Multi-scale modeling reveals the influence of opposing dynamics of TNF and IL-10 in *Mycobacterium tuberculosis* infection

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Tuberculosis (TB) is a global health problem responsible for ~ 2 million deaths per year. *Mycobacterium tuberculosis* (Mtb) infection leads to the formation of granulomas in the lung, spherical collections of immune cells that immunologically constrain and physically contain bacteria. These structures are comprised of lymphocytic and monocytic cells surrounding a core of infected macrophages. If granulomas are able to contain the infection, the host develops latent TB; otherwise the disease progresses and is classified as active TB. Key cytokines relevant to granuloma formation and function are tumor necrosis factor-α (TNF), an inflammatory cytokine critical to the formation and maintenance of granulomas, and interleukin-10 (IL-10), an anti-inflammatory cytokine that mediates processes including down regulation of TNF. It is not known how the actions of TNF and IL-10 together influence granuloma formation and function, as these actions are embedded in the context of numerous other cellular processes and it has proved difficult to study any one process individually *in vivo*. There is a crucial need for an *in silico* platform that can help us understand the actions of these two opposing cytokines.

We developed a hybrid multi-scale model of the immune response to Mtb that incorporates events on the tissue, cellular, and molecular scales. Tissue and cellular scales are described by well-known immune mechanisms (CD8+ CTL killing, macrophage infection, etc.), and simulated with an agent-based model. Single cell level molecular scale processes, which include TNF and IL-10 receptor/ligand dynamics and trafficking, are simulated by a set of coupled non-linear ordinary differential equations and diffusion, described by a partial differential equation. The cellular and molecular scales are linked via TNF- and IL-10-induced processes including TNF-induced apoptosis or NF-κB activation and IL-10 induced regulatory T cell phenotype. We first establish a baseline set of parameters that simulates stable control of infection in a granuloma (called 'containment'), which is consistent with both mouse and non-human data. Uncertainty and sensitivity analyses are performed using Latin Hypercube Sampling, to simultaneously vary multiple model parameters, and PRCC (Pearson Rank Correlation Coefficients) to determine the effect on infection outcome(s). We simulate immunomodulation by modeling I.V. administration of TNF and IL-10 using a simple pharmacokinetic model of a vascular compartment and a flux of these molecules from the vasculature to the lung tissue. Our model also allows us to explore perturbations to the system, such as immunomodulation therapies, that may augment the immune response.