The dynamics of TNF signaling control tuberculosis granuloma formation

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***Short Abstract* — Tumor necrosis factor-α (TNF) plays a key role in control of immune response to *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis. TNF has been experimentally characterized to have the following activities: macrophage activation, apoptosis, and chemokine and cytokine production. Using a multi-scale computational model, we study how the dynamics of TNF-associated molecular scale processes, including TNF receptor dynamics and intracellular NF-κB dynamics, influence the outcome of infection during the long-term immune response to Mtb. Our modeling suggests that both the extent and the timing of TNF-induced responses could be used as new targets for therapy.**

I. Background

TUBERCULOSIS (TB), a disease caused by the intracellular pathogen *Mycobacterium tuberculosis* (Mtb), is responsible for 2-3 million deaths per year [1]. Multiple immune factors control host responses to Mtb infection, including the formation of granulomas, aggregates of immune cells whose function may reflect success or failure of the host to contain infection [2,3]. One such factor is tumor necrosis factor-α (TNF). TNF (in conjunction with the cytokine IFN-γ) induces macrophage activation, enhances immune cell recruitment to site of infection, and augments chemokine and cytokine expression by macrophages through activation of the NF-κB signaling pathway [4]. TNF availability within a granuloma has been proposed to play a critical role in immunity to Mtb [5]. However, *in vivo* measurement of the TNF concentration and activities within a granuloma are not experimentally feasible. Further, there are differences among dynamics of each of NF-κB-associated responses as a result of differences in molecular processes (e.g. RNA and protein degradation rates) downstream of TNF-induced NF-κB activation [6]. We use a systems biology approach to determine the effects of dynamics of TNF-associated molecular scale processes on the long-term immune response to Mtb.

II. Results

We developed a multi-scale computational model that describes the immune response to Mtb in lung over three biological length scales: tissue, cellular and molecular. We use our model to identify processes that regulate TNF concentration and cellular behaviors and thus influence the outcome of infection within a long-term immune response to Mtb. At the level of TNF/TNF receptor dynamics, TNF receptor internalization kinetics are shown to significantly influence TNF concentration dynamics, macrophage and T cell recruitment to site of infection as well as macrophage activation and apoptosis. These processes play a critical role in control of inflammation and bacterial levels within a granuloma.

At the level of intracellular signaling, we predict the impact of NF-κB associated response dynamics on the outcome of infection. Our model suggests that the timing of these responses (i.e. chemokine expression, TNF expression and macrophage activation), in addition to the extent of response, plays a critical role in control of infection and inflammation within a granuloma. Manipulations in the dynamics of these responses lead to different outcomes, including clearance of bacteria, containment of bacteria within a stable granuloma, uncontrolled growth of bacteria, or excessive inflammation. Thus, the model elucidates intracellular NF-κB associated signaling molecules and processes involved in immunity to Mtb that may be new targets for therapy.

III. Conclusion

Multi-scale analysis of the TNF-regulated immune response to Mtb can elucidate novel immune targets for immunotherapy and control of TB.

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