UNIVERSITY of HOUSTON | ENGINEERING

Department of Biomedical Engineering

Ph.D. Dissertation Defense

Experimental and Computational Modeling of the Dynamic Formation of the Proinflammatory Microenvironment in Response to Francisella tularensis LVS Infection

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ABSTRACT:

The proinflammatory microenvironment (PME) plays a critical role in determining the outcome of infection. Intracellular pathogens can elicit immune responses within host immune cells that cause the release of cytokines, chemokines, and effector molecules within the surrounding microenvironment. Neighboring immune cells recruited into the PME can be primed and activated by cytokine exposure acquiring the ability to more robustly eliminate any subsequent infection. Early responders such as macrophages and NK cells are critical in the formation of an effective proinflammatory microenvironment. However, some pathogens have adopted immune evasion mechanisms, thus, attenuating the formation of an effective PME. Accordingly, in silico computational models can capture the biological complexity of host-pathogen interactions within a series of mathematical equations. These models possess the ability to predict the time-course dynamics of infection, can be utilized to test biological hypotheses in silico, and are cost-efficient when compared to experimental techniques.

In the research presented here, we developed a systems biology based computational and experimental model to investigate the dynamics of infection for the gram-negative bacterium and potential biowarfare agent, Francisella tularensis subsp. holarctica (Live Vaccine Strain (LVS)). Two key cytokines have been elucidated as key players in the PME against F. tularensis LVS infection, namely, TNF-α and IFN-γ. We therefore engineered an input driven, in silico model that is able to capture the dynamics of intracellular responses and gene expression profiles in response to pathogenic and cytokine stimulation found in the extracellular compartment. Our model captures key regulatory mechanisms of the proinflammatory response under gram-negative bacteria and specifically, F. tularensis LVS infection. In addition, we utilized the model to investigate the effects of the changing PME on the intracellular bacterial load under IFN-γ

and/or TNF-α priming. To validate our model, we first developed an in vitro macrophage experimental platform to test the effects of F. tularensis LVS infection on host macrophages. However, in order to quantify the endogenous production of IFN-γ, we expanded the model into an ex vivo platform with bone-marrow derived macrophages and splenic NK cells to better understand the mechanisms underlying the in vivo outcome of infection.

The in silico model we developed has the potential to highlight key immunomodulatory sites for targeted drug therapy. Further, by successfully optimizing our model to *F. tularensis* specific data and simulating similar outcomes to our ex vivo platform, our model also provides a basis to test other bacterial infection systems.