (56,57). In IFN-γ-activated macrophages, the host protein ubiquilin 1 is required for xenophagy activation and intracellular Mtb control, as it promotes accumulation of Ub, p62, and LC3 around Mtb bacilli (58). Mtb Ag-induced IFN-γ responses are correlated with the autophagy level in CD14-positive cells from healthy donors and patients with TB (59).

After ubiquitination of bacterial phagosomes, autophagy adaptors including p62 and NDP52 interact with Ub and deliver Mtb phagosomes to autophagosomes through LC3-interacting regions (53,54). In lysosomal and phagosomal damage models, TRIM16 controls ubiquitination and autophagy by recognizing endosomal/lysosomal damage and interacting with the cytosolic lectin, Galectin-3. Furthermore, TRIM16 interacts with the key autophagic core proteins ATG16L1, ULK1, and Beclin 1, and is required for the translocation of Mtb to autolysosomal compartments. Importantly, TRIM16 and Galectin-3 are required to control intracellular Mtb infection (60). Galectin-8 regulates xenophagy through interacting with mTOR complex in damaged endomembrane/lysosomal damage during Mtb infection (61).

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Modulation of autophagy by Mtb

Mtb-derived effectors regulate host xenophagy, LC3-associated phagocytosis (LAP), and macroautophagy. The ESX-1 system, which includes ESAT-6 and EspB, intereferes with autophagy to inhibit microbial clearance from host cells (62,63). The Mtb enhanced intracellular survival (*eis*) gene is involved with the regulation of autophagic cell death and redox balance, but is not directly involved in host innate immunity *in vivo* (64). In addition, CpsA, a LytR-CpsA-Psr domain-containing protein of Mtb, promotes evasion of host defense mechanisms involving NADPH oxidase and LAP (65). The Mtb components required for escaping from autophagy are unclear. Further studies should characterize Mtb effectors that modulate autophagy.

Host factors that regulate xenophagy

Polymorphisms of GTPase family M protein (IRGM) modulate autophagy and antimicrobial effector function (66-69). IRGM interacts with core autophagy regulators including ULK1 and Beclin 1, and activates Beclin 1 to promote autophagy and host antimicrobial defense (70). Although xenophagy controls intracellular Mtb replication *in vitro*, its role *in vivo* is unclear. Mice with an Atg5 deficiency in monocyte-derived cells and neutrophils exhibited increased susceptibility to Mtb infection because of enhanced pathological inflammation (53,71,72). However, the lack of Smurf1, an E3 Ub ligase essential for xenophagy of Mtb, led to an increased bacterial load and accelerated mortality due to chronic Mtb infection. Therefore, autophagy may play a role in chronic infection *in vivo* (55). Galectin-8 is critical in the host defense against Mtb, because Galectin-8-knockout mice are susceptible to Mtb infection (61). Mechanistically, Galectin-8 is required for the activation of autophagy via the mTOR-AMP activated protein kinase pathway (61).

The C-type lectin receptor CLEC4E, which associates with TLR4, suppressed Mtb growth in mouse and guinea pig models (73). Importantly, combination therapy using agonists of both CLEC4E and TLR4 together with antibiotic treatment activated host defensive pathways at least partially through macroautophagy/autophagy (73). Mitochondrial sirtuin 3 promotes host antimycobacterial defense in macrophages and *in vivo* by enhancing antibacterial autophagy and controlling mitochondrial homeostasis (74). A variety of host factors modulate autophagy to enhance or inhibit the host antimicrobial response to Mtb infection (75). It is important to identify new therapeutic agents that restrict the survival of Mtb (**Fig. 1**).

MODULATION OF APOPTOSIS BY Mtb

The survival of Mtb in host cells is promoted by its interactions with the apoptosis, necrosis, necroptosis, and autophagy pathways (76). Apoptosis is an important mechanism by which host cells suppress intracellular replication of Mtb (77,78). Virulent Mtb strains evade apoptosis (79,80). Several mycobacterial effectors inhibit apoptosis by various mechanisms, thus enhancing virulence (76,78). However, apoptosis during later stages of Mtb infection is implicated in dissemination (81).

Several Mtb proteins/Ags induce apoptosis. ESAT-6 induces apoptosis in macrophages by activating the intrinsic pathway and ROS signaling (82) and by targeting miRNA-155 and the SOCS1 pathway (83). In addition, ESAT-6, in cooperation with phthiocerol dimycocerosate, induced the rupture of phagosomal membranes and host cell apoptosis, thus contributing to virulence (84). The PGRS domain of Rv0297 (Rv0297PGRS), which is required for

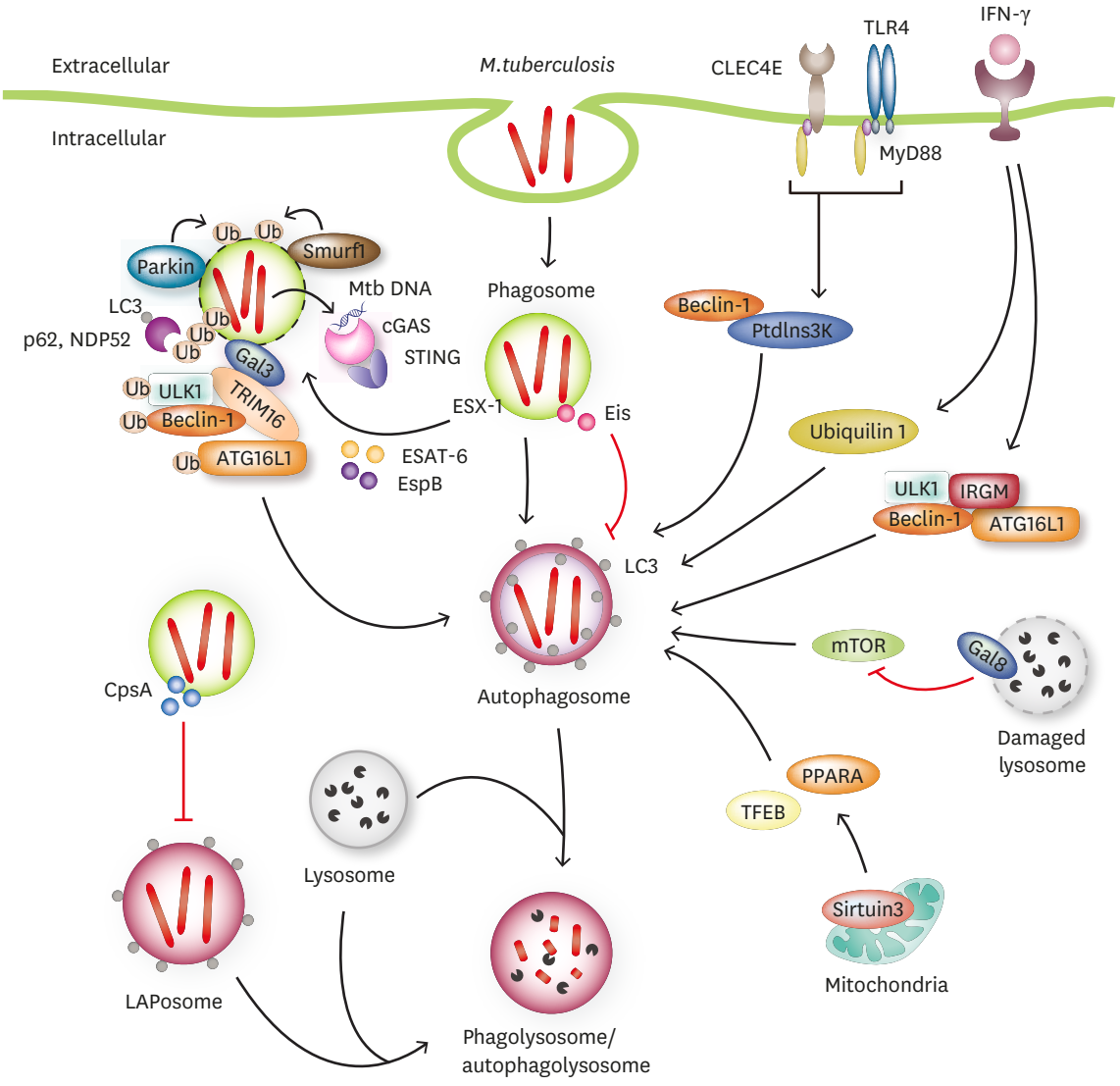

Figure 1. Crosstalk between Mtb and xenophagy.
ESX-1 secretion system damage Mtb-contained phagosome and resist from xenophagic pathway. Parkin1 and Smurf1 ubiuitinate damaged Mtb-contained phagosome to control Mtb survival. During Mtb infection, cGAS binds Mtb DNA and then activate type I interferons through STING pathway. In addition, damaged phagosome recruits Galectin-3, resulting in Galectin-3-TRIM16-ULK1-Beclin-1-ATG16L1 complex and initiation of autophagy. Galectin-8 suppresses mTOR activity in response to lysosomal damage. In IFN-γ-activated macrophages, ubiquilin 1 promotes ubiquitin, p62, and LC3 around Mtb and IFN-γ-induced IRGM interacts with autophagy machinery such as Beclin 1, ULK1, and ATG16L1. Mtb *eis* gene play role in regulating of autophagy. Furthermore, CpsA, protein of Mtb, evades from LAP and inhibits LAPosome formation during Mtb infection. In mouse and guinea pigs model, agonists for both CLEC4E and TLR4 activate autophagy, thereby reducing bacterial load. Sirtuin 3 enhances autophagy through TFEB and PPARA.

endoplasmic reticulum (ER) localization, is implicated in caspase-8-mediated apoptosis and ER stress-induced cell death (81). Wang *et al.* (85) reported that the Mtb Ag MPT83 (Rv2872), a secreted lipoprotein, activated apoptosis of macrophages via a mechanism involving the TLR2/p38 MAPK/cyclooxygenase (COX)-2 signaling pathway. The Mtb-derived TLR2 ligand, Rv1016c lipoprotein, induces macrophage apoptosis and inhibits MHC-II expression induced by IFN-γ, resulting in escape from immune surveillance and promoting chronic infection (86). The Mtb lipoprotein known as 38-kDa Ag induces MCP-1, which in turn induces MCP-1-induced protein and enhances the production of ROS and ER-stress-induced apoptosis (87).

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Mannose-capped lipoarabinomannan inhibits host-cell apoptosis by inducing antiapoptotic B-cell CLL/lymphoma 2 family member A1 (88). Interestingly, the Mtb chaperone protein Cpn60.2 suppresses apoptosis by interacting with mitochondrial mortalin, thereby enhancing intracellular Mtb survival (89). The Mtb PE/PPE family protein PE_PGRS18 promotes pathogenesis by attenuating macrophage apoptosis (90). LpqT from Mtb inhibits TLR2-dependent inflammatory signaling and apoptosis (91). Mycobacterial acyl carrier protein (Rv2244), which is involved in mycolic acid biosynthesis, inhibits macrophage apoptosis by suppressing the ROS/JNK signaling pathway, contributing to Mtb virulence (92). SP110b, an IFN-induced nuclear protein, exerts a protective effect by modulating NF-κB-mediated inflammatory signaling and ameliorating cell death and necrotic lung lesions (93). The protective effect from Ag-mediated regulation of apoptosis is context dependent (**Table 2**). Further studies should clarify the role of Ags in antimycobacterial immunity. There is a strong relationship between apoptosis and autophagy in various biological responses. However, the roles of mycobacterial Ag(s) in regulating apoptosis and autophagy during Mtb infection are unclear.

REGULATION OF HOST CELL NECROSIS BY Mtb

The cells that are frequently observed to participate in inflammatory pathology in actively necrotic granulomas are thought to be neutrophils (94). Indeed, intra-alveolar neutrophil

Table 2. Ag-mediated regulation of host cell apoptosis

Proteins/antigen	Experimental model	Mechanism of action	Effects	Ref.
Induction of host cell apoptosis				
ESAT-6	Mouse BMDM	TLR2 mediated ROS-MAPK dependent caspase-9 and caspase 3 activation	Apoptosis	(82)
	Human PBMCs, RAW264.7 cells	Targeting the miRNA-155-SOCS1 interaction, where miRNA-155 expression is dependent on TLR2/NF-κB activation	Enhance protective immune response	(83)
DIM	THP-1 cells, human MDMs	DIM contributes, along with ESX-1, to induce phagosomal membrane damage and rupture	Host cell apoptosis	(84)
Rv0297PGRS	RAW264.7 cells, HEK293T cells	TLR4 dependent ER-stress-mediated cell death, disrupted Ca^{2+} homeostasis and increased NO and ROS leading to caspase-8 activation	Host cell apoptosis	(81)
MPT83	Mouse BMDM, THP-1 cells, *in vivo* mouse model	TLR2 mediated p38 MAPK activation and COX-2 expression	Protection from mycobacterial infection	(85)
Rv1016c	THP-1 cells, MDMs	Acts as a TLR2 ligand and inhibition IFN-γ induced expression of CIITA IV through TLR2 and MAPK signaling	Increased survival of mycobacteria	(86)
38-kDa antigen	Mouse BMDM, RAW264.7 cells	TLR-mediated MAPK activation leading to MCPIP activation, ROS production and ER stress induction	Host cell apoptosis	(87)
Inhibition of host cell apoptosis				
ManLAM	Mouse BMDMs, J774A.1 cell line	Upregulation of Bcl2 family member A1, upregulation of STAT5α in a PPARγ-dependent manner	Attenuation of host cell apoptosis	(88)
Cpn60.2	THP-1, RAW264.7 cells	Interacts with mortalin, a member of HSP70 gene family	Anti-apoptotic action	(89)
PE-PGRS18	THP-1 cells	Modulation of cytokine production and attenuation of apoptosis	Enhance survival of *M. smegmatis* in macrophages	(90)
LpqT	Mouse BMDMs, RAW264.7 cells, mouse *in vivo* study	Reduction of TLR2 mediated NF-κB and MAPK activation	Increase mycobacterial survival in macrophage and mice	(91)
AcpM; Rv2244	Mouse BMDM, RAW264.7 cells	Inhibition of ROS/JNK signaling	Enhance intracellular survival of Mtb	(92)
SP110b	THP-1, U937, HEK293T, human MDMs, human subject study	Downregulation of NF-κB-induced TNF-α and upregulation of anti-apoptotic gene expression	Less severe necrotic lung lesion and reduced tuberculosis susceptibility	(93)

BMDM, bone marrow-derived macrophage; CIITA, class II transactivator; HSP70, 70 kilodalton heat shock protein; MCPIP, MCP-1-induced protein; MDM, monocyte-derived macrophages; NO, nitric oxide; PPAR, peroxisome proliferator-activated receptor; SOCS, suppressor of cytokine signaling.

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infiltration and an excessive inflammatory response play key roles in the progression to active TB, which is characterized by initial caseous and later liquefactive necrosis in the lung (95,96). Neutrophil necrosis induced by Mtb contributes to Mtb growth in host cells, thus sustaining the infection (97). Interestingly, this can be ameliorated by inhibiting ROS production (97). Mtb infection renders human macrophages necrotic, favoring Mtb replication (98). Also, Mtb rapidly proliferate as a clump inside dead cells rather than in live cells (99). Mtb induces neutrophil extracellular traps (NETs) that promote the recruitment and activation of effector cells (100).

Several Mtb proteins activate necrosis of host macrophages *in vivo*. ESAT-6 triggers intracellular Ca^{2+} influx, inducing neutrophil necrosis and production of NETs, ultimately contributing to necrotic pathology and TB transmission (94). Therefore, the virulence protein ESAT-6 is an important therapeutic target (101). In addition, PPE11 (Rv0453), which has been found in infected guinea pig lung, promoted mycobacterial survival under stressful conditions by enhancing inflammation, organ pathology, and host-cell death (102). Recombinant PE17 (Rv1646) inhibits the production of proinflammatory cytokines (IL-6, IL-12, and TNF-α) and enhances macrophage necrosis (**Table 3**) (103). The degree of tissue necrosis and lung inflammation may be strain-specific—TLR2-deficient mice infected with Mtb W-Beijing exhibited increased neutrophil infiltration (104). Characterization of the functions of Mtb proteins and lipids in inducing host cell necrosis will provide insight into its virulence mechanisms (105).

The local expression of CXC chemokines such as CXCL5, primarily by epithelial cells, enhances the recruitment of polymorphonuclear leukocytes, promoting pulmonary inflammation and a defective host defense (106). Also, IL-17A expression by non-hematopoietic cells is involved in neutrophil infiltration during mycobacterial infection (107). Excessive pulmonary inflammatory responses, mainly induced by neutrophils, promote pathologic inflammation by increasing CXCL5 and TNF-α levels and suppressing host defenses during Mtb infection (74). The detrimental effects of type I IFN and its receptor (IFNAR1) in pulmonary TB is due in part to CXCL5/CXCL1-induced infiltration of neutrophils (108). The molecular mechanisms by which Mtb and its effectors aggravate host cell necrosis during TB are unclear. Understanding the mechanisms of induction of host cell necrosis would facilitate the development of novel therapeutic approaches (109).

CONCLUSIONS

Several Mtb effectors participate in escape from phagolysosomal acidification. Xenophagy is an important lysosomal degradation pathway that activates host antimicrobial defenses. Mtb has evolved several mechanisms to exploit autophagy. Several Mtb effectors modulate apoptosis and so influence host antimicrobial defenses in a context-dependent manner. The roles of autophagy and apoptosis in the host-Mtb interaction are unclear. Additionally, Mtb

Table 3. Ag-mediated regulation of host cell necrosis

Proteins/Ag	Experimental model	Mechanism of action	Effects	Ref.
ESAT-6	Human neutrophils	Ca^{2+} mediated calpain activation	NETosis	(94)
PPE11	THP-1 cells, *in vivo* studies	Imbalance of pro-inflammatory and anti-inflammatory cytokines	Establishment of a persistent infection	(102)
PE17	Mouse peritoneal macrophages, *in vivo* studies	Nuclear damage, loss of cytoplasmic membrane integrity, reduction of pro-inflammatory cytokines	Enhance bacterial survival and bacterial burden in mice	(103)

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and its components induce inflammation, which is implicated in both protective immune responses and pathogenic necrosis. Neutrophils aggravate pathologic inflammation and necrosis, highlighting their involvement in the pathogenesis of TB.

Several questions remain to be addressed. What are the determinant(s) of the complexity of the interactions between Mtb and host cells? In addition, the mechanisms by which Mtb and its components inhibit autophagy and apoptosis are unclear. The *in vivo* functions of autophagy need to be clarified to enable the development of autophagy-targeted adjunctive therapies. Do host signaling factors orchestrate apoptosis and necrosis to promote antimicrobial defense? Also, the molecular mechanism that controls necrosis warrants further investigation. Our understanding of the immune, autophagic, and cell-death responses during TB is incomplete. Further studies will provide insight into the molecular dialogue between Mtb and host cells, and so facilitate the development of novel therapeutics for TB and other chronic intracellular infections.

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