P0155
Poster Session I
Basic science: pathogenesis

MYCOBACTERIUM TUBERCULOSIS PE_PGRS33 PROMOTES ENTRY INTO MACROPHAGES THROUGH TLR2.

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Objectives: PE_PGRS represent a large homologous protein family characterized by an N-terminal PE domain followed by a large Gly-Ala repeat-rich C-terminal domain, whose presence is restricted to pathogenic mycobacteria. Despite their abundance in the *Mycobacterium tuberculosis* (*Mtb*) genome their role and function in the biology and pathogenesis still remains elusive. In this study we aim at investigating the functional role of PE_PGRS33 in the pathogenesis of Mtb infection.

Methods: We generated and characterized an *Mtb* H37Rv mutant (*Mtb*?33) in which the structural gene of PE_PGRS33, a prototypical member of the protein family, was inactivated. The Mtb *Mtb*?33 was complemented with the full length gene and with a panel of functional deletion mutants and these strains have been used to infect macrophages in in vitro assays.

Results: We showed that this mutant entered macrophages, with an efficiency ten times lower than parental or complemented strains, while its efficiency in infecting pneumocytes remained unaffected. Interestingly, the lack of PE_PGRS33 did not affect the intracellular growth of these mutants that entered macrophages. We also demonstrated that the PGRS domain is required to mediate cell entry into macrophages, but also mutations in the PE domain impact the ability of PE_PGRS33 to mediate host cell invasion. PE_PGRS33-mediated entry into macrophages was abolished in TLR2-deficient mice, as well as following treatment with wortmannin or an antibody against the complement receptor 3 (CR3).

Conclusions: The results indicate that interaction with TLR2 promotes *Mtb* phagocytosis, further establishing the critical role of PE_PGRS33 in the pathogenesis of TB.