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

Jess A. Millar[1*], JoAnne L. Flynn[2], Jennifer J. Linderman[3], Denise E. Kirschner[1,4]

1. Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI., 2. Microbiology & Molecular Genetics, University of Pittsburgh, Pittsburgh, PA.,
3. Chemical Engineering, University of Michigan, Ann Arbor, MI., 4. Microbiology & Immunology, University of Michigan, Ann Arbor, MI.
*For correspondence: jamillar@umich.edu

ABSTRACT

Background
- Granulomas are hallmark of *Mycobacterium tuberculosis* (Mtb) infection
- Collections of host immune cells (macrophages and T cells)
- Contain and eliminate the infection
- Expect to be enriched substantially in Mtb-responsive T cells (cells producing cytokines in response to Mtb)
- However, low frequency of Mtb-responsive T cells (~ 10%) in granulomas have been observed
- Important to determine why the frequency of functional T cells in granulomas is so low
- Hypothesis: T cells are being down-regulated directly by Mtb

Methods
- Use a multi-scale modeling (MSM) approach
- Agent based model (ABM), known as GranSim tracks bacteria and individual immune cells as agents
- System of ODEs captures Mtb-mediated down-regulation of MHC II presentation of peptides in macrophages
- Combine ABM and ODEs in MSM that spans intracellular to tissue scales

Results
- Mid range down regulation of MHC II transcription most advantageous for Mtb
- Down regulation of MHC II maturation lowered T cell response

Discussion
- Can provide insights into mechanisms that could be either enhanced or inhibited to therapeutically increase frequencies of Mtb-responsive T cells
- Help to understand what mechanisms may be contributing to the extremely low levels of responsiveness

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

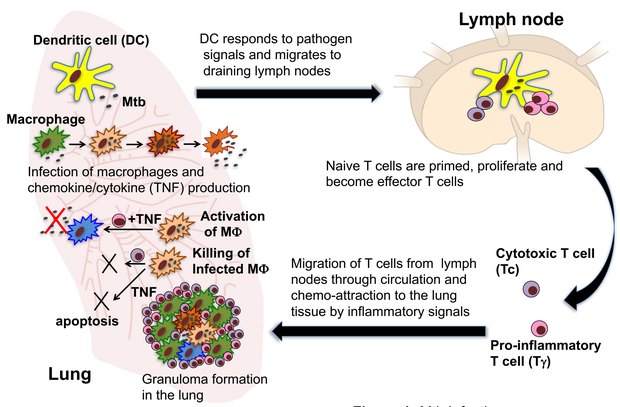


Figure 1: Mtb infection process.

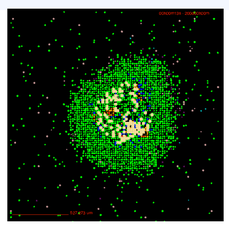
GOALS OF THE STUDY

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

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.



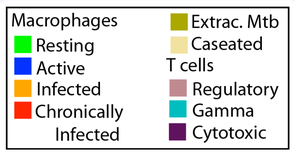


Figure 2: Example time point in GranSim and different types of agents on the grid.

Intracellular Model

- Chang *et al* 2005[5] ODE model captures Mtb-mediated down-regulation of MHC II presentation of peptides in macrophages
- GranSim has the ability to insert ODEs into individual agents, creating a multi-scale hybrid agent based model that is stochastic and discrete in nature
- Allows observation of interaction between tissue, cellular, & molecular scales

Integrated Multi-Scale Model

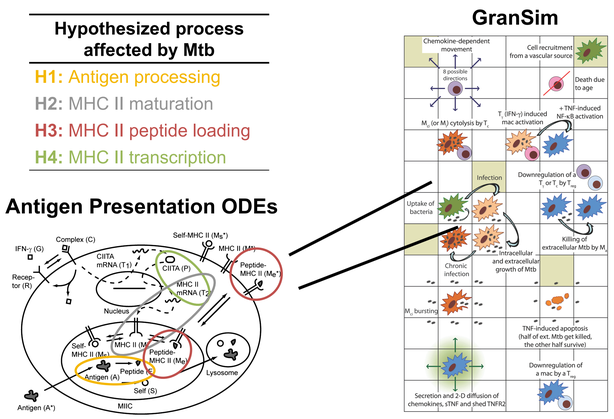
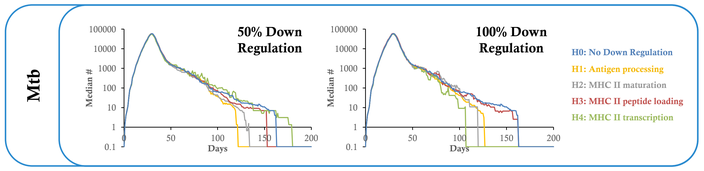


Figure 3: Model schematics of GranSim and ODEs and how they relate to each other as a multi-scale model. Colored circles represent different processes hypothesized to effect antigen presentation by Mtb.

RESULTS

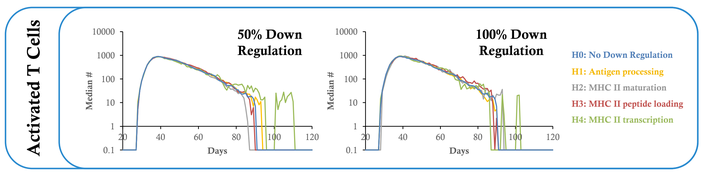
1. Mid range down regulation of MHC II transcription most advantageous for Mtb

- 50% down regulation of MHC II transcription allows Mtb infection to persist longer, along with increased MHC II
- 100% down regulation has the opposite effect



2. Mid range down regulation of MHC II maturation reduces activated T cell response

- 50% down regulation of MHC II maturation stops the activated T cell response about 5 days earlier
- 100% down regulation allows it to continue for a few more days



DISSCUSSION / CONCLUSIONS

- Mid range MHC II transcription reduction may reduce MHC II complex recycling, more chance of presenting self peptide vs Mtb
- Mid range MHC II maturation reduction results in less MHC II complexes, likely leading to less activated T cells
- In both cases, there was a "goldilocks zone" where too much down regulation was detrimental to Mtb
- With this in mind, intervention in Mtb infection could possibly consist of blocking these MHC II processing steps in macrophages within granulomas

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: 3472–3483.
4. Cilfone NA, et al. *PLoS One*. 2013; 8: e68680.
5. Chang ST, et al. *Proc Nat Acad Sci*. 2005; 102: 4530–4535.

ACKNOWLEDGEMENTS

This research was supported by NIH grants R01AI123093-01 and U01HL131072. This research also used resources of the National Energy Research Scientific Computing Center, which is supported by the Office of Science of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231 and XSEDE (MCB140228). JM was supported by a NSF GRFP (DGE-1638278) and the Rackham Merit Fellowship through University of Michigan. We thank Paul Wolberg for computational assistance.