Exploring the Direct Effects of *Mycobacterium tuberculosis* on T Cell Responsiveness

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ABSTRACT

The pathologic hallmark of infection with Mycobacterium tuberculosis (Mtb) are granulomas, collections of host immune cells (e.g. macrophages and T cells) that organize in an attempt to contain and eliminate the infection. Since granulomas are the sites of infection within lungs, we expect them to be enriched substantially in Mtb-responsive T cells (cells producing cytokines in response to Mtb). Surprisingly, a low frequency of Mtb-responsive T cells (~ 8%) in granulomas have been observed. As an increase in Mtb specific T cells early post-infection is thought to lead to quicker clearance of the pathogen, it is important to determine why the frequency of functional T cells in granulomas is so low. One hypothesis is that T cells are being down-regulated directly by Mtb. To study this dynamic, we use a multi-scale modeling approach. Our lab has previously created an agent based model (ABM), known as GranSim, that tracks bacteria and individual immune cells as agents. This allows us to capture Mtb heterogeneity in terms of growth and division by tracking its environment to predict the impact of bacterial factors on T cell behavior. To allow fine tuning at the molecular level of macrophage-T-cell interaction, we will integrate a system of ODEs that captures Mtb-mediated down-regulation of MHC II presentation of peptides in macrophages that we have previously published directly into cells within GranSim, creating a MSM that spans intracellular to tissue scales. This work can provide insights into mechanisms that could be either enhanced or inhibited to therapeutically increase frequencies of Mtb-responsive T cells and at the same time help to understand what mechanisms may be contributing to the extremely low levels of responsiveness.

BACKGROUND

- Tuberculosis (TB): Infectious disease caused by *Mycobacterium tuberculosis* (Mtb). One–third of the world's population is infected with Mtb, 2 million deaths/year[1]
- Host immune cells (macrophages and T cells) form granulomas to attempt to contain the infection
- Only ~8% T cells in granulomas respond to Mtb[2]
- It's unknown why T cell response at site of infection is low

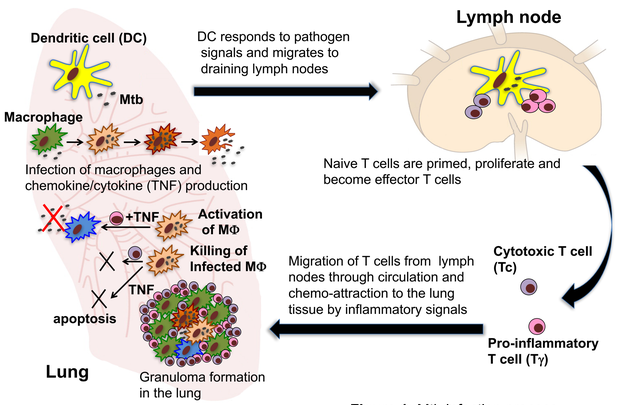


Figure 1: Mtb infection process.

AIMS

- Use model to predict how Mtb regulates T cells at the molecular level (antigen presentation)
- Use model to predict how Mtb regulates T cells at cellular/ tissue level (T cell, macrophage movement, interaction)
- Combine both models to explore how they interact, look for emergent behavior

BUILDING PIECES OF MULTI-SCALE MODEL

1. Agent Based Model (ABM)

- In ABMs, cells are agents that react to their environment
- GranSim[3,4] captures discrete cellular dynamics between immune cells and Mtb leading to tissue scale outcomes
- Comprised of decision-making heuristics via a set of well-described interactions, calibrated using experimental data, and implemented in C++ code with Boost and FFTw libraries.

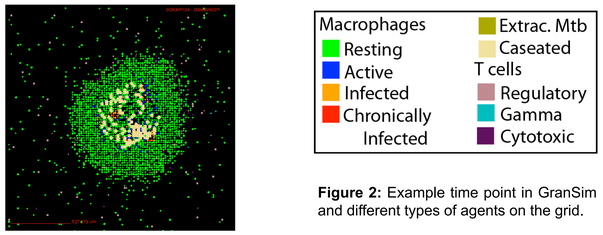
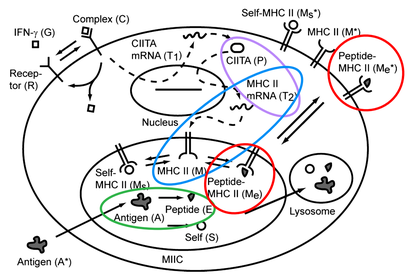


Figure 2: Example time point in GranSim and different types of agents on the grid.

2. Ordinary Differential Equations (ODEs)

- ODEs represent molecular scale behaviors associated with cells
- Chang *et al* 2005[5] model captures Mtb-mediated down-regulation of MHC II presentation of peptides in macrophages
- Comprises 16 non-linear ODEs, solved in MatLab



Hypothesized process affected by Mtb

- **H1:** Antigen processing
- **H2:** MHC II maturation
- **H3:** MHC II peptide loading
- **H4:** MHC II transcription

Figure 3: ODE model schematic representing MHC II antigen presentation. Colored circles represent different processes hypothesized to effect antigen presentation by Mtb.

CREATING A HYBRID MULTI-SCALE MODEL

- GranSim has the ability to insert ODEs into individual agents
- Allows for observation of the interaction between tissue, cellular, and molecular scales
- Emergence of behaviors that arise from interactions between agents that would otherwise be impossible to know a priori[6,7]

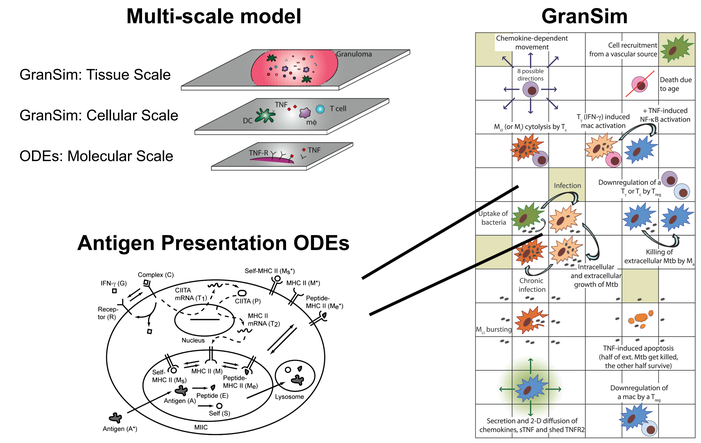


Figure 4: Model schematics of GranSim and ODEs and how they relate to each other as a multi-scale model.

ONGOING AND FUTURE WORK

- Incorporate ODEs into GranSim, linking through INFγ T cell secretion, exogenous antigen through bacterial agents, and T cell-macrophage interactions
- Conduct inter- and intra-compartmental uncertainty and sensitivity analysis
- Incorporate other mechanisms where Mtb affects T cells

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