Multi-scale analysis of TNF-regulated immune response to *Mycobacterium tuberculosis* infection

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Tuberculosis (TB) granulomas are organized collections of immune cells that form in the lung as a result of immune response to *Mycobacterium tuberculosis* (Mtb) infection. Formation and maintenance of granulomas are essential for control of Mtb infection and are regulated in part by a pro-inflammatory cytokine, tumor necrosis factor-α (TNF).

We developed a multi-scale computational model that includes molecular, cellular and tissue scale events that occur during TB granuloma formation. At the molecular scale, we focused on TNF. We used the results of sensitivity analysis as a tool to suggest appropriate wetlab experiments needed to measure critical model parameters in an artificial experimental model of a granuloma induced in the lungs of mice following injection of mycobacterial antigen-coated beads. Using these parameters we derived, we identified processes that regulate TNF concentration and cellular behaviors and thus influence the outcome of infection within a granuloma. TNF/TNF receptor binding kinetics, intracellular trafficking, and cellular organization within a granuloma determine a TNF concentration gradient that may spatially coordinate TNF-induced immunological functions. TNF receptor internalization kinetics are predicted to play a critical role in infection outcome, controlling whether there is clearance of bacteria, excessive inflammation, containment of bacteria in a stable granuloma, or uncontrolled growth of bacteria. Our results suggest that there is an inter-play between TNF and bacterial levels in a granuloma that is controlled by the combined effects of both molecular and cellular scale processes. We also used the model to explain what mechanisms lead to clinically observed differential effects of TNF-neutralizing drugs (generally used to treat anti-inflammatory diseases) on reactivation of TB. At the level of intracellular signaling, we showed that the stability of mRNA transcripts corresponding to NF-κB-mediated responses significantly controls bacterial load in a granuloma, inflammation level in tissue, and granuloma size. Because we incorporate intracellular signaling pathways explicitly, our analysis also elucidates NF-κB-associated signaling molecules and processes that may be new targets for infection control. Ultimately, these results can help to elaborate relevant features of the immune response to Mtb infection, identifying new strategies for therapy and prevention of tuberculosis .