Title: Multi-Scale Modeling Predicts a Balance of Tumor Necrosis Factor-α and Interleukin-10 Controls the Granuloma Environment During Mycobacterium tuberculosis Infection

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Interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α) are key anti- and pro-inflammatory mediators elicited during the host immune response to Mycobacterium tuberculosis (Mtb). Understanding the opposing effects of these mediators is difficult due to the complexity of processes acting across different spatial (molecular, cellular, and tissue) and temporal (seconds to years) scales. We take an in silico approach and use multi-scale agent based modeling of the immune response to Mtb, including molecular scale details for both TNF-α and IL-10. Our model predicts that IL-10 is necessary to modulate macrophage activation levels and to prevent host-induced tissue damage in a granuloma, an aggregate of cells that forms in response to Mtb. We show that TNF-α and IL-10 parameters related to synthesis, signaling, and spatial distribution processes control concentrations of TNF-α and IL-10 in a granuloma and determine infection outcome in the long-term. We devise an overall measure of granuloma function based on three metrics – total bacterial load, macrophage activation levels, and apoptosis of resting macrophages – and use this metric to demonstrate a balance of TNF-α and IL-10 concentrations is essential to Mtb infection control, within a single granuloma, with minimal host-induced tissue damage. Our findings suggest that a balance of TNF-α and IL-10 defines a granuloma environment that may be beneficial for both host and pathogen, but perturbing the balance could be used as a novel therapeutic strategy to modulate infection outcomes.