Title: The sigma factor SigE's role in mycobacterial granulomas.

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Infections caused by *Mycobacterium tuberculosis* (*Mtb*) are one of the top causes of death from an infectious agent, resulting in 1.5 million deaths per year. One of the hallmark characteristics of the disease is the granuloma, where macrophages form a structure that contains the infecting bacteria but are unable to eradicate them. Within the granuloma, pathogenic mycobacteria are able to survive within this host environment that exposes them to pH changes, hypoxia, and antimicrobial peptides. However, mycobacteria produce a unique, lipid-rich cell envelope thought to protect them from many of these external stressors and that also modulates the host immune response.
Even though tuberculosis granulomas have been studied for over 150 years, the bacterial factors involved in this immune structure, especially those related to the cell envelope are relatively understudied due to the challenges of modelling granulomas *in vivo*. The zebrafish-*Mycobacterium marinum* is a unique model that recapitulates key aspects of tuberculosis disease and allows us study bacterial specific factors in an *ex vivo* context through granuloma imaging and extraction. Through this system we have found that the bacterial sigma factor, SigE affects both bacterial survival and host immune responses within the granuloma through infection-specific alterations in the bacterial cell envelope.

SigE is a bacterial sigma factor with known impacts on the immune response. To elucidate its role in infection and granulomas, I infected zebrafish larvae with fluorescent bacteria and used both host (macrophages) and bacterial fluorescent markers to observe and quantify granuloma observations. I found that *ΔsigE Mm* (Δ*sigE*) has a significant growth defect in zebrafish larvae. Despite the decrease in bacteria, I observe a unique phenotype where the granuloma structure is maintained, and host inflammation persists. **This holds even when fish are infected with heat-killed bacteria, suggesting this unusual response is modulated by the cell envelope surface**. Because sigE's regulon includes several genes of unknown function in the cell envelope, I hypothesize that SigE alters mycobacterial cell envelope composition, which is recognized by the host immune system to maintain granuloma structure.

TB granulomas have been studied for over 150 years; however, the interface between bacterial and host defense mechanisms remains understudied. This research reveals novel host-pathogen interactions within the granuloma. This proposal highlights a bacterial factor, SigE, that has a unique phenotype in granulomas of bacterial death couple with host inflammation. This highlights a bacterial factor with a novel role in the granuloma, which can unveil potential drug targets and therapies to treat TB infections. Understanding the bacterial factors that allow *Mtb* to persist in the granuloma can unveil potential drug targets and therapies to treat tuberculosis infections.