

Combining quantitative experiments and modeling to understand kinetics of T cell response

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ABSTRACT: T cell response is a crucial factor in clearing intracellular infections. The magnitude, the duration and the rapidity of the T cell response dictate the clinical course and the eventual outcome of the infection. Determining the factors that control the strength and the time course of the T cell response is an active area of ongoing research, which can potentially provide better ways of treatment and vaccination against viral and bacterial intracellular pathogens. Understanding the kinetics of T cell response requires combination of quantitative experiments and computational modeling. Together with experimental collaborators, we have designed theoretical tools and performed quantitative experiments in order to quantify *in vivo* kinetics of T cell activation, proliferation and decline during the acute response to an intracellular bacterial infection, using a transgenic mouse model. I will describe the motivation and the goals of the project, outline the computational model based on the theory of age- and generation-structured branching processes, and show the preliminary application of the theory to the experimental data

I. BACKGROUND

Immune system protects higher multi-cellular organisms from infections with external pathogenic microorganisms. Encounter with invading pathogenic microorganisms triggers immune response that is mediated by several different cell types. It includes upregulation of expression of numerous genes, which leads to secretion of various signaling molecules (cytokines) that regulate the global response to the infection.

The T lymphocytes play a central role in the immune response and formation of immune memory. They are especially crucial in combating the intracellular pathogens, such as viruses, and certain types of bacteria. The T cells come in two flavors: ‘helper’ (CD4) T cells, and ‘killer’ (CD8) T cells. While the CD4 cells are crucial for the proper immune response, they participate by secreting cytokines and assisting in the activation and regulation of CD8 ‘killer’ cells. By contrast, the activated CD8 cells perform the actual killing of the infected cells.

The killer T cells are activated by an encounter with an ‘antigen’, a piece of the proteins that comprise the invading microorganisms, which is sensed by a special receptor in the

T cells, the ‘T cell receptor’ (TCR). The antigens are processes intra-cellularly, and are presented on the surfaces of infected cells, and of special ‘antigen-presenting cells’. In the course of a typical infection, activated T cells start growing and proliferating at a very rapid rate (expansion) until after several days they reach a maximum, after which most of them as rapidly die by apoptosis (contraction).

Normally, if the organism is to survive, the pathogen is cleared during the expansion phase of the T cell response. Until recently, it has been assumed that it is the clearing of the pathogen inhibits the proliferation of the T cells, eventually leading to the contraction. However, recent experiments show that both the expansion, and the contraction of the T cell response do not depend on the rate of the antigen clearance. Moreover, further experimentation has shown that the CD8 T cell response is extremely robust, and is maintained even when many of the factors that potentially regulate T cell behavior, are eliminated. This has become known as the T cell activation ‘program’.

II. MODELING.

Elucidating the different mechanisms behind the ‘programmed’ T cell activation requires quantitative modeling on two fronts: 1) development of a comprehensive model of the population dynamics of the proliferating and dying lymphocyte populations that, in particular, is capable of taking into account the stochasticity of the cell division and inter-cell variability as well as variability from one division to the next even in the same cell line. 2) development of quantitative experimental protocols that allow quantitative measurement of the *in vivo* of the kinetics of the T lymphocyte proliferation and death.

We present a general mathematical model based on the theory of age- and generation-structured branching processes, and show the preliminary application of the theory to the experimental data[5].

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