Two Signal Cell Activation
Explored with Simple Mathematics

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Abstract

This paper explores the effect of a two-signal activation requirement on immune system cells. By using simple mathematical models I compare different hypotheses about the signalling process in the context of available data. In particular I demonstrate that it is possible to explain the phenomenon of high zone tolerance in this way.

Introduction

There is a great and increasing variety of cells and chemicals known to be involved in the generation of an immune response against infection [1]. The class of cells known as T helper lymphocytes is believed to play a central role in this complex set of interactions, and an understanding of the way such cells respond to stimulation is vital, not only when attempting to build mathematical models of the T helper cell response, but also when trying to understand the immune response as a whole. A characteristic feature of T helper cell stimulation is high zone tolerance: the suppression of proliferation at high doses of specific antigen [2,3,4] (Figure 1).

A number of systems have been characterised where anergy, or unresponsiveness to further stimulation, is induced in T cells following delivery of a stimulus normally expected to induce proliferation. A second, co-stimulatory, signal is required to activate the cell and avoid anergy [5,6]. If the cell does become anergic, it not only fails to proliferate, but becomes refractory to further stimulation, no matter how well presented.

It is clear that this two-signal mechanism imposes a limit to proliferation at high doses, since when the antigen is in excess, the second, antigen-independent signal, becomes the rate-limiting step. My primary aim in this paper is to determine whether the same costimulatory requirement is also sufficient to reduce the proliferation observed at high doses. Further, I wanted to explore, and compare, additional hypotheses about the provision of signals to T cells in the context of available data. In fact, at least one of my apparently reasonable, and relatively similar, models does not conform with the data. Thus it becomes possible to draw conclusions about the induction mechanism from the modelling process. For more details about the background to this work the reader is referred to a forthcoming expansion of the material covered here [7].
Figure 1. Proliferative responses of T cells to varying numbers of antigen presenting cell and dose of antigen redrawn from Matis et al. [14]. The left hand graph shows the data as a function of antigen dose, the second as a function of antigen presenting cell density, and the third as a function of the product of these two numbers.

Mathematical Formulation

My goal is to create simple mathematical models with discriminatory power among different assumptions. In order to do this I have deliberately ignored many possible complicating factors, including questions of density dependence, toxicity and finite proliferative capacity. The broad framework of the models is shown in Figure 3. In all the models, the first step is for a naive T cell to get a first signal from an antigen, presented by an antigen presenting (APC) or macrophage. Once it has received this first signal it moves into a second class in which it either receives the correct second signal and moves into a proliferating class, or fails to receive it and becomes nonfunctional. The second signal is always in contact with an antigen presenting cell.

The differences among the models emerge when we consider how delivery of the second signal is asserted to fail.

In the first model there is a fixed average time in which cells can receive the second signal, while in the second model their responsiveness is terminated by a repeat signal of the presented antigen. The third model follows the first in
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Figure 2. The proliferative response of a T cell clone as a function of macrophage density in the presence of a constant antigen dose. Redrawn from Lamb et al. [2].

assuming that cells require the two signals to move into the proliferating class, but it is when they receive the signal in the proliferating class that they switch to nonresponsiveness.

I can now give the mathematical formulation corresponding to these assumptions.

Model 1: Naive unstimulated cells $T_0$ are stimulated by antigen ($A$) and macrophages ($M$) at a rate $\sigma$ to move temporarily into the $T_r$ class. Once there they are either stimulated by an APC at rate $\mu$ into the proliferating class $T$, or decay at a rate $\kappa$ into a nonfunctional class.

$$
\dot{T}_0 = -\sigma M A T_0 \\
\dot{T}_r = \sigma M A T_0 - \mu M T_r - \kappa T_r \\
\dot{T} = \mu M T_r + \lambda T
$$

I start with an initial number $\tau$ of naive cells, so that at $t = 0$, $T_0 = \tau$, $T_r = T = 0$.

Model 2: The second model is identical to the first save that the rate at which cells move out of the $T_r$ class is now dependent on the density of presented antigen and equal to $\kappa M A$.

$$
\dot{T}_0 = -\sigma M A T_0 \\
\dot{T}_r = \sigma M A T_0 - \mu M T_r - \kappa M A T_r \\
\dot{T} = \mu M T_r + \lambda T
$$
Figure 3. Diagrammatic representation of the models.

**Model 3:** The previous models are modified so that recontact with antigen moves the cells out of the proliferating class.

\[
\begin{align*}
\dot{T}_0 &= -\sigma MAT_0 \\
\dot{T}_r &= \sigma MAT_0 - \mu MT_r \\
\dot{T} &= \mu MT_r + (\lambda - \kappa MA)T
\end{align*}
\]

**Results**

These models are all linear and have explicit if inelegant solutions. This means that it is simple to discover the qualitative behaviour of the models independently of any particular choice of parameter values. Nevertheless it is easiest to illustrate the results with numerical solutions at specific parameter values. All of the qualitative features discussed in this section can be shown to hold, not merely for the particular parameter values for which they are plotted, but also in general, by appropriate mathematical manipulations of the known analytic solutions [7].

Model 1 (Figure 4), perhaps the simplest, fails to reproduce the key feature of high zone tolerance. However, for Model 2 (Figure 5), the dose response curve does come down for large values of \(A\). Moreover, the macrophage dependence is predicted to saturate. Model 3 (Figure 6) also creates the right kind of dose response curve. The macrophage curve is also suppressive at high levels.

I can now compare these qualitative results with those found in experimental data. Matis et al. observed a set of dose-response curves clearly showing high-zone
Figure 4. The dose-response curves generated by model 1. This model fails to generate high-zone tolerance. The response was taken to be the proliferation rate $\lambda T - t$. By suitable rescalings of $M$, $A$ and time we can set the rates $\mu = \kappa = \sigma = 1$. Since the system is linear, the initial condition $\tau$ is irrelevant and we can also set it to 1. This leaves us with the three free parameters $\lambda$, $M$ and $A$, together with a choice for the time $t$ at which the assay is to be performed. Of these, $A$ and $M$ are varied over wide logarithmic ranges in the plots, leaving us with the growth rate $\lambda$ and the time of assay $t$. The effect of changing $\lambda t$ is to change the absolute magnitude of the dose response curves, but not to the relative shapes, provided that we do not take $\lambda t$ too small. I choose $\lambda = 2$ and $t = 1$.

Figure 5. Dose response curves generated by Model 2. This model does generate high zone tolerance, and high levels of macrophage also suppress proliferation. Parameter values as Figure 4.
tolerance [4] (Figure 1). These can be found in many other papers, including one by Lamb et al. [2] which also, interestingly from the current perspective, has a macrophage number-T cell response curve (Figure 2) which appears to saturate at high doses in contrast to the result of Matis et al [4]. Thus model 1 is inconsistent with the observed data, while models 2 and 3 both have data to support them. Given that the observations of the qualitative shape of the macrophage response curve can distinguish between my different models it may prove fruitful to pursue further research in this area.

**Discussion**

I have shown, perhaps unsurprisingly, that two-signal models can indeed provide a consistent explanation of high-zone tolerance. More interestingly, if this is indeed a valid explanation we can draw conclusions about the precise stage at which non-proliferation is induced.

My conclusion is that, under the conditions considered here, it is only when a cell has been successfully stimulated and is proliferating that it is vulnerable to proliferative inhibition by restimulation. This accords with earlier speculation [3] and with recent work on possible biochemical pathways for the inhibition of proliferation [8]. Models in which anergy is only induced at an early stage by the lack of a second signal are incapable of producing the kind of dose-response curves so commonly seen.

While I have explicitly concentrated on events early on in immune responses, it will be possible to use this framework to explore the more general anergic effects
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found upon later restimulation of the cells. It would of course also be possible to include factors such as density-dependent growth into the models, but the added complications and the loss of explicit solutions seem unlikely to be repaid with increased insight. A further refinement would be to the very structure of the model. It may be that my division of the cell population into unactivated and activated cells is artificial, and a more appropriate model would be to represent the mean activation level of the cells in a population (Charlotte Hetzel, Imperial College, unpublished data).

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References


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