

ERD notes: Role of regulatory T cells in
producing a robust immune response and
maintaining immunodominance

Peter Kim

Notes by Andrew Basinski

April, 2009

The Immune System

The adaptive immune system can be loosely divided into T-cells and B-cells. B-cells are generally known for producing antibodies that inhibit the growth and reproduction of pathogens, whereas T-cells are mostly responsible for destroying infected host cells and tumour cells. These notes describe a model of the T-cell component of the immune system developed by Peter Kim.

T-Cells: Rapid Growth and Control

During an immune response, T-cells rapidly divide - increasing the population of T-cells by 3 to 4 orders of magnitude. Typically, this rapid growth is followed by an equally rapid decline once the pathogen has been fought off. To prevent damage to the host, the immune response has to be carefully controlled. One only has to glance at the variety of autoimmune diseases that result from an uncontrolled immune response to see how dangerous it can be. Exactly how T-cell numbers are controlled so precisely remains an interesting mystery. The two current paradigms are the proliferation program hypothesis and the Resource saturation hypothesis.

The resource saturation camp believes that the APC (antigen presenting cells) control the expansion and contraction of T-cell numbers by the density of presented pathogens. When APC cells are covered with pathogens, T-Cells are allowed to divide, whereas sparsely covered APC cells do not allow trigger this response in T-cells. The proliferation program hypothesis states that T-cells are programmed to undergo a fixed number of divisions when activated, after which they undergo apoptosis (programmed cell death).

Experimental studies have found that T-cell growth kinetics are determined within the first 24 hours of infection, and once initiated this growth is independent of the amount and duration of antigen stimulus. Apoptosis has been found crucial to terminating the immune cell growth stage. All of these points match nicely with the proliferation program hypothesis. However, a T-cell mediated immune response typically ends with a nearly simultaneous apoptosis of the T-cell population - while the proliferation program describes T-cells constantly dying off throughout the duration of the immune response. This mass suicide is better explained as the result of antigen levels falling below some threshold level. This would suggest the resource saturation model is correct.

While both hypotheses account for some experimentally obtained results, neither accounts for the recently found relationship between the number of T-cells at the peak of the immune response and the initial number of T-cells. The basic proliferation program predicts that the peak number of cells will result from a fixed time period of exponential growth - resulting in a slope of 1 on log-log plot (the peak population is directly related to the initial number). Experimentally results have shown that actual population growth is much slower - the peak number being roughly the cubed root of the initial number of cells. While this evidence isn't enough to overthrow the proliferation, it hints at an

additional control protocol by negative feedback.

The Model

In Peter's model, this additional negative feedback comes from the accumulation of regulatory T-cells. These cells are derived from standard T-Cells, and are responsible for inhibiting replication in the T-cell population. These regulatory T-cells result in a peak T-cell population that is much smaller than that which is suggested by the proliferation program.

Peter's model of the negative feedback provided by regulatory T-cells is the following system of differential equations:

$$\begin{aligned}
 \text{Immature APCs} \quad \frac{dA_0}{dt} &= s_A - d_0 A_0 - a(t)A_0 \\
 \text{Mature APCs} \quad \frac{dA_1}{dt} &= a(t)A_0 - d_1 A_1 \\
 \text{Naive T-cells} \quad \frac{dN}{dt} &= s_N - \delta_0 N - kA_1 N \\
 \text{Effector T-cells} \quad \frac{dE}{dt} &= 2^m k_1 A_1(t - \sigma)N(t - \sigma) - kA_1 E \\
 &\quad + 2kA_1(t - \rho)E(t - \rho) - (\delta_1 + r)E - kRE \\
 \text{Regulatory T-cells} \quad \frac{dR}{dt} &= rE - \delta_1 R
 \end{aligned}$$

Short Explanation of Equations

(see paper for parameter explanations). First note that immature APCs and naive T-Cells are produced at a constant rate. Also, all cell types have a constant death rate (total death being proportional to the population size). Immature APC's develop into mature APCs at a rate of $a(t)$. Effector T-Cells are derived from Naive T-cells with a delay of σ , but are also "produced" by running into Mature APCs (as described by a mass action term). The effector T-Cell population is reduced by a mass action term involving the number of regulatory T-Cells in addition to the death rate. Regulatory T-Cells are produced at a constant rate from Effector T-Cells.

Results

This model has been found to closely match the experimentally observed peak T-Cell count vs initial T-Cell count log-log slope of .3. The conclusion is that negative feedback by regulatory T-Cells may be an important control mechanism on T-Cell population size.

Hierarchical Immunodominance

The next issue that Peter addressed was the observed dynamics of simultaneous T-Cell responses corresponding to different antigens. It has been found that when simultaneous T-Cell responses occur, one response tends to dominate and suppress the others. The other responses are much less active than they would have been if they had occurred alone. Blocking a dominant response tends to result in another response being dominant and suppressing any remaining T-Cell responses. Peter refers to this as "hierarchical suppression of multiple T-Cell Responses." Why this occurs is a topic of great interest.

To help find out, Peter adapted his model to include multiple T - Cell populations, with each population specific to a particular antigen. The hypothesis is that the regulatory T-Cells produced by each population are able to suppress T-Cells in general - regardless of what population they belong to. The response that is prevalent first will produce enough regulatory T-Cells to prevent any other significant immune responses from occurring. The regulatory cells will suppress the dominant population too, of course, but not enough to prevent the hallmark "explosion" from occurring.

Simulations found that the primary response is likely determined by the initial concentrations of T-Cells in each population, with the largest initial population becoming the dominant one. The plots of population sizes agreed quite well with those obtained experimentally. Varying the reactivity of the different T-Cell populations also reproduced the pattern, but less accurately.

Summary

Negative feedback on T-Cell replication by regulatory T-Cell explains the population dynamics of T-Cells. This phenomena is also able to explain the occurrence of hierarchical dominance of T-Cells during an immune response.

References

Kim, Peter, Lee, Peter, Doron, Levy. Emergent Group Dynamics Governed by Regulatory Cells Produce a Robust Primary T Cell Response. *Bulletin of Mathematical Biology* (2009).