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Immunome Research

Review article

PE/PPE Proteins as Central Regulators of Autophagy Suppression, Immune Modulation, and Intracellular Persistence in Mycobacterium tuberculosis

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ABSTRACT

Mycobacterium Tuberculosis (*Mtb*), the etiological agent of Tuberculosis (TB), has evolved sophisticated strategies to survive and persist within host macrophages despite robust innate and adaptive immune defenses. A growing body of evidence highlights the crucial role of the Proline-Glutamic Acid/Proline-Proline-Glutamic Acid (*PE/PPE*) family of proteins, unique to pathogenic mycobacteria and constituting nearly 10% of the *Mtb* genome, in orchestrating immune evasion. Among the host defense pathways targeted by *Mtb*, autophagy has emerged as a critical cell-intrinsic antimicrobial mechanism that restricts intracellular bacterial growth and facilitates antigen presentation. However, virulent *Mtb* strains actively suppress autophagy through diverse molecular strategies, many of which are mediated by *PE/PPE* proteins. In this Review, we synthesize genomic, structural, molecular, and immunological evidence demonstrating how *PE/PPE* proteins function as master regulators of autophagy, apoptosis, ubiquitin signaling, and inflammatory responses. We integrate mechanistic paradigms involving *PE_PGRS47*- and *PE_PGRS20*-mediated inhibition of canonical autophagy, *PPE51*-driven rewiring of *TLR2-MAPK* signaling, *PE6*-dependent *MTOR* activation, and the paradoxical ubiquitin-dependent xenophagy mediated by *Rv1468c*. We propose a unifying model in which *PE/PPE* proteins act as modular effectors that fine-tune autophagy and immune signaling to promote long-term persistence, facilitate drug tolerance, and enable transmission. Finally, we discuss the translational implications of targeting *PE/PPE*-autophagy interfaces for host-directed therapies, vaccine design, and biomarker development in drug-resistant TB.

Keywords: *PE/PPE* proteins; Autophagy inhibition; Xenophagy; Host-pathogen interactions; Innate immune evasion; Ubiquitin signaling; Drug-resistant tuberculosis.

INTRODUCTION

Tuberculosis remains a major global health burden, with approximately 10.6 million new cases and more than 1.3 million deaths annually despite decades of research and therapeutic advances [1-3]. The disease continues to disproportionately affect low- and middle-income countries, and the emergence of Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) Mycobacterium Tuberculosis (*Mtb*) strains has further complicated global control efforts. The success of *Mtb* as a pathogen lies not only in its intrinsic resistance to environmental stress and antibiotics but also in its remarkable ability to manipulate host immune defenses at multiple levels. These immune-modulatory strategies enable *Mtb* to persist within the

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Received: 16-Jan-2026, Manuscript No. IMR-26-40055; **Editor assigned:** 08-Jan-2026, PreQC No. IMR-26-40055 (PQ); **Reviewed:** 22-Jan-2026, QC No. IMR-26-40055; **Revised:** 29-Jan-2026, Manuscript No. IMR-26-40055 (R); **Published:** 05-Feb-2026, DOI: 10.35248/1745-7580.25.22.331

Citation: Shariq M, Ehtesham NZ, Ahuja Y, Alam A, Thakuri D, Fayaz H, Shrivastava G, Sheikh JA, Hasnain SE (2025). *PE/PPE* Proteins as Central Regulators of Autophagy Suppression, Immune Modulation, and Intracellular Persistence in Mycobacterium tuberculosis. Immunome Res. 22:331.

host for prolonged periods, often resulting in latent infection that can reactivate years or even decades later [3-7].

Following inhalation, *Mtb* is phagocytosed by alveolar macrophages, which constitute the first line of cellular defense in the lung. Rather than being eliminated, *Mtb* establishes a protected intracellular niche within these cells, where it actively subverts phagosomal maturation, resists lysosomal degradation, and adapts to hostile conditions such as hypoxia, nutrient limitation, and oxidative stress [4, 8, 9]. This intracellular persistence is a defining feature of *Mtb* pathogenesis and underlies both latent infection and chronic disease. Macrophages deploy a wide array of antimicrobial mechanisms to control intracellular pathogens, including the production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), secretion of inflammatory cytokines, activation of programmed cell death pathways, and induction of autophagy. Among these, autophagy has emerged as a central host defense mechanism against intracellular pathogens, including *Mtb* [10-12]. Autophagy not only mediates the lysosomal degradation of bacteria through xenophagy but also contributes to immune regulation by enhancing antigen processing and presentation, thereby bridging innate and adaptive immunity [11, 13-19]. Through these dual functions, autophagy plays a critical role in shaping the outcome of *Mtb* infection.

Pharmacological induction of autophagy using agents such as rapamycin, vitamin D, metformin, and gefitinib has been shown to restrict intracellular *Mtb* growth *in vitro* and *in vivo*, revealing the therapeutic potential of targeting this pathway (16, 20-22). These observations have fueled interest in Host-Directed Therapies (HDTs) that augment autophagic responses to improve bacterial clearance and treatment outcomes, particularly in drug-resistant TB. However, virulent *Mtb* strains actively counteract autophagy. Increasing evidence indicates that this suppression is not a passive consequence of infection but rather the result of targeted bacterial effector functions that interfere with autophagy initiation, progression, or completion. Among the most prominent mediators of this immune evasion are the Proline–Glutamic Acid/Proline–Proline–Glutamic Acid (*PE/PPE*) family of proteins, unique to pathogenic mycobacteria and massively expanded in the *Mtb* genome [5, 18, 19, 23-27]. While *PE/PPE* proteins were initially associated with antigenic variation and immune modulation, recent studies have uncovered their direct involvement in autophagy suppression, ubiquitin signaling, apoptosis regulation, and inflammatory pathway rewiring [3, 28-30].

This Review critically examines the role of *PE/PPE* proteins as central regulators of autophagy and immune evasion in *Mtb* infection. By integrating genomic organization, molecular mechanisms, lineage-specific variation, and translational implications, we provide a comprehensive framework for understanding how these proteins shape host-pathogen interactions and contribute to TB pathogenesis.

Genomic organization and structural diversity of *PE/PPE* proteins

The *Mtb* genome encodes approximately 168 *PE/PPE* proteins, including 99 *PE* and 69 *PPE* family members, representing nearly 10% of the coding capacity [19, 23, 31]. This extraordinary expansion contrasts sharply with the reductive evolution observed in many intracellular pathogens and suggests a strong selective advantage for maintaining and diversifying these proteins. Such a large investment of genomic resources implies that *PE/PPE* proteins perform functions critical for survival, virulence, and adaptation within the host. *PE* proteins are characterized by a conserved ~110-amino-acid N-terminal Proline-Glutamic Acid (PE) motif, whereas *PPE* proteins possess a longer ~180-amino-acid Proline-Proline-Glutamic Acid (*PPE*) motif [19, 32]. These conserved domains are thought to provide a structural scaffold that supports heterodimerization, stability, and secretion. In contrast, the C-terminal regions of *PE/PPE* proteins are highly variable in both length and amino acid composition, conferring functional diversity and enabling interactions with a wide range of host targets.

Based on C-terminal features, *PE/PPE* proteins are further classified into subfamilies such as *PE_PGRS* (polymorphic GC-rich repetitive sequence) and *PPE-MPTR* (major polymorphic tandem repeat), which exhibit extensive polymorphism and repetitive sequences [33-35]. This variability is believed to contribute to immune evasion by altering antigenic epitopes and modulating host immune recognition. Moreover, polymorphisms within these regions often show lineage-specific patterns, suggesting roles in host adaptation and epidemiological success. *PE/PPE* genes are non-randomly distributed across the *Mtb* genome and frequently occur as bicistronic operons, with a *PE* gene positioned immediately upstream of a *PPE* gene (Figure 1) [35, 36]. This genomic arrangement facilitates co-transcription and the formation of stable *PE-PPE* heterodimers. Many of these operons are associated with *ESX* type VII secretion system loci, particularly *ESX-1* and *ESX-5*, suggesting co-evolution of secretion machinery and effector proteins [37-39]. The *ESX* systems are essential for exporting *PE/PPE* proteins across the mycobacterial cell envelope and delivering them to host cell compartments.

Structural studies of *PE25/PPE41* and *PE8/PPE15* complexes revealed that conserved N-terminal domains mediate dimerization, whereas variable C-terminal domains project outward to interact with host targets [40-44]. These findings support a modular model in which the conserved regions ensure structural integrity, while the variable regions drive functional specificity. Comparative genomics across mycobacterial species highlights the pathogenic relevance of *PE/PPE* proteins. Pathogenic species such as *Mtb*, *M. bovis*, and *M. ulcerans harbor* large *PE/PPE* repertoires, whereas non-pathogenic mycobacteria encode far fewer such proteins (45, 46). Moreover, lineage-specific polymorphisms in certain *PE/PPE* genes correlate with geographic distribution, virulence, and immune evasion, suggesting roles in host adaptation and disease outcome [27, 36].

Autophagy as a cell-intrinsic defense against *Mtb*

Autophagy is a conserved cellular process that maintains homeostasis by degrading damaged organelles, protein aggregates, and invading pathogens [11, 17, 19]. Canonical autophagy is initiated by activation of the *ULK1* complex, followed by nucleation of the phagophore membrane through the class III PI3K complex and elongation mediated by *ATG* proteins and *LC3* lipidation [47, 48]. The completed autophagosome subsequently fuses with lysosomes to form autolysosomes, where cargo is degraded. During *Mtb* infection, autophagy is induced by multiple stimuli, including nutrient deprivation, inflammatory cytokines, and phagosomal damage [49-52]. The *ESX-1* secretion system plays a central role by permeabilizing the phagosomal membrane, allowing mycobacterial DNA to access the cytosol [50, 51]. Cytosolic DNA is sensed by cyclic GMP-AMP Synthase (*cGAS*), leading to STING activation, *TBK1* recruitment, and induction of autophagy and type I interferon responses [50, 51, 53]. This pathway represents a key link between pathogen sensing and autophagic defense.

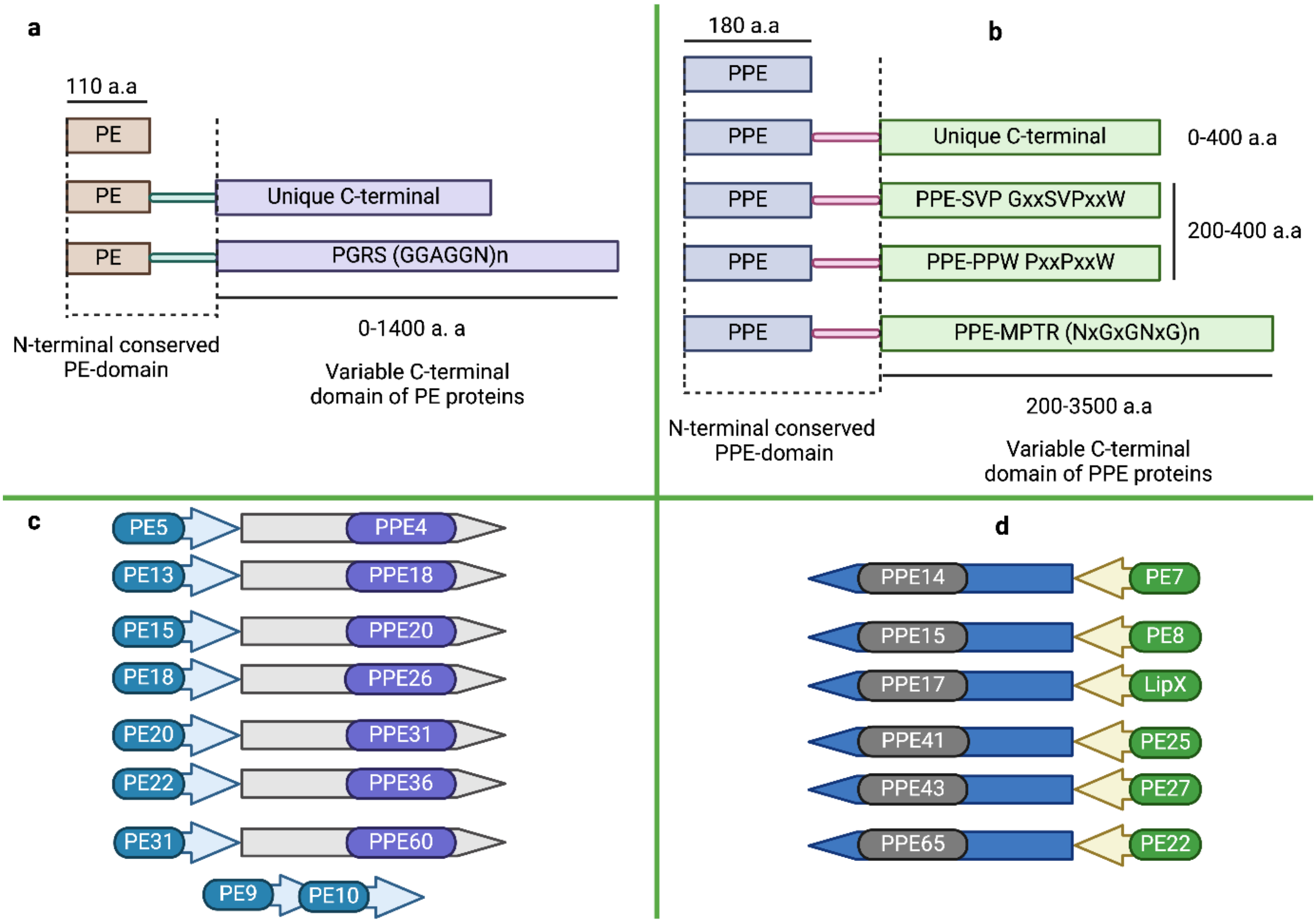

Figure 1: Genomic organization and structural diversity of *PE* and *PPE* proteins in *Mtb*. This figure illustrates the genomic arrangement and structural features of the *PE* and *PPE* protein families in *Mtb*. *(a, b)* Conserved N-terminal *PE* and *PPE* domains that mediate heterodimerization and secretion are shown alongside highly variable C-terminal regions that confer functional diversity. Representative gene structures highlight subfamily-specific motifs, including PE_PGRS and *PPE-MPTR* regions. (c, d) Operonic organization of *PE-PPE* gene pairs is depicted, emphasizing their frequent co-transcription and association with *ESX* type VII secretion systems. Collectively, the figure illustrates how structural modularity and genomic organization underpin the functional versatility and evolutionary expansion of *PE/PPE* proteins in pathogenic mycobacteria.

In parallel, exposed bacteria are ubiquitinated by host E3 ligases such as Parkin (*PRKN*), *SMURF1*, and *NEDD4*, enabling recognition by autophagy receptors including *p62*, *OPTN*, *NBR1*, and *TAX1BP1* (Figure 2) [54-56]. These receptors bridge ubiquitinated bacteria to *LC3*-decorated membranes, facilitating xenophagic degradation. Autophagy also enhances antigen processing and MHC class II presentation, thereby linking innate and adaptive immunity and promoting effective T cell responses [57-59]. Despite these defenses, virulent *Mtb* strains efficiently suppress autophagic flux, demonstrating the importance of bacterial countermeasures that directly target autophagy-related pathways.

PE/PPE proteins as direct inhibitors of canonical autophagy

PE_PGRS47 and *PE_PGRS20*: Inhibition of *ULK1*-dependent autophagy

A growing body of evidence demonstrates that a functionally defined subset of *PE/PPE* proteins acts as direct inhibitors of canonical autophagy (Figure 3) [60]. Among these, *PE_PGRS47* emerged as a key regulator of autophagy and antigen presentation. Deletion of *PE_PGRS47* resulted in enhanced *LC3* lipidation, increased autophagic flux, improved antigen presentation, and attenuated bacterial growth during chronic infection in mice [61].

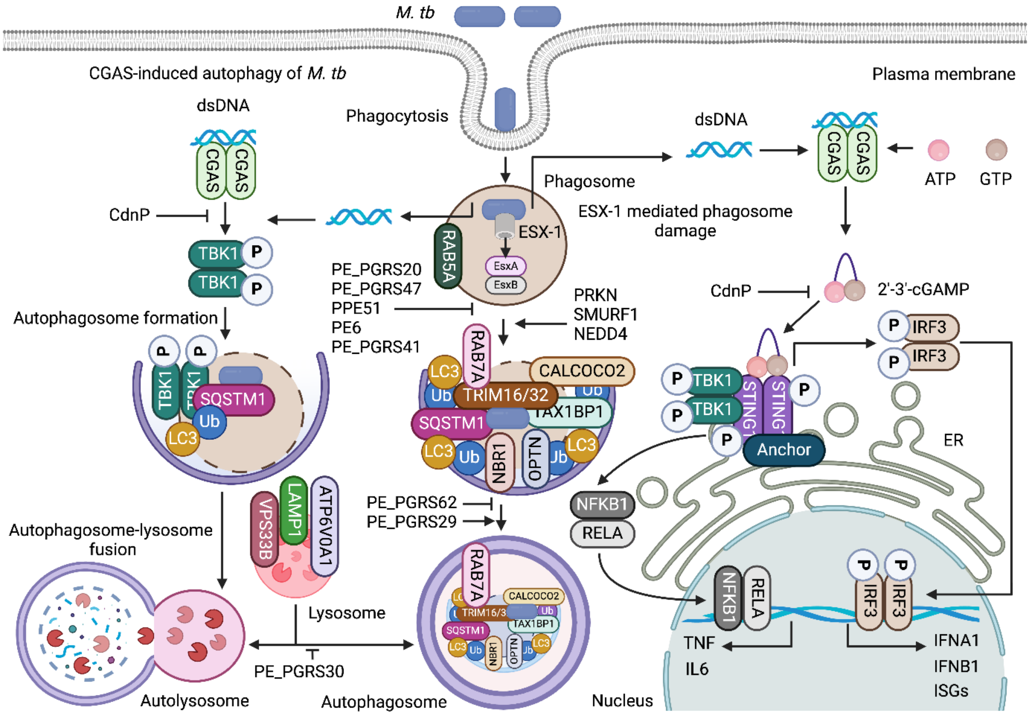

Figure 2: Host ubiquitin- and *cGAS-STING*-dependent xenophagy targeting *Mtb* and its inhibition by *PE/PPE* proteins. Following phagocytosis, *Mtb* damages the phagosomal membrane through the *ESX-1* secretion system, exposing bacterial components to the host cytosol. Host E3 ubiquitin ligases, including *PRKN*, *SMURF1*, and *NEDD4*, catalyze ubiquitination of bacteria, promoting recruitment of autophagy receptors and delivery to *LC3*-positive autophagosomes. In parallel, cytosolic bacterial DNA activates the *cGAS-STING* pathway, inducing type I interferon responses and autophagy. The figure highlights multiple points at which *PE/PPE* proteins interfere with ubiquitin signaling, autophagosome maturation, lysosomal fusion, and immune signaling, illustrating how *Mtb* subverts xenophagy to enable intracellular persistence.

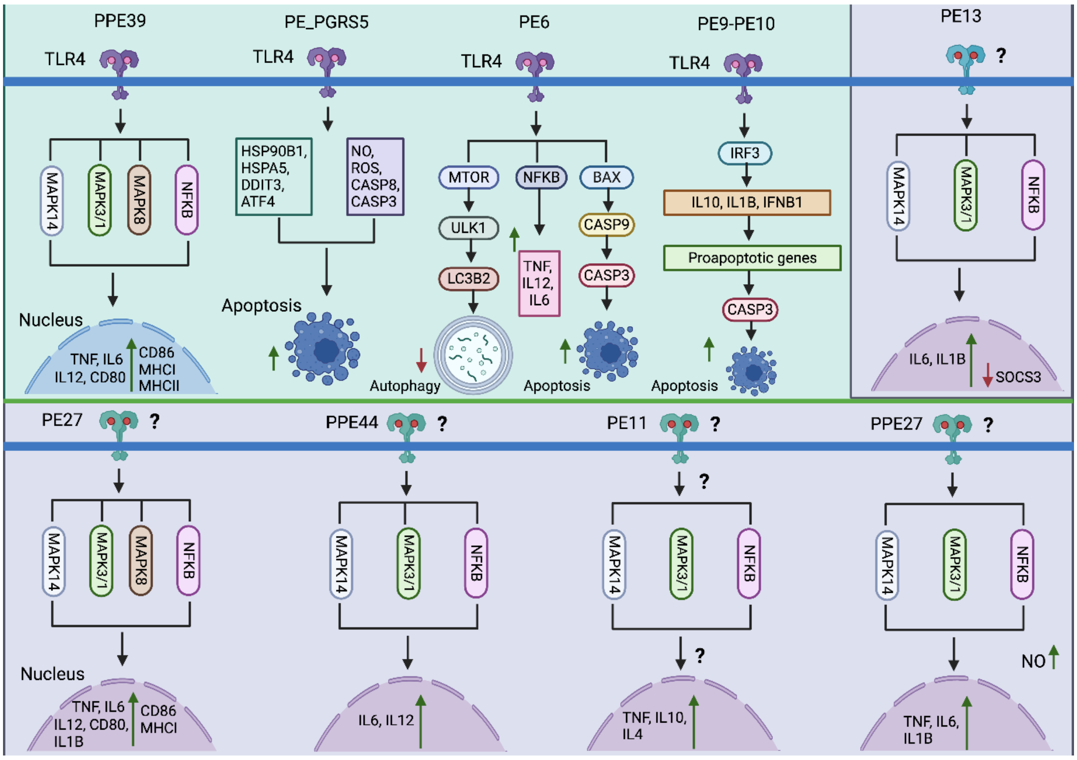

Figure 3: ***FPE/PPE*-mediated modulation of innate immune signaling and autophagy during *Mtb* infection**. *PE/PPE* proteins modulate macrophage innate immune responses by engaging Toll-like receptors and other surface or intracellular host targets. These interactions activate or reprogram NF-κB and *MAPK* signaling pathways, resulting in altered cytokine production, oxidative stress responses, and regulation of apoptosis and autophagy. The figure highlights how *PE/PPE*-driven signaling influences key antimicrobial pathways, including *ULK1*-dependent autophagy initiation and *MTOR*-mediated autophagy suppression, thereby promoting intracellular survival and persistence of *Mtb*.

These findings provided the first direct genetic evidence linking a *PE/PPE* protein to autophagy suppression *in vivo*. Mechanistically, *PE_PGRS47* and the related *PE_PGRS20* interact with the host GTPase *RAB1A*, a critical regulator of vesicular trafficking and autophagy initiation [61]. *RAB1A* is required for recruitment and activation of the *ULK1* complex at nascent autophagosome formation sites. By sequestering *RAB1A*, *PE_PGRS47* and *PE_PGRS20* impair *ULK1* activation and block canonical autophagy at an early stage. Importantly, this inhibition selectively targets canonical autophagy without broadly compromising host cell viability or other trafficking pathways [61]. Beyond autophagy suppression, *PE_PGRS47* inhibits MHC class II-restricted antigen presentation, thereby impairing $CD4^+$ T cell activation and linking autophagy inhibition to adaptive immune evasion [61, 62]. Together, these findings illustrate how distinct *PE/PPE*-encoding genes converge on autophagy initiation, antigen presentation, and vesicular trafficking to promote intracellular survival of Mtb (Table 1).

Table 1: *PE/PPE* proteins employ diverse mechanisms to suppress autophagy and modulate host immunity in *Mtb*. This table summarizes key *PE* and *PPE* proteins implicated in autophagy regulation and immune modulation, highlighting their host targets, affected signaling pathways, functional roles, and immunological consequences. The table integrates evidence from genetic, biochemical, and infection studies to illustrate how distinct *PE/PPE* proteins converge on common host defense pathways, such as autophagy, apoptosis, and inflammatory signaling, to promote bacterial survival and pathogenesis.

Protein	Host target	Pathway affected	Functional role	Immune consequence	References
PE_PGRS47	*RAB1A*	Canonical autophagy	Inhibits autophagosome maturation	Reduces antigen presentation and intracellular killing	Saini, N.K., et al., Suppression of autophagy and antigen presentation by Mycobacterium tuberculosis *PE_PGRS47*. Nat Microbiol, 2016. 1(9): p. 16133.
PE_PGRS41	CASP3/9, *MAP1LC3B2*	Apoptosis, autophagy	Suppresses apoptosis and autophagy	Enhances intracellular persistence	Deng, W., et al., Mycobacterium tuberculosis *PE_PGRS41* Enhances the Intracellular Survival of M. smegmatis within Macrophages Via Blocking Innate Immunity and Inhibition of Host Defense. Sci Rep, 2017. 7: p. 46716.
PPE51	TLR2 → MAPK1/3	Autophagy signaling	Blocks phagolysosomal fusion	Modulates ROS and cytokine release	Strong, E.J., et al., Mycobacterium tuberculosis *PPE51* Inhibits Autophagy by Suppressing Toll-Like Receptor 2-Dependent Signaling. mBio, 2022. 13(3): p. e0297421.
PE6	*TLR4*, *MTOR*	Immune signaling, apoptosis	Alters cytokine signaling, triggers apoptosis	Increases bacterial replication	Sharma, N., et al., Mycobacterium tuberculosis Protein PE6 (*Rv0335c*), a Novel *TLR4* Agonist, Evokes an Inflammatory Response and Modulates the Cell Death Pathways in Macrophages to Enhance Intracellular Survival. Front Immunol, 2021. 12: p. 696491.
Rv1468c (PE_PGRS29)	Ubiquitin associated (UBA) domain	Xenophagy	Mediates host ubiquitin binding	Modulates inflammation via xenophagy	Chai, Q., et al., A Mycobacterium tuberculosis surface protein recruits ubiquitin to trigger host xenophagy. Nat Commun, 2019. 10(1): p. 1973.
PE_PGRS20	MTOR, S6K	Autophagy signaling	Inhibits autophagosome formation *via MTOR* pathway	Enhances intracellular survival; suppresses pro-inflammatory cytokines (TNF-α, IL-1β)	Strong, E.J., et al., Identification of Autophagy-Inhibiting Factors of Mycobacterium tuberculosis by High-Throughput Loss-of-Function Screening. Infect Immun, 2020. 88(12).
PE_PGRS21	*MTOR*	Autophagy signaling	Suppresses *LC3B-II* conversion and autophagosome formation	Reduces antigen processing and favors bacterial persistence	Strong, E.J., et al., Identification of Autophagy-Inhibiting Factors of Mycobacterium tuberculosis by High-Throughput Loss-of-Function Screening. Infect Immun, 2020. 88(12).

PE_ PGRS30	*MTOR*	Autophagy inhibition	Activates *MTOR*, reduces *LC3* puncta in macrophages	Impedes xenophagic clearance	Strong, E.J., et al., Identification of Autophagy-Inhibiting Factors of Mycobacterium tuberculosis by High-Throughput Loss-of-Function Screening. Infect Immun, 2020. 88(12).
PPE44	Unknown	Autophagy inhibition	Reduces autophagy markers in macrophages	Promotes intracellular persistence	Strong, E.J., et al., Identification of Autophagy-Inhibiting Factors of Mycobacterium tuberculosis by High-Throughput Loss-of-Function Screening. Infect Immun, 2020. 88(12).

PPE51: Rewiring *TLR2-MAPK* signaling to suppress autophagy

PPE51 exemplifies an alternative strategy for autophagy suppression through manipulation of innate immune signaling. *PPE51* interacts with Toll-like Receptor 2 (TLR2), triggering downstream *MAPK* signaling that paradoxically suppresses autophagic flux rather than activating antimicrobial responses (Figure 4) [63]. This atypical signaling outcome reflects the ability of the corresponding *PE/PPE* proteins to reprogram host receptor pathways for immune evasion. *PPE51*-mediated signaling disrupts ERK1/2-dependent autophagy induction and impairs phagolysosomal fusion, thereby enhancing intracellular bacterial survival [63]. In addition, *PPE51* influences cytokine production and ROS generation, further shaping the intracellular environment to favor persistence. This mechanism unveils how *PE/PPE* proteins exploit pattern recognition receptors to subvert host defenses.

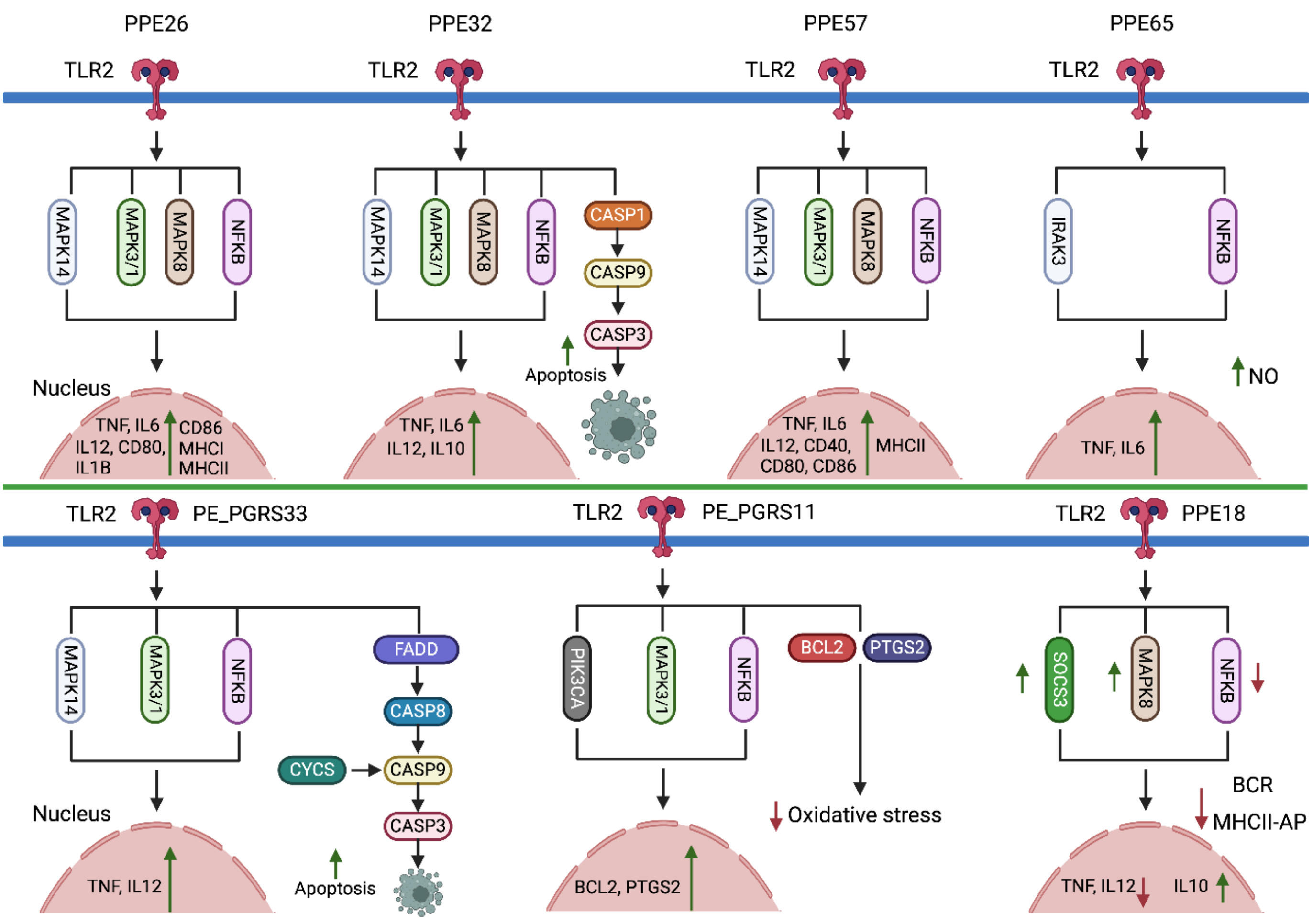

Figure 4: TLR2-dependent immune modulation by *PE/PPE* proteins in *Mtb* infection. Multiple *PE/PPE* proteins interact with TLR2 to initiate downstream signaling cascades that regulate inflammatory cytokine production, antigen presentation, reactive oxygen and nitrogen species generation, and apoptotic responses. Activation of NF-κB, *MAPK*, and regulatory pathways such as SOCS signaling shapes macrophage antimicrobial functions and adaptive immune engagement. This figure illustrates how *PE/PPE*-TLR2 interactions recalibrate innate immune signaling to favor bacterial survival while maintaining a controlled inflammatory environment.

PE6: *mTOR* activation and integrated control of autophagy and apoptosis

PE6 (*Rv0335c*) is a multifunctional *PE* protein that integrates autophagy inhibition with modulation of inflammatory signaling and cell death pathways. *PE6* interacts with *TLR4*, activating the *MYD88-NF-κB* axis and inducing pro-inflammatory cytokines [19]. Concurrently, *PE6* activates *MTOR* signaling, suppressing *ULK1* activation and autophagy initiation, thereby antagonizing a key antimicrobial pathway. *PE6* localizes to multiple cellular compartments, including mitochondria and the nucleus, and its C-terminal domain is essential for inducing mitochondrial dysfunction, ER stress, and caspase-dependent apoptosis [64]. This dual regulation enables *PE6* to fine-tune host cell fate, balancing inflammation, autophagy suppression, and apoptosis to optimize bacterial persistence and dissemination.

Ubiquitin-dependent xenophagy and the paradoxical role of *Rv1468c*

Rv1468c (*PE_PGRS29*) represents a unique exception within the *PE/PPE* gene family. This surface-exposed protein contains a eukaryotic-like Ubiquitin-Associated (UBA) domain that directly binds host ubiquitin chains, promoting recruitment of the autophagy receptor *p62* and delivery of bacteria to autophagosomes [10, 65]. Surprisingly, loss of *Rv1468c* leads to increased bacterial burden and heightened inflammation, suggesting that controlled xenophagy may benefit *Mtb* by limiting excessive immune activation [65]. This finding supports a model in which *Mtb* fine-tunes autophagy rather than completely abolishing it, balancing bacterial clearance with host tolerance.

Integration of autophagy, cell death, and inflammatory pathways

PE/PPE proteins exert pleiotropic effects on host cell death pathways, including apoptosis, necrosis, and pyroptosis. *PE_PGRS41* suppresses caspase-3 and caspase-9 activation while inhibiting autophagy, thereby enhancing bacterial persistence (Figure 5) [66]. *PPE60* and *PPE32* promote inflammasome activation and IL-1β maturation, contributing to inflammatory pathology [67, 68]. These overlapping functions emphasize that *PE/PPE* proteins target interconnected host defense pathways, autophagy, apoptosis, and inflammatory signaling, through diverse yet convergent mechanisms (Table 1).

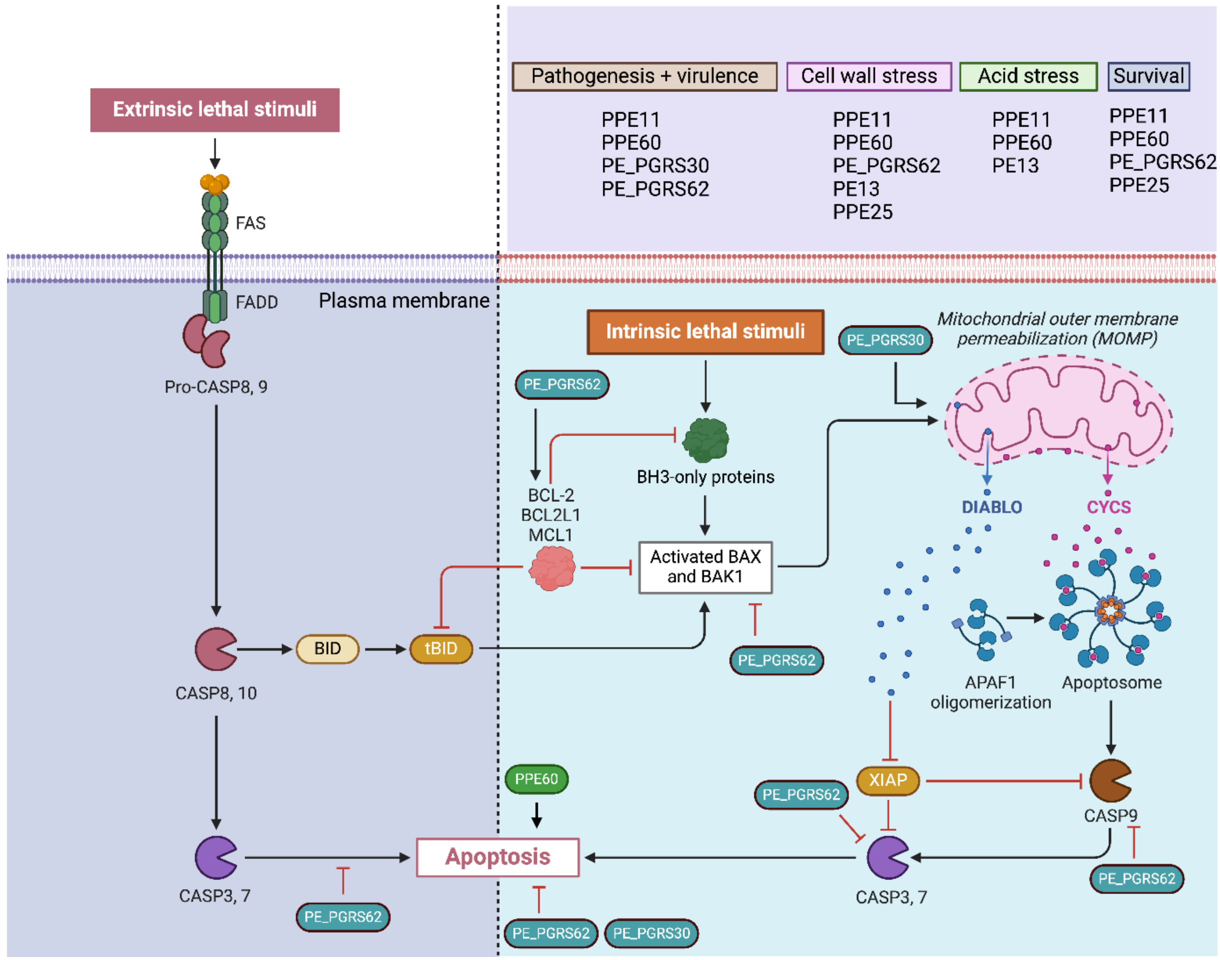

Figure 5: Regulation of extrinsic and intrinsic apoptotic pathways by *PE/PPE* proteins. *PE/PPE* proteins modulate both death receptor-mediated (extrinsic) and mitochondrial (intrinsic) apoptotic pathways in infected macrophages. These proteins influence activation of initiator and executioner caspases, alter the balance between pro-apoptotic and anti-apoptotic BCL2 family members, and regulate mitochondrial outer membrane permeabilization and cytochrome c release. Through these mechanisms, *PE/PPE* proteins fine-tune host cell death decisions, balancing apoptosis suppression or induction to optimize *Mtb* survival, persistence, and pathogenesis.

Lineage-specific variation, persistence, and drug resistance

Lineage-specific variation in *PE/PPE* genes is increasingly recognized as a determinant of virulence and immune evasion. The Beijing lineage, strongly associated with MDR and XDR TB, exhibits enhanced capacity to suppress autophagy and phagolysosomal maturation [4, 30, 51]. Differential expression and polymorphism of *PE/PPE* proteins may contribute to these phenotypes. Importantly, *PE/PPE* proteins are among the most sequence-diverse gene families in the *Mtb* genome, and many members, particularly *PE_PGRS* and *PPE-MPTR* proteins, display hypervariable regions that can alter protein folding, secretion efficiency, and host-target engagement. Such diversity is likely to shape how individual lineages tune macrophage responses, influencing both intracellular fitness and transmissibility. In this context, the Beijing lineage may represent an evolutionary solution in which augmented autophagy suppression and altered inflammatory calibration enable sustained bacterial replication while limiting bactericidal clearance.

Beyond sequence variation, lineage-associated differences in *PE/PPE* transcriptional programs may also contribute to pathogenic outcomes. Infection-stage-specific regulation, early establishment versus chronic persistence, could allow *Mtb* to deploy distinct *PE/PPE* modules depending on immune pressure and tissue microenvironment. For example, in early infection, enhanced inhibition of canonical autophagy and antigen presentation may promote successful establishment in naive macrophages, whereas during chronic infection, modulation of inflammatory thresholds may prevent excessive tissue damage that could compromise bacterial persistence. Moreover, as *PE/PPE* proteins frequently interface with secretion systems and cell envelope components, lineage-dependent alterations may indirectly affect phagosomal trafficking, membrane damage, or bacterial surface ubiquitination, each of which influences xenophagic targeting and downstream immune activation [26, 36, 69-74].

Autophagy suppression may also facilitate phenotypic drug tolerance by stabilizing intracellular niches that favor bacterial quiescence and reduced antibiotic susceptibility [75, 76]. In macrophages, autophagy intersects with immunometabolic remodeling, lysosomal biogenesis, and redox homeostasis, processes that collectively influence bacterial stress exposure. If *PE/PPE* proteins dampen autophagic flux and lysosomal maturation, intracellular bacteria may experience reduced exposure to acidic, proteolytic, and oxidative conditions, thereby lowering the efficacy of antibiotics whose activity is enhanced by host-mediated stress. In parallel, suppression of autophagy may promote persistence by limiting cytosolic surveillance pathways (for example, ubiquitin-mediated xenophagy), which otherwise constrain bacterial subpopulations that enter slow-growing or drug-tolerant states. This is particularly relevant for MDR/XDR disease, where prolonged chemotherapy provides a selective landscape in which phenotypic tolerance can bridge the gap to genetic resistance. Host-directed therapies that restore autophagy, such as metformin and vitamin D, improve treatment outcomes and may counteract *PE/PPE*-mediated immune evasion (77-80). These approaches are conceptually attractive because they target host pathways that are less prone to bacterial mutation-driven escape, and they may synergize with standard regimens by increasing autophagic delivery of bacteria to lysosomes and enhancing antigen presentation.

Translational implications: host-directed therapy, vaccines, and biomarkers

At a time when drug resistance threatens global TB control, targeting *PE/PPE*-autophagy interfaces offers a particularly compelling avenue for host-directed intervention [24, 81, 82]. A critical advantage of host-directed autophagy induction is the potential to collapse intracellular persistence niches by simultaneously enhancing xenophagic clearance, promoting phagolysosomal maturation, and reinforcing antimicrobial effector programs (including ROS/RNS regulation and antimicrobial peptide pathways). Additionally, as several *PE/PPE* proteins operate upstream at pathway “gatekeeper” nodes, such as *ULK1* initiation (via *RAB1A*), receptor-proximal signaling (*TLR2-MAPK*), or nutrient-sensing regulators (*MTOR*), therapeutic strategies could be designed to either (i) Directly counteract these nodes pharmacologically or (ii) Strengthen parallel pathways that bypass *PE/PPE* blockade to restore autophagic flux. For instance, combining autophagy-inducing agents with lysosome-boosting approaches may be particularly effective in settings where *Mtb* suppresses autophagosome maturation rather than initiation.

PE/PPE proteins also represent potential vaccine antigens and diagnostic biomarkers, although their immunomodulatory properties necessitate careful epitope selection [83-85]. While *PE/PPE* proteins can be highly immunogenic, the same domains that drive immune recognition may also contribute to immune suppression, antigen presentation blockade, or inflammatory dysregulation. Thus, vaccine strategies may benefit from focusing on conserved, protective epitopes that elicit robust T cell responses while avoiding regions implicated in autophagy inhibition or immune diversion. Similarly, diagnostic or prognostic applications may leverage lineage-specific *PE/PPE* signatures as markers of virulence potential, immune modulation profiles, or risk of drug-resistant disease. In this framework, integrating *PE/PPE* sequence variation with host-response biomarkers, such as autophagy-related transcriptional signatures or inflammatory cytokine profiles, could improve stratification of TB patients and guide adjunct host-directed interventions [86-88].

CONCLUSION

PE/PPE proteins have emerged as central orchestrators of autophagy suppression, immune modulation, and intracellular persistence in *Mtb*. By targeting critical nodes in autophagy initiation, ubiquitin signaling, innate immune receptor pathways, and cell death machinery, these proteins enable *Mtb* to evade host defenses, tolerate antibiotic stress, and establish chronic infection. Importantly, the collective evidence suggests that *PE/PPE* proteins should be viewed not as isolated virulence factors but as components of a distributed regulatory network that tunes host pathways in a context-dependent manner, across infection stages, tissue environments, and bacterial lineages.

Future research should prioritize systems-level analyses of *PE/PPE* networks, validation in human macrophages and clinical isolates, and translational exploration of *PE/PPE*-targeted host-directed therapies. Mechanistic dissection of *PE/PPE*-host interactions at high resolution (protein-protein interfaces, post-translational modifications, and compartment-specific signaling effects) will be essential to identify druggable nodes. Parallel efforts should integrate lineage-resolved genomics with functional immunology to determine how *PE/PPE* polymorphisms shape autophagy suppression, inflammation, and treatment outcomes in real-world patient populations. Understanding how *PE/PPE* proteins regulate autophagy will be essential for developing next-generation interventions against drug-resistant TB.

STATEMENTS AND DECLARATIONS

ACKNOWLEDGMENTS

JAS was funded by a Start-up Research Grant from the University Grant Commission and the Department of Science and Technology Science and Engineering Research Board. MS acknowledges SEED and MURTI fellowships provided by GITAM university as part of internal funding to support research and developments. SEH is a Robert Koch Fellow at the Robert Koch Institute, Germany, and National Science Chair, Department of Science and Technology, New Delhi, India.

COMPETING INTERESTS

The authors have no relevant financial or nonfinancial interests to disclose.

DATA AVAILABILITY

All data have been included in the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

All the authors have read the final version of the manuscript and agree with its publication.

AUTHOR CONTRIBUTIONS

MS, NZE, YA, and SEH conceptualized the study and contributed to the drafting and finalization of the manuscript. MS, JAS, and YA conceptualized and designed the figures. YA, MS, DT, HF, JAS, GS, HF, and AA contributed to various stages of the initial drafting, preparation, and finalization of the figures.

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