

FIGHTING TB MIGHT BE A MATTER OF 'FLIPPING A SWITCH' IN IMMUNE RESPONSE

by

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In the lung, alternatively activated macrophages (AAM) form the first line of defense against microbial infection. Due to the non-inflammatory nature of AAM, the lung can be considered as an immunosuppressive organ for respiratory pathogens. However, as infection progresses in the lung, another population of macrophages, known as classically activated macrophages (CAM) enters. CAM are far more effective than AAM in clearing the microbial load, producing pro-inflammatory cytokines and anti-microbial defense mechanisms necessary to mount an adequate immune response. Because AAM have been classified as non-inflammatory macrophages, they could be one important cause for the delay in the lung's protective immune response as reported in the literature. Their research was concerned with determining the first time when the population of CAM becomes more dominant than the population of AAM. This proposed "switching time" may have important implication in vaccine and therapy development.



As a preliminary investigation into the concept of a "switching time", MBI Postdoctoral Fellow Judy Day and collaborators Larry Schlesinger, M.D. (Director, Center for Microbial Interface Biology at OSU Medical Center) and Avner Friedman (OSU, Department of Mathematics) sought to mathematically model the host response of the lung to the intracellular pathogen, *Mycobacterium tuberculosis*. They developed a mathematical model that describes the interactions among immune cells, bacteria populations (intracellular and extracellular), and cytokines (soluble proteins involved in cell signaling) in the context of a tuberculosis infection. The model, based on a system of differential equations, represents a useful tool to analyze

strategies for reducing the switching time, and to generate hypotheses for experimental testing. Previous models of tuberculosis infection did not focus on the early stages of the infection, nor did they specifically consider the role of alternatively activated macrophages in the course of the infection.

The model predicted a switching time of 50 days. This duration corresponds well with the time it takes from initial exposure to MTb to a positive skin test (6-12 weeks), which is indicative of a noticeable immune response. In addition, Day performed simulated experiments in order to shorten the switching time so that the more effective immune cells would enter the picture sooner in hopes of better containing the infection. The results showed that the use of a particular therapy did help reduce the

switching time, and that this most often corresponded to reduced bacterial loads. A reduction in bacterial loads may imply a reduction in the duration of treatment of latent infection, the likelihood of reactivation, and the latent pool or resistant bacteria. However, this therapy alone was not sufficient to eradicate the infection, a result that resonated with the literature describing clinical trial outcome using this therapy. In addition, sensitivity analysis revealed that early signaling from the AAM is important in the development of protective immunity and that therapies should reduce bacterial loads but not at the expense of a reduction in signaling to downstream immune mediators.

This current work is the beginning of a larger aim envisioned by Day and collaborators, which is to understand the host response of the lung to a variety of airborne pathogens in addition to tuberculosis, such as anthrax and tularemia. Depending on the type of pathogen, the initial immune response of the lung can vary a great deal. For instance, *M. Tuberculosis* is a host-adaptable microbe where both host and microbe can co-exist. On the other hand, anthrax inhalation is lethal to the host in a very short amount of time after initial exposure due to a potent immune response that overwhelms the host. The authors are currently preparing an opinion piece for the journal *Tuberculosis* that will highlight the role of mathematical modeling and encourage collaborations among mathematicians and experimentalists in the development of vaccinations and therapeutic strategies for combatting tuberculosis infection.