Mycobacterium tuberculosis polyketide synthase 12 manipulates the macrophage microenvironment

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*), is history's most devastating infectious disease. In 2021, 10.6 million people fell ill, and 1.6 million died from TB. Following phagocytosis, *Mtb* manipulates macrophages to persist and replicate. During infection, the host-pathogen interface is the *Mtb* cell wall. This study aimed to elucidate the role of the cell wall glycolipid mannosyl-β-1-phosphomycoketide (MPM), synthesized by polyketide synthase 12 (*pks12*), during *Mtb* infection. To study the role of MPM, we generated a Δ*pks12* strain and infected macrophages with *Mtb* WT and *Mtb* Δ*pks12*. First, we observed that *pks12* deletion leads to the overexpression of the downstream gene in the operon *rv2047c*. Interestingly, *pks12* deletion does not impact *Mtb* intracellular survival in macrophages. Nonetheless, *pks12* deletion enhances macrophage death. The average survival of macrophages infected by the WT strains was 75%, while the viability of the macrophages infected by the Δ*pks12* was 50% at 4 days post-infection. Additionally, *pks12* deletion also exacerbates the release of pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, and IL-6) and chemokines (CXCL1 and CXCL2). Overall, the data suggests that alterations in MPM biosynthesis modulate the innate immune response to *Mtb* infection and reveal new pathogen factors that manipulate innate immune cells.

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