University of Basel

DBM Basel
Department of Biomedicine

DECIPHERING THE ROLE OF MYOBACTERIUM TUBERCULOSIS PE/PPE PROTEINS IN HOST-PATHOGEN INTERACTIONS

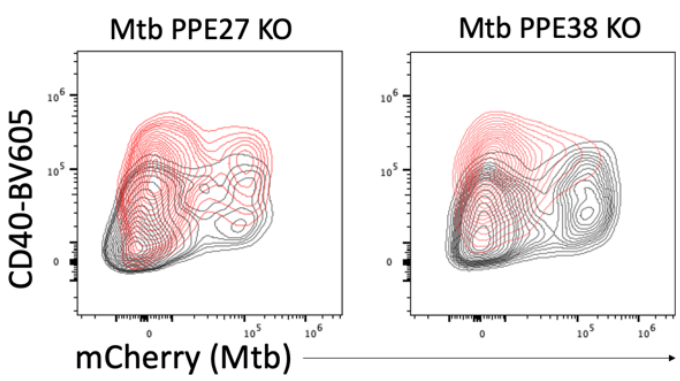
Background

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains one of the leading causes of death from a single infectious agent worldwide. Despite the availability of antibiotic treatment, Mtb infects roughly a quarter of the global population, establishing a spectrum of outcomes ranging from asymptomatic latent infection to active pulmonary disease. The pathogen's success stems from its ability to persist within host macrophages and to evade or subvert protective immune responses. A deeper understanding of the molecular mechanisms underlying Mtb-host interactions is therefore essential for the development of improved vaccines, diagnostics, and host-directed therapies.

Mtb encodes a large family of PE and PPE proteins, which together constitute roughly 10% of its coding genome. These proteins are characterized by Pro-Glu (PE) or Pro-Pro-Glu (PPE) motifs and are oKen associated with the bacterial cell wall or secreted via specialized ESX secretion systems. PE/PPE protein have previously been implicated in modulating host-pathogen interactions, including immune evasion, antigenic variation, and manipulation of host innate and adaptive immune responses. However, this protein family has historically been overlooked due to substantial technical challenges, including high sequence similarity and gene:c redundancy that complicate functional studies. As a result, the biological roles of most PE/PPE proteins remain poorly understood, representing a major gap in our knowledge of Mtb virulence and an important opportunity for discovery.

Short project description

Using a recently developed CRISPR interference (CRISPRi) approach, selected individual PE/PPE genes will be specifically targeted and knocked down in an attenuated Mycobacterium tuberculosis strain compatible with BSL-2 conditions. Mouse or human macrophages will be infected with these strains, and infection outcomes will be assessed by spectral flow cytometry, cytokine and chemokine quantification in culture supernatants, and real-time quantitative PCR analysis of host inflammatory genes. Preliminary data from our laboratory suggest a link between the expression of specific PE/PPE genes, host cell mitochondrial damage, and the induction of pro-inflammatory cytokines. Accordingly, multiple markers of mitochondrial dysfunction will be evaluated in infected macrophages, and key signaling pathways will be selectively inhibited to determine their functional relevance.



We offer

- A highly collaborative, international and interactive environment and a place to learn and advance as a scientist
- Opportunity to develop skills in basic bacterial and mammalian cell culture, in vitro infec:on studies, flow cytometry and quantitative PCR analysis

Contact

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