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THE PE-PPE PROTEINS OF *MYCOBACTERIUM TUBERCULOSIS*: MINI-REVIEW ARTICLE

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Abstract
Mycobacterium tuberculosis also known as Koch's bacillus is a species of pathogenic bacteria in the family *Mycobacteriaceae* and the causative agent of tuberculosis. It is one of the oldest known human diseases. The tubercle bacillus does not always manifest itself in the classical rod shape.They appear as granular rod, round, Y-, V-, ovoid and club shapes. These variable shapes can beseen as a maker of virulence of biological defense against specific immune responses or of celldivision. The success of *Mycobacterium tuberculosis* has recently been attributed in part to the PE-PPE family. These are the unique collections of 168 proteins that are fundamentally involved inpathogenesis of *Mycobacterium tuberculosis*. The PE-PPE proteins has been forefront of intenseresearch efforts since discovery. This review consolidates about the PE-PPE family proteins of *Mycobacterium tuberculosis* and with respect to the latest developments in elucidating their evolution, structure, sub-cellular localization, function and immunogenicity. The PE-PPE familymembers have captivated researchers since their discovery and whilst our knowledge of this familyhas evolved and advanced tremendously thus the many important questions remain unanswered regarding their biological significance.

Keywords: Immunogenicity,Biologicalsignificance,Familyproteins,Granular,Pathogenic.

INTRODUCTION

Pathogenic the host's macrophages area place where Mycobacterium species can persist. *Mycobacterium tuberculosis*is one of these which is very effective pathogen that interferes with two host mechanisms. In addition to preventing the creation of a localised, productive immune response that can stimulate the host cell, it also halts the phagosome's usual transition into an acidic, hydrolytically active compartment. To standard, easy staining techniques, these bacteria are comparatively resistant. Carbol Fuschin stained cells are categorised as acid-fastbecause they cannot be decolored with acid alcohol. This trait reflects the peculiar structure of the cell wall,which contains a significant amount of lipids. These lipids are in charge of mycobacteria's ability to with stand environmental challenges like drying. The bacilli attach to one of numerous phagocyticreceptors and then enter macrophages. While within the hostcell, Mycobacteria are kept in aphagocytic vacuole until the host cell undergoes necrosis or apoptosis, which kills the cell. Thesevacuoles do not fuse with lysosomes, but they do maintain their fusion competence, pick up certain"lysosomal" proteins from the host cell's biosynthesis pathway, and do fuse with other endosomalvesicles. As phagosomes are taken up by the macrophage, Mycobacterium uses specific molecularpathways to stop them from maturing.

In order to defend themselves from intracellular parasites like Mycobacterium, host cells have also created defence mechanisms. NRAMP1(natural-resistance-associated macrophage 1),for instance, confers inherent resistance form macrophages against the growth of specific intracellular bacteria and may have an impact on vacuolarp H. The chemicals that Mycobacterium employs to keep the host a habitable habitat are expected to be revealed by new genetic screening.
When a positive immunological response is induced, Mycobacteria try to prevent it from happening as much as possible, and once it does, they block the effector cascade. The mechanism by which mycobacteria accomplish this is believed to be sequestering vacuoles away from the usual antigen-processing and -presentation machinery and by modifying the environment in close proximity to the infected macrophage.
Improved medication delivery should be made possible by knowing where infected vacuoles are located in the endosomal pathway. This calls for a deeper comprehension of the endosomal-lysosomal environment.

The pathogen Mycobacterium tuberculosis is very effective in parasitizingthe macrophages of its host. Its success is strongly related to its capacity to control the phagosome itresides in and inhibit the phagosome's usual maturation into an acidic, hydrolytic compartment.Because the macrophage is crucial to eradicating the infection, the pathogen and its host cell interact in an ongoing struggle for dominance (Russell,D.G.(2001).
The members of the PE-PPEfamily were designated and based on the presence of either a conserved proline-glutamic acid (PE) orproline-proline-glutamic acid (PPE) motif, within the highly conserved N-terminal domain of the protein, which are~100or~180 long residues respectively. The N-terminal domains are conserved within each family, they are not homologous.In contrast, the C-terminal domains of these proteins are highly variable both proteins are very efficient in terms of their sequence and length**.** (Cole etal,1998)
Tuberculosis is still the world's greatest cause of death after the Koch discovered about the bacillusand the disease was justifiedafter one hundredyears of Koch’s discovery. Despite enormous medicinal and technological advancements, the causative agent, *M.tuberculosis*, is still unconquered and is regarded as one of humanity's most successful predators. It is one of the most difficult organisms to work with, the virus had an exceptionally durable cell wall, very slow growth,a high contagiousness, and a variety of sophisticated defense mechanisms. Globally, it affects two billion people and results in three million annual fatalities, eight million new cases of pulmonary tuberculosis, and eight million new infections (Mukhopadhyay, S.,&Balaji,K.N.2011).
The 'bacille de Calmette et Guérin' (BCG), the only vaccine now on the market, has been proven tohave extremely varying degrees of efficiency, notably against pulmonary disease, despite the fact that tuberculosis is still one of the top causes of mortality in the world (Fine,P.E.1995).
During the research, the *Mycobacterium tuberculosis* H37Rv strain unveiled several previously unknown features of the biology of this significant disease (Cole et al 1998). The discovery thattwo sizable unrelated gene families that encode the PE and PPE proteins accounted for 8% of the possible coding capacity that was the one of the biggest surprises (Cole,S.T.1999).

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The names PE and PPE come from the Pro-Glu (PE) and Pro-Pro-Glu (PPE) motifs that are oftenlocated close to the N-terminus of these glycine- and alanine-rich proteins in conserved domains of around 110 and180 amino acid residues ,respectively.(Cole,S.&Brosch,1998).

Pro-Glu (PE) and Pro-Pro-Glu (PPE) motifs are found close to the N-terminus of the gene productsof the PE family, which contains around 100 genes, and the PPE family, which has about 70 genes.24, 38 although having conserved PE and PPE motifs, the PE/PPE proteins have the potential to bethe main source of antigenic diversity due to inter-strain polymorphism. 17, 20, 48, 92, 93, 94 ThePPE MPTR polypeptides are abundant in repetitions with the distinctive Asn-X-Gly-X-Gly-Asn-X-Gly motif, whereas many members of the PE family exhibit numerous copies of polymorphic GC-rich repetitive sequences (PGRS) at the C-terminal end, which are referred to as PE PGRS family of proteins 15.(Mukhopadhyay,S.,&Balaji,K.N. (2011).

On the basis of their domain structures, the PE family can be classified into three classes. 29proteins include the PE domain alone, while eightmore have the PE domain followed by C-terminal regions with distinctive sequences. The PE-PGRS subfamily is the biggest class of the PEfamily, with 67 membersin *M. tuberculosis* H37Rv. These proteins have the PE domain followedby a C-terminal extension with several tandem repetitions of Gly-Gly-Ala or Gly-Gly-Asn, whichare encoded by the PGRS motif (polymorphic GC-rich repetitive sequences). Up to 1900 aminoacids and up to50% of which may be glycine, are estimated tobe presentin PE-PGRS proteins.The PGRS genes are extremely GC rich. Approximately 80%and a significant contributor to polymorphism in the *M. tuberculosis* complex exhibits remarkable genetic uniformity and a dearthof single-nucleotide polymorphisms. According to the functional characteristics. (Sreevatsan etal.1997) PE-PPE proteins are frequently assumed to either be secreted or to be displayed on the cell surface**.** (Sampson,S.L.2011)

There are two sub-families of the PPE family: PPE and PPE-Major Polymorphic Tandem Repeat (PPE-MPTR). An Asn-X-Gly-X-Gly-Asn-X-Gly motifis frequently repeated inPPE-MPTR subfamily members. Members of the PPE-MPTR family are likewise disproportionately big, particularly for secreted proteins with lengths of more than 3000 amino acids. (Hermans et al1919).

In accordance with phylogenetic analysis, the PPE family can be divided into 5 sub-lineages.

Geyvan Pittius and colleagues (2006) PPE 68 belongs to sub-lineage I. The 10 PPE-PPW members thatmakeupsub-lineageIIarerecognizedbyaconservedPxxPxxWpatternintheirC-terminaldomains. The members of sub-lineage III include PPE36, PPE41, PPE57, PPE58, PPE59, andPPE69. The largest sub-group, sub-lineage IV, has 26 PPE-SVP members, which are identified bythe presence of a conserved GxxSVPxxW motif in their C-terminal domains. The PPE-MPTRsubfamilyisrepresented bysub-lineageV.(D'Souza,C.,Kishore,U.,&Tsolaki,A.G.(2023).

CONCLUSION

It is understood that the multiples factors are involved in the successful establishment of infectionthrough *Mycobacterium tuberculosis* inside the hosts. Therefore, a detailed knowledge of the

set ofgenes are expressed by the intracellular pathogens during the infections through the Mycobacterium tuberculosis. Although the functions are important to understand the strategies adapted by thebacteria to endure the pressure from the host environment in order to maintain the stable infectious state. The bacterium tuberculosis is responsible for tuberculosis (TB) often revolves around its impact on public health, the challenges in diagnosis and treatment and ongoing efforts in research and public health interventions to control its spread, It is crucial to emphasize the importance of early detection, proper treatment adherence and vaccination programs in combating TB. Additionally addressing social determinants of health and improving access to healthcare are essential in reducing the burden of tuberculosis globally.

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