Towards a Virtual Immune System: Multi-Scale Modeling of CD4+ T Lymphocytes

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Abstract

The immune system is regulated by biological and biochemical networks integrated across multiple scales (*e.g.*, signal transduction, metabolism, *etc*). There are networks within each individual cell and at the cell population level. In order to understand the dynamics of the immune system under healthy and diseased conditions, multi-scale models are needed to fully leverage mathematical and computational tools. Herein, we discuss the first step we have taken towards describing the immune system in such a computational, system-level framework, exemplified by a multi-scale model of CD4+ T lymphocytes, including naive, effector (Th1, Th2, and Th17), regulatory, and memory cells. Within this framework, the following scales about CD4+ T lymphocytes are integrated: metabolism (described by constraint-based models), gene regulation and signal transduction (logical model), the population level (agent-based model), and extracellular cytokine concentrations (ordinary differential equations). Furthermore, the framework is oriented in space within three compartments, namely an infection site, a draining lymph node, and the circulatory system. The model was validated by reproducing known phenomena using a Monte Carlo method, including the phenotypic plasticity of CD4+ T lymphocytes, the effects of IL-2 on their proliferation and survival, and the effects of chronic inflammation.

Introduction

- The immune system is a complex network of cells, cytokines, and antibodies; they infiltrate the whole body [1]. Its complexity is shown in figure 1.
- Innate and adaptive immune systems: a central component of the adaptive system (antigen-specific, slow-forming, and long-lasting) is formed by CD4+ T lymphocytes and their associated cytokines [1].
- Their life cycle is shown in figure 2.
- They differentiate into different phenotypes according to the cytokine inputs and secrete cytokines to enhance the functions of other immune cells, such as macrophages and CD8+ T lymphocytes [2]. Their differentiation scheme is shown in figure 3.

Methodology

- We developed a multi-scale model of CD4+ T lymphocytes by leveraging ordinary differential equations (ODEs), agent-based modeling (ABM), logical modeling (LM), and metabolic modeling (MN).
- The spatial orientation is shown in figure 4, the logical model is shown in figure 5, and the flow of information between different scales is shown in figure 6.
- The other immune cells and the invading antigen are abstracted into a user-defined signal.
- We used the model to reproduce the dynamics of CD4+ T lymphocytes to influenza A (A/PR/8/34) [3] and their differentiation due to different cytokine inputs [4].

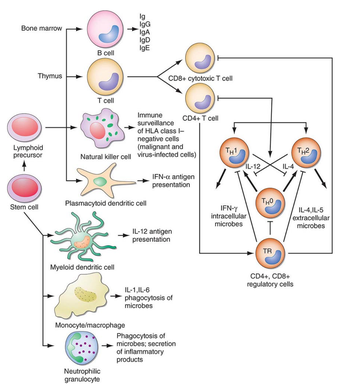

Figure 1 The immune system is a complex network of cells and molecules [5].

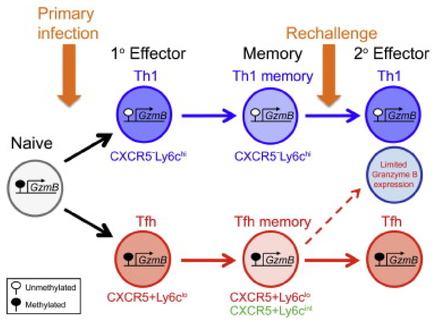

Figure 2 CD4+ T lymphocytes activate upon exposure to antigens, divide rapidly and perform their functions, and die or become memory cells [6].

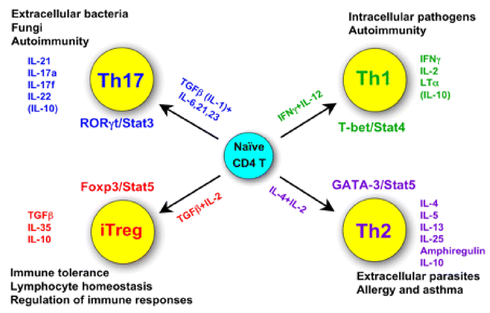

Figure 3 CD4+ T lymphocytes differentiate into different phenotypes to perform different functions [7].

Results: Multi-Scale Model

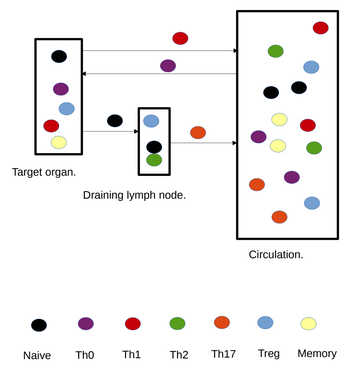

Figure 4 Spatial orientation of the model.

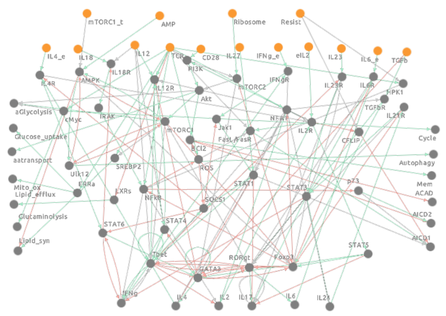

Figure 5 Logical model of the signaling events and gene regulation inside a CD4+ T lymphocyte.

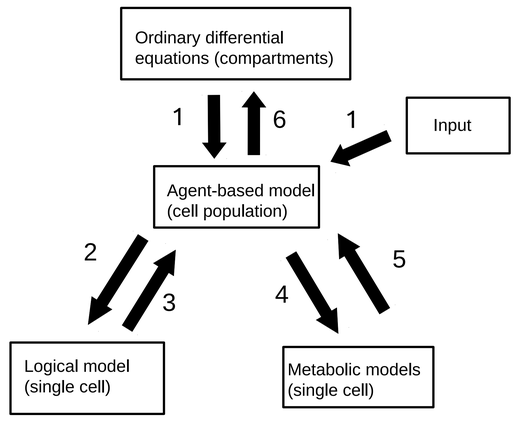

Figure 6 Information flow between different scales in the model.

- Input: a user-defined signal which represents the invading antigen and the immune system minus CD4+ T lymphocytes. It roughly corresponds to the antigen load.
- Compartments: an infection site (target organ), the draining lymph node, and the circulation. The target organ is where the modeled infection occurs, the draining lymph node is where CD4+ T lymphocytes activate, and the circulation roughly corresponds to the rest of the body.
- Ordinary differential equations: 11 sets of three ODEs. They describe the concentration dynamics of 11 cytokines (IL-2, IL-4, IL-6, IL-12, IL-17, IL-18, IL-21, IL-23, IL-27, IFNg, and TGFb) in the three compartments. Within each set, the equations are coupled through the convective transport terms.
- Agent-based model: a shell that mediates information flow in the model (figure 6). Each cell is described as a discrete, autonomous agent. It can activate, divide by going through the cell cycle, differentiate (Th0, Th1, Th2, Th17, and Treg), produce cytokines, die, and form memory.
- Logical model: 73 nodes and 156 edges. It describes cell signaling and gene regulation as a Markov chain [8-9].
- Metabolic models: five metabolic models for five phenotypes (Th0, Th1, Th2, Th17, and Treg). Around 3000 metabolites and 4000 metabolic fluxes *per* model. They are solved by flux balance analysis (linear programming).

Results: Validation

Validation 1: CD4+ T lymphocyte dynamics in response to influenza A (A/PR/8/34). Qualitative agreement with an experimental study (figures 7 and 8).

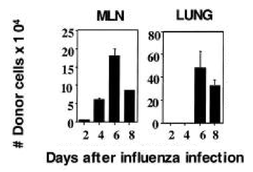

Figure 7 Population dynamics of CD4+ T lymphocytes in response to influenza A (experimental study) [3].

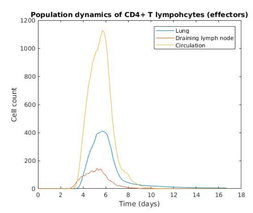

Figure 8 Population dynamics of CD4+ T lymphocytes in response to influenza A (model prediction).

Validation 2: CD4+ T lymphocyte differentiation in response to different cytokines; qualitative agreement with an experimental study (table 1). A higher dosage leads to a stronger response (figure 9).

Table 1 Phenotypes induced by different cytokines in both an experimental study [4] and our model predictions.

Cytokine Combination	Phenotype
IL-12	Th1
IL-2 and IL-4	Th2
TGFb and IL-6	Th17
TGFb and IL-2	Treg

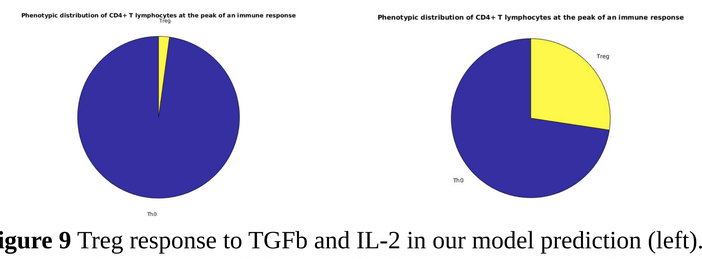

Figure 9 Treg response to TGFb and IL-2 in our model prediction (left). Ten times the experimental dosage, a higher Treg response (right).

Conclusions

We have developed a multi-scale model of CD4+ T lymphocytes. It is compartmental and spans multiple scales: extracellular concentration dynamics of cytokines (ODEs), cell population (ABM), intracellular signal transduction (LM), gene regulation (LM), and metabolism (MNs). We validated the model by reproducing experimentally observed dynamics of CD4+ T lymphocytes in response to influenza A and their differentiation due to different cytokine inputs. The next step is to apply multi-scale modeling to the remaining immune cell types and model their interactions.

Acknowledgements

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