The effects of *Mycobacterium tuberculosis* on T cell responsiveness in granulomas

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GOALS OF THE STUDY

- Use a computational model to predict how Mtb interferes with both T cells at the molecular level (via antigen presentation) and the cellular/tissue level (via T cell, macrophage movement, interaction)
- Combine molecular and cellular/tissue level models to explore the emergent dynamics and predict where and how inhibition occurs

TCELLS IN MTB

- 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 contain the infection in lungs
- Only ~8% T cells derived from tuberculosis granulomas respond to Mtb[2]
- It's unknown why T cell response at site of infection is low

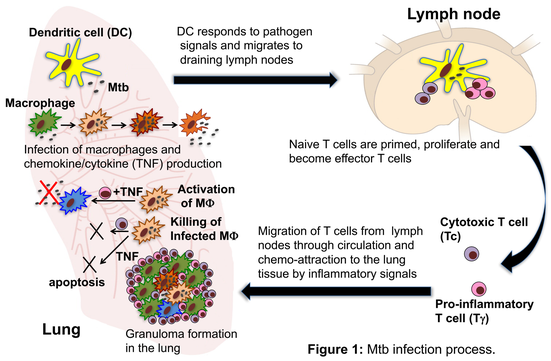
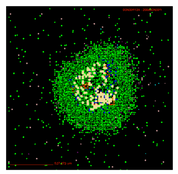


Figure 1: Mtb infection process.

MULTI-SCALE MODELING

Tissue/Cellular Model

- 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.



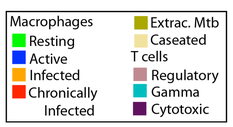
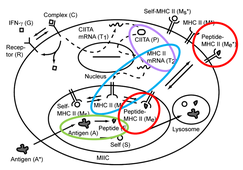


Figure 2: Example time point in GranSim and different types of agents on the grid.

Intracellular Model

- Chang *et al* 2005[5] ODE 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.

MULTI-SCALE MODELING

Integrated 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]

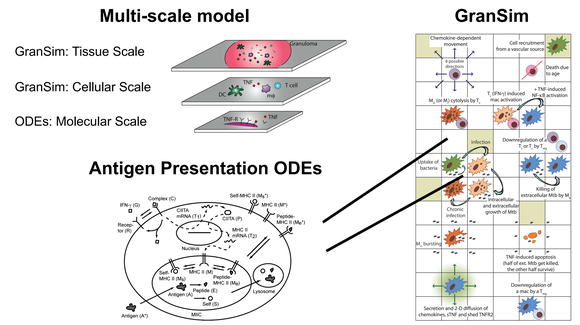


Figure 4: Model schematics of GranSim and ODEs and how they relate to each other as a multi-scale model.

RESULTS

1. Delayed T cell response leads to more coordinated attack on Mtb later in infection

- Delayed T cell response (delayed time after which T cell recruitment is enabled) leads to higher initial Mtb, followed by increases in T cells in the granuloma and MHC II presentation
- Increasing the probability of macrophage recruitment leads to less T cells that can reach the granuloma

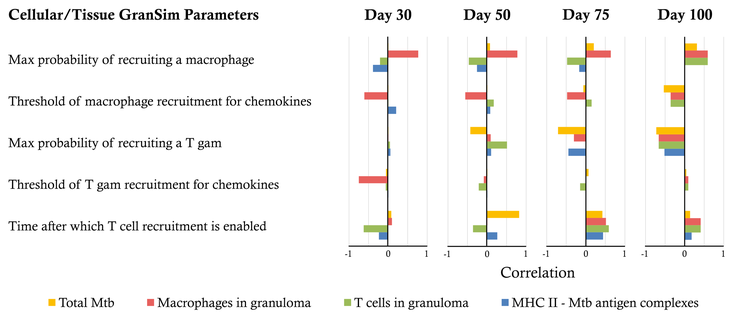


Figure 5: Partial rank correlation coefficient sensitivity analysis of GranSim model parameters on recruitment variables.

2. MHC II presentation of Mtb antigens influenced most by antigen uptake, processing, and degradation

- Increasing Mtb antigen processing increases MHC II presentation, but wanes by 100 days
- Increasing Mtb antigen degradation or decreasing MHC II-Mtb antigen association decreases MHC II presentation throughout infection

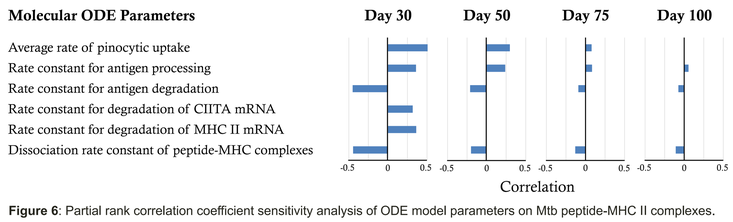


Figure 6: Partial rank correlation coefficient sensitivity analysis of ODE model parameters on Mtb peptide-MHC II complexes.

RESULTS

3. A majority of T cells don't reach macrophages within the granuloma

- During peak T cell activation (~40 days post infection), only ~30% of T cells travel far enough within the granuloma to be in the maximum radius of macrophages
- These levels drop to half by 75 days post infection

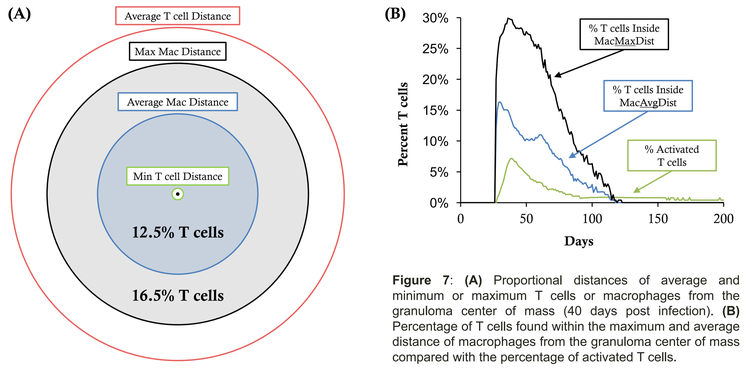


Figure 7: **(A)** Proportional distances of average and minimum or maximum T cells or macrophages from the granuloma center of mass (40 days post infection). **(B)** Percentage of T cells found within the maximum and average distance of macrophages from the granuloma center of mass compared with the percentage of activated T cells.

4. The ability of T cells to reach macrophages in the center of the granuloma is a good predictor of T cell activation

- ~73% of the variance in the amount of T cells that travel far enough within the granuloma to be in the maximum radius of macrophages can be predicted from the amount of activated T cells observed

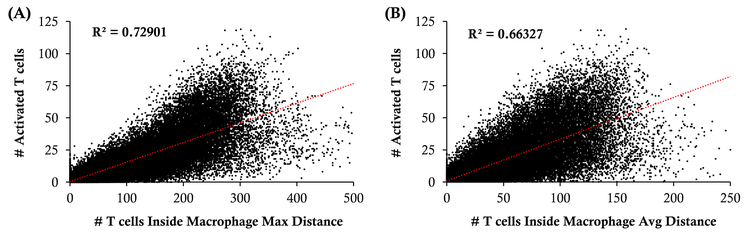


Figure 8: Relation of the number of activated T cells with the number of T cells found within the **(A)** maximum or **(B)** average distance of macrophages from the granuloma center of mass.

DISCUSSION / CONCLUSIONS

- The fact that only 8% of T cells respond from granulomas likely has more to do with the spatial layout of the granuloma, that consists of outer layers of T cells
- To increase T cell activation, intervention could possibly consist of creating a way T cells could better migrate inside the granuloma to get to infected macrophages

REFERENCES

1. WHO. Global tuberculosis report 2014. Report number WHO/HTM/TB/2014.08.
2. Gideon HP, et al. *PLoS Pathog*. 2015; 11: e1004603.
3. Fallahi-Sichani M, et al. *J Immunol*. 2011; 186: 3472.
4. Cilfone NA, et al. *PLoS One*. 2013; 8: e68680.
5. Chang ST, et al. *Proc Nat Acad Sci*. 2005; 102: 4530.
6. Segovia-Juarez JL, et al. *J Theor Biol*. 2004; 231: 357.
7. Christian J, et al. *J Immunol*. 2009; 182: 3706.

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