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Th1 or Th2: How an Appropriate T Helper Response can be Made

CLAUDIA BERGMANN AND J. LEO VAN HEMMEN

Physik-Department T35,
Technical University Munich,
D-85748 Garching, Germany
E-mail: bergmann@physik.tu-muenchen.de

LEE A. SEGEL

Department of Computer Science and Applied Mathematics,
Weizmann Institute,
IL-76100 Rehovot, Israel

Two types of T helper (Th) cells have been defined on the basis of their cytokine secretion patterns. The decision of a naive T cell to differentiate into Th1 or Th2 is crucial, since to a first approximation it determines whether a cell-mediated or humoral immune response is triggered against a particular pathogen, which profoundly influences disease outcome. Here we show that the internal behaviour of the T helper system, which emerges from regulatory mechanisms 'built into' the T helper system, *itself* can usually select the appropriate T helper response. This phenomenon arises from an initial Th1 bias together with the induction of Th1 $\rightarrow$ Th2 switches when Th1 effectors do not lead to efficient antigen clearance. The occurrence of these shifts is based on the antigen dose dependence of T helper differentiation, which is a consequence of asymmetries in cross-suppression. Critical for this feature is the rate with which Th2 cells undergo antigen-induced cell death.

1. INTRODUCTION

T helper (Th) lymphocytes can be divided into distinct subsets of effector cells based on their functional capabilities and cytokine profiles. Th1 cells, producing IFN-γ and IL-2, help in the induction of delayed-type hypersensitivity responses via macrophage activation and generation of cytotoxic T lymphocytes. In addition, Th1 cells provide limited help for production of those antibody isotypes that promote opsonization. Th2 cells, on the other hand, powerfully trigger B cells to produce and secrete antibodies, in particular, certain isotypes such as IgE and IgA, which neutralize intercellular pathogens and help opsonization, complement, mast cell, and eosinophil activation [for reviews see Mosmann and Sad (1996) and Romagnani (1997)]. Due to these functional differences it is not surprising that Th1 and Th2 cells are not equally efficient in the elimination of a particular

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pathogen. Examples of diseases that can be cleared successfully by type 1 responses are mycobacterial infections such as tuberculosis, leprosy, leishmaniasis, and schistosomiasis—all of them intracellular—and certain viral diseases; Th2 responses on the other hand give protection against helminths and some bacteria such as pneumo- and meningococci.

Th1 and Th2 cells do not arise from distinct lymphocyte lineages but develop from a common precursor called Th0 (Seder and Paul, 1994). Differentiation of $CD4^+$ T-helper cells in response to invasion by an infectious pathogen represents a crucial event in determining the nature and outcome of the immune response, i.e., persistence of the pathogen, protection of the host or immunopathogenesis.

Studies of *in vivo* immune responses have described infectious agents with a predisposition to induce either cell-mediated or humoral forms of immunity. Defense against intracellular pathogens tends to be associated with Th1 dominance and resultant cellular cytolytic activity, whereas resistance to extracellular infectious agents is most often dominated by Th2 effectors, which lead to the production of high levels of antigen-specific immunoglobulins. It therefore seems that the immune system is able to *select* the appropriate immune response, which is triggered by one of the T helper types. Many publications, both experimental and theoretical, have been written to elucidate the influence of a large number of different factors on the Th1/Th2 balance. The principal novelty of the present paper is its attempt to deal with the central problem of to what extent all these factors provide responses that are *appropriate* to the variety of different challenges that the immune system faces.

Concerning the question of how the immune system selects the appropriate T helper type that efficiently destroys a particular pathogen, several possible mechanisms have been proposed:

- Pattern recognition by the innate immune system (Medzhitov and Janeway, 1997).
- 'Diffuse feedback' (Segel and Lev Bar-Or, 1999).
- 'Voting' of memory cells (Borghans and De Boer, 2000).

All these mechanisms require additional information on the pathogen to be provided by other immune system components in the form of signals that promote one T helper type. Here we want to show by means of a mathematical model that the T helper system *itself* can—under certain circumstances—select the most efficient immune response. For this process no additional external information is required because it is based only on the relevant cytokine interactions and on Fas-mediated apoptotic signals.

This paper is organized as follows. Section 2 will review the relevant biological background. We analyse a simple mathematical model in Section 3 in order to understand the internal behaviour of the T helper system in reaction to varying antigen levels. In Section 3.1 we argue for a role of the cell-cycle dependence of the T helper cytokine production in giving an initial Th1 bias. The relevant steady

Table 1. Cytokines produced by Th(i) ($i = 1, 2$) or in the presence of Th(i) cytokines.

T helper subset Th(i) ($i = 1, 2$)	Cytokine produced by T helper subset Th(i)	Cytokine produced in presence of Th(i) cytokines
Th1	IFN-γ	IL-12
Th2	IL-4, IL-10	TGF-β

states and their properties are presented in Section 3.2 and the impact of unequal Th1/Th2 activation and proliferation parameters are analysed in Section 3.3. We study the necessity of Th1 biases in Section 4.1 and discuss the role of antigen dose dependence of the Th1/Th2 ratio in Section 4.2. Finally, we present a mechanism for the selection of the appropriate T helper response in Section 4.3 and discuss the important effects of differences in susceptibility for antigen-induced cell death between Th1 and Th2 cells in that context (Section 4.4).

2. Regulation within the T helper System

We recently presented a model of cytokine-modulated regulation of helper T cell populations under a constant antigenic stimulus (Yates *et al.*, 2000). This model did not consider pathogen removal and growth but concentrated instead on the evolution of the T helper response under antigen exposure, owing to cytokine and Fas/FasL interactions. A novel feature of the model presented here is that we explicitly include antigen clearance and growth.

T helper cells and other immune system components produce cytokines with which immune cells exchange commands or information on the state of the system. The cytokines form a multi-functional signalling network and play important roles in such different stages of the immune response as activation, proliferation, and death. Table 1 summarizes the cytokines that are important for the regulation of the T helper system.

We describe the rate equations for T helper populations in the simple form

$$\text{Rate of change of antigen-specific Th1/Th2 cell population} = \text{differentiation} + \text{proliferation} - \text{death}.$$

At all stages T helper subsets are regulated by cytokines produced by the corresponding or competing T helper type. The main interactions, which we will explain below, are summarized in Fig. 1.

Both T helper subsets exhibit positive feedback on their own differentiation from a naive Th0 state with the help of the cytokines IL-4 for Th2 and a positive loop between IL-12 secreted by antigen-presenting cells (APCs) and IFN-γ for Th1. We assume that there is a sufficient pool of Th0 cells owing to proliferation before they become committed to Th1 or Th2 cells. Therefore we do not model Th0

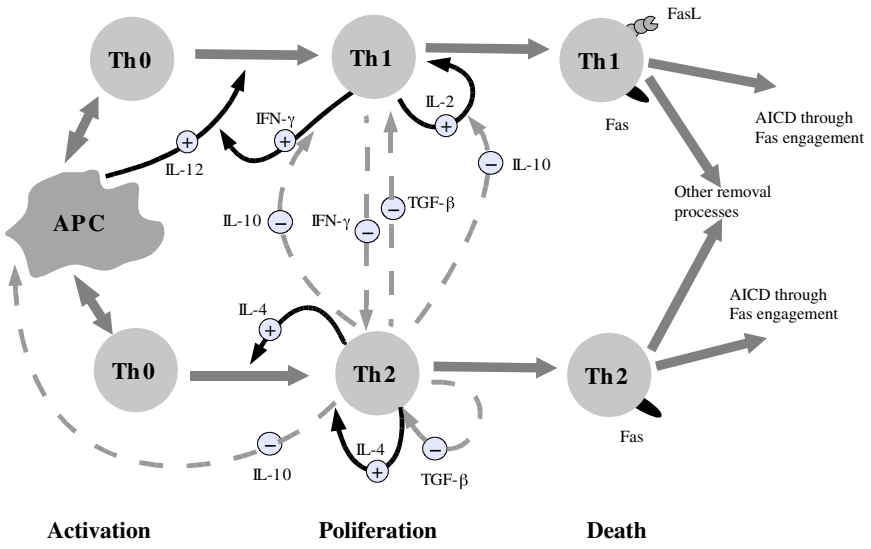

Figure 1. Schematic representation of the interactions governing the T helper system. (AICD = antigen-induced cell death.)

concentrations explicitly. Although activation clearly saturates as a function of the pathogen density, owing to limited antigen presentation capacity, we assume—to keep terms as simple as possible—that only the linear range of the saturation curve is of relevance for our model and thus activation linearly depends on the pathogen concentration and differentiation-driving cytokines. After differentiation, T lymphocyte populations are reinforced by proliferation initiated by growth factors IL-2 and IL-4 that are produced by the T helper subsets Th1 and Th2, respectively. In contrast to the model of Yates *et al*. (2000), we assume that IL-2 and IL-4 induce proliferation and that IL-2 up-regulates FasL on Th1 cells in an autocrine way, which makes the mathematical analysis much simpler. We feel justified in doing so because studies of a system with systemic growth factors have shown that the critical features are not affected by the different roles of IL-2 and IL-4 and that the crucial asymmetries within Th1/Th2 regulation lie in the differences in the cross-suppression and susceptibility for Fas-mediated apoptotic signals and not in the way growth factors act (unpublished observations). In addition, we suggest that the autocrine mode is a much more natural way to act. Why should a T cell that has received a signal to proliferate also encourage its neighbours to proliferate? Note that since the local concentrations of growth factors can be deemed to be constant for each secreting cell, these can be directly incorporated into the proliferation rate.

T helper populations are polarized between Th1 and Th2 by an asymmetric cross-suppression. Whereas the Th1 cytokine IFN-γ inhibits proliferation of Th2 cells, IL-10 secreted by Th2 cells suppresses cytokine production of Th1 cytokines, which indirectly down-regulates proliferation and differentiation of Th1, owing to a lack of growth factors and stimulators of differentiation. Inhibitory effects

Table 2. Biological interpretation of the dimensionless parameters in equations (4), (5) and (6).

Parameter ($i = 1, 2$)	Interpretation
σ_i	Activation strength, weighted for its Th(i)-inducing properties
π_i	Efficiency of growth factors at maintaining activated cells in cycle
δ_i	Susceptibility of Th(i) cells to activation-induced cell death
r	Growth rate of pathogens
ν_i	Pathogen elimination efficiency of Th(i)-induced effectors

of cytokines are represented in our model by saturating Hill functions of the cytokine signal strength, where k^{-1} is the concentration at half-maximum. Additionally, IL-10 exhibits general regulatory effects on activation of naive T cells through down-regulation both of MHC-II expression on APCs and of IL-12 production. We regard this function, together with the inhibiting effect of TGF-β—a cytokine related to Th2—as a mechanism for avoiding explosions of Th2 population sizes under persistent antigen stimulation (Yates *et al*., 2000). Th1 population sizes, however, are limited by activation-induced cell death (AICD). AICD is a process that causes activated T cells to undergo apoptosis after repeated ligation of CD3/TCR. AICD is triggered by Fas-ligand (FasL), which is mainly expressed on activated Th1 cells. AICD appears to be bounded. We suggest that this occurs because of dependence on re-stimulation by APCs, which is limited by antigen presentation capacity. With the same argument as above we neglect these saturation effects. We showed (unpublished observations) that the overall system behaviour is unchanged if we assume some FasL expression in Th2 cells. Here, however, we neglect this for simplicity. Analysis of the susceptibility of T helper cells to activation-induced cell death in response to CD3/TCR ligation indicates that AICD mainly occurs in Th1 clones whereas Th2 clones are more resistant (Varadhachary *et al*., 1999), owing to differences in the Fas signal transduction pathway.

In order to reduce the number of variables, we assume that the majority of important cytokines involved can be classified as either type 1 or type 2, of concentrations S_1 and S_2, according to whether they are produced (perhaps indirectly) predominantly by Th1 or Th2 cells, respectively. The time scales of cytokine production, receptor binding, and decay are typically small compared to those of the cell population dynamics. We therefore make a steady-state assumption for S_1 and S_2 and relate them directly to cell concentrations. The expressions for the cytokine signals

then take the form

$$S_1 = \frac{\alpha_1 T_1}{1 + k\alpha_2 T_2}, \qquad S_2 = \alpha_2 T_2,$$

where the α_i are the proportionality constants.

The preceding discussion yields the following equations:

$$\frac{\mathrm{d}T_1}{\mathrm{d}t} = \underbrace{\frac{\xi_1 P S_1}{1 + kS_2}}_{\text{activation}} + \underbrace{\frac{\beta_1 T_1}{1 + kS_2}}_{\text{proliferation}} - \underbrace{\Delta_1 T_1^2 - \mu T_1}_{\text{death}}, \tag{1}$$

$$\frac{\mathrm{d}T_2}{\mathrm{d}t} = \underbrace{\frac{\xi_2 P S_2}{1 + kS_2}}_{\text{activation}} + \underbrace{\frac{\beta_2 T_2}{(1 + kS_1)(1 + kS_2)}}_{\text{proliferation}} - \underbrace{\Delta_2 T_1 T_2 - \mu T_2}_{\text{death}}, \tag{2}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \varrho P - \omega_1 T_1 P - \omega_2 T_2 P. \tag{3}$$

We rescale to the following dimensionless combinations of variables: $x_i = k\alpha_i T_i$, $p = rP$, $\tau = \mu t$. This gives rise to the dimensionless parameters

$$\sigma_i = \xi_i \alpha_i / \mu r, \qquad \delta_i = \Delta_i / \mu k \alpha_i, \qquad \pi_i = \beta_i / \mu,$$
$$\nu_i = \omega_i / \alpha_i k \mu, \qquad \text{and} \qquad r = \varrho / \mu.$$

(The biological significance of the parameters is summarized in Table 2.) With the above expressions for the cytokine signals S_1 and S_2, the resulting dynamical equations are

$$\frac{\mathrm{d}x_1}{\mathrm{d}\tau} = \frac{\sigma_1 x_1 p}{(1 + x_2)^2} + \frac{\pi_1 x_1}{(1 + x_2)} - \delta_1 x_1^2 - x_1, \tag{4}$$

$$\frac{\mathrm{d}x_2}{\mathrm{d}\tau} = \frac{\sigma_2 x_2 p}{(1 + x_2)} + \frac{\pi_2 x_2}{(1 + x_1 + x_2)} - \delta_2 x_1 x_2 - x_2, \tag{5}$$

$$\frac{\mathrm{d}p}{\mathrm{d}\tau} = p(r - \nu_1 x_1 - \nu_2 x_2). \tag{6}$$

3. ANALYSIS

In our analysis we will address the following issues:

- Can the T helper system *itself* choose the most appropriate T helper type?
- What are the important parameters for the decision-making process?
- Under which conditions does the choice mechanism work? What is the role of AICD?

- Is there any role for apparent artefacts such as antigen dose dependence of T helper differentiation and cell-cycle dependence of cytokine production?
- Are there any default responses? If so, what are they?
- Under which conditions do infections become chronic? Is it equally likely for Th1- or Th2-dominated situations to become chronic?

3.1. ***Initial conditions.*** What are the initial conditions for our model? We consider as initial conditions the state at the beginning of the period during which the model is expected to be valid, not the situation at the beginning of the experiment. If the adaptive immune system is challenged with a particular pathogen that it has not seen before, then antigen peptides are presented to not-yet-differentiated Th0 cells, which produce—apart from the growth factor IL-2—the Th1 and Th2 cytokines IL-4 and IFN-γ. On the population level this can be interpreted as low levels of Th1 and Th2 populations. This resolves the mathematical bootstrap situation where—in the absence of stimuli from other immune system components—new T helper cells of both phenotypes can only be generated in the presence of Th1/Th2 signals, which in turn rely on already existing T helper populations. In our integrations we therefore consider the initial conditions for a truly naive response, with no assistance from cross-reactive memory T cells, as represented by trajectories beginning at low initial values of Th1 and Th2.

Effector cytokine expression has been shown to be cell-cycle dependent. IFN-γ expression increases in frequency with successive cell cycles, while IL-4 secretion does not start before three cell divisions are completed (Bird *et al.*, 1998). These relationships were consistent regardless of time-dependent variation in the distribution of Th1 and Th2. Additionally, it has been shown that IFN-γ mRNA is induced within 6 h in activated, IL-12 primed cells, while IL-4 mRNA is induced only after 48 h, even when cells are cultivated in the presence of rIL-4 (Lederer *et al.*, 1996). Therefore cell cycle provides fundamental order to the differentiation of Th cells. A naive cell is increasingly likely to become a Th1 cell after each successive cell cycle, but can only become a Th2 cell when eight siblings have been born. Due to the cell-cycle dependence of cytokine patterns we assume that initial values for Th1 are higher than those for Th2, which gives the system an initial Th1 bias. In Section 4.1 we will argue for the *need* for a Th1 bias.

3.2. ***Steady states and their stability.*** To keep the number of free parameters small, because of lack of data, and to extract a system behaviour independent of preferences for one of the T helper types, we assume that proliferation and activation rates of Th1 and Th2 cells are equal: $\sigma_1 = \sigma_2 = \sigma, \pi_1 = \pi_2 = \pi$. Implications of unequal parameters will be discussed in the Appendix.

We are only interested in steady states in the positive quadrant. We analyse the conditions for existence and stability of those fixed points, which will be represented by a vector $\Omega = (x_1, x_2, p)$.

- naive state: $\Omega_{\text{naiv}} = (0, 0, 0)$, with eigenvalues $\{\pi - 1, \pi - 1, r\}$. This steady state is never stable, since we assume that the proliferation rate is high enough to counterbalance cell death, i.e., $\pi > 1$.
- 'cure:Th2': $\Omega_{\text{cure:Th2}} = (0, \pi - 1, 0)$. Eigenvalues for this fixed point are $\{0, -1 + 1/\pi, r + \nu_2(1 - \pi)\}$. It only becomes stable if Th2-induced effectors are efficient enough in pathogen destruction and elimination, i.e., if $\nu_2 > r/(\pi - 1) > 0$. Otherwise antigen is persistent and infection becomes chronic. The smaller the replication rate r for the pathogen, the larger is the set of initial conditions that lead to antigen clearance.
- 'chronic:Th2':

$$\Omega_{\text{chronic:Th2}} = \left(0, \frac{r}{\nu_2}, \frac{r}{\sigma\nu_2} + \frac{1-\pi}{\sigma}\right)$$

  with eigenvalues

$$\lambda_1 = \frac{-r + \nu_2(\pi - 1)}{(r + \nu_2)^2}, \quad \lambda_{2,3} = \frac{-r \mp \sqrt{r(r - 4(r + \nu_2)(r + \nu_2(1 - \pi)))}}{2(r + \nu_2)}.$$

  The condition $r + \nu_2(1 - \pi) > 0$ that $\Omega_{\text{chronic:Th2}}$ has to be in the first quadrant implies that—if the steady state exists—all eigenvalues have negative real parts. The more destructive the Th2 effectors are (larger ν_2), the less Th2 effectors and antigen are involved in the chronic interactions. Increasing ν_2 exchanges stability between a Th2-dominated chronic infection and a successful Th2 response, leading to cure.
- 'cure:Th1': $\Omega_{\text{cure:Th1}} = (\frac{(\pi-1)}{\delta_1}, 0, 0)$. Study of the eigenvalues

$$\left\{1 - \pi, -1 + \frac{\delta_1\pi}{(-1 + \delta_1 + \pi)} - \frac{\delta_2(\pi - 1)}{\delta_1}, r + \frac{\nu_1(1 - \pi)}{\delta_1}\right\}$$

  shows that the efficiency of Th1-induced effectors determines whether antigen is cleared by Th1 effectors or remains persistent in a chronic situation. If $\nu_1 > \delta_1 r/(\pi - 1)$ and $\delta_2 > \delta_1(\delta_1 - 1)/(\delta_1 + \pi - 1)$, then this steady state is stable. If $\nu_1 < \delta_1 r/(\pi - 1)$ the system ends up in Th1- or Th2-dominated chronic situations or antigen is cleared by Th2 effectors, depending on other parameters such as ν_2 and on the initial conditions.
- 'chronic:Th1':

$$\Omega_{\text{chronic:Th1}} = \left(\frac{r}{\nu_1}, 0, \frac{\delta_1 r}{\sigma\nu_1} + \frac{1-\pi}{\sigma}\right).$$

  A necessary condition for existence of this steady state is $\nu_1 < \delta_1 r/(\pi - 1)$; this is the case if the first eigenvalue of 'cure:Th1' is positive, which is equivalent to a situation where 'cure:Th1' is unstable. The last two eigenvalues

$$\lambda_{2,3} = \frac{-\delta_1 r \mp \sqrt{{\delta_1}^2 r^2 - 4r\nu_1(\delta_1 r + \nu_1(\pi - 1))}}{2\nu_1}$$

always have negative real parts if the existence condition is fulfilled. The first eigenvalue

$$\lambda_1 = \frac{(\delta_1 - \delta_2)r}{\nu_1} - \frac{\pi r}{(r + \nu_1)}$$

becomes negative if $\nu_1 > r(\delta_1 - \delta_2)/(\pi - \delta_1 + \delta_2)$. The two conditions for stability and existence can only be fulfilled simultaneously if $\delta_2 > \delta_1(\delta_1 - 1)(\delta_1 + \pi - 1))$. For this choice of δ_2 there exists a parameter window—illustrated in Fig. 3—where Th1-chronic is stable; the width of this window is dependent on the rate with which Th2 cells undergo AICD. Note that AICD for Th2 only influences the stability of both types of Th1-dominated steady states 'cure:Th1' and 'chronic:Th1'. We will come back to this issue in Section 4.4.

- 'cure:Th1/Th2':

$$\Omega_{\text{cure:Th1/Th2}} = \left(-\frac{\delta_1 + \delta_2 - \sqrt{\delta_1 - \delta_2}\sqrt{\delta_1 - \delta_2 + 4\delta_1\delta_2\pi}}{2\delta_1\delta_2}, \right.$$
$$\left. \frac{\delta_1(1 - 2\delta_1 - 2\delta_2) - \delta_2 + \sqrt{\delta_1 - \delta_2}\sqrt{\delta_1 - \delta_2 + 4\delta_1\delta_2\pi}}{2\delta_1(\delta_1 - \delta_2)}, 0 \right).$$

  We have analysed the stability of this steady state numerically for a wide range of parameters. The result is that it cannot be stable and positive at the same time, because conditions for existence and stability are incommensurable. This is illustrated for typical parameters in Fig. 2.
- 'chronic:Th1/Th2': Steady states with coexistence of Th1 and Th2 under persistent antigen stimulation cannot be calculated analytically. Instead, we have investigated large parameter ranges numerically and find that chronic situations are polarized in their T helper response.

The conditions for existence and stability of the relevant steady states are summarized in Table 3. The main features of the steady-state analysis are summarized in Fig. 3, a diagram of the two-dimensional pathogen-elimination parameter space (ν_1, ν_2). From this analysis we reach the following conclusions.

- After pathogen elimination our system ends up in a non-zero Th1-dominated or Th2-dominated steady state. To keep the analysis simple and to fully concentrate on T helper regulation during the ongoing immune response we did not incorporate into the model that T helper cells, which have fulfilled their task, will partly become deactivated or memory cells of the same T helper subset. Therefore the states 'cure:Th1' and 'cure:Th2' could also be interpreted as memory states.
- If only one T helper type leads to pathogen destruction ($\nu_1 \approx 0, \nu_2 > 0$ or $\nu_2 \approx 0, \nu_1 > 0$) we find bistability either with a successful Th1 response and a chronic Th2-dominated situation or vice versa. This means that initial conditions decide whether pathogen clearance or chronic disease is obtained.

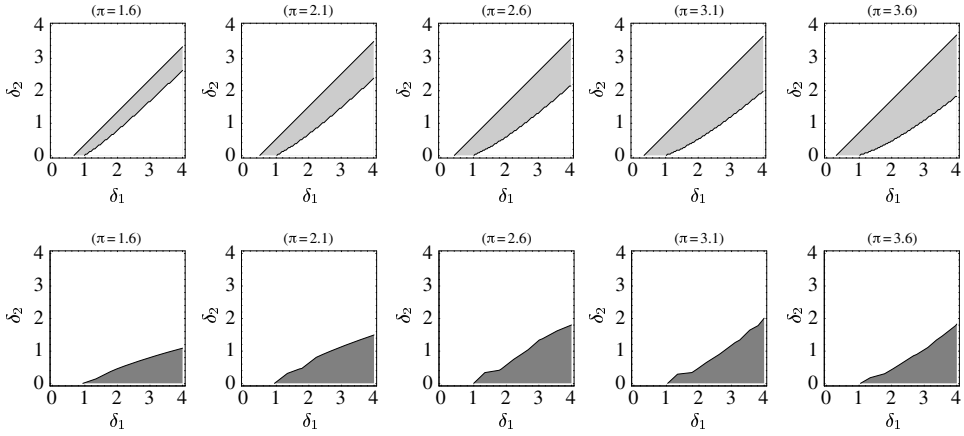

Figure 2. Existence and stability of the 'cure:Th1/Th2' steady state. For different values of the proliferation rate π we plot areas of stability (dark grey) and areas where the 'cure:Th1/Th2' steady state is in the positive quadrant (light grey) on the AICD parameter plane. These two conditions are not fulfilled simultaneously, implying that a steady state with coexisting populations of Th1 and Th2 after antigen clearance cannot be reached. The remaining parameters are $\sigma = 2$, $r = 1$, $\nu_1 = 2$, and $\nu_2 = 0.01$, which reflect scenarios with the largest areas of existence and stability for the parameter ranges that have been studied.

- Although T helper responses will be polarized towards one of the phenotypes after reaching the steady states we find a transient coexistence of both. Trajectories that reach the pure Th2 steady state often exhibit long 'detours'; an initial Th1 dominance is later taken over by Th2 dominance. This is illustrated in Fig. 4.
- The rate with which Th2 cells undergo AICD does not change the location and local stability of both Th2-dominated steady states but decreases the real parts of the eigenvalues corresponding to the Th1-dominated steady states and in that sense stabilizes them.

Table 3. Steady states and conditions for their existence and stability. As noted in the text, we assume that $\pi > 1$.

Steady state	Existence	Stability
naive state	exists always	$\pi < 1, r < 0$
'cure:Th2'	$\pi > 1$	$\nu_2 > r/(\pi - 1)$
'chronic:Th2'	$\nu_2 < r/(\pi - 1)$	stable when existent
'cure:Th1'	$\pi > 1$	$\nu_1 > \frac{\delta_1 r}{\pi - 1}, \delta_2 > \frac{\delta_1(\delta_1 - 1)}{\delta_1 + \pi - 1}$
'chronic:Th1'	$\nu_1 < \frac{\delta_1 r}{\pi - 1}$	$\nu_1 > \frac{r(\delta_1 - \delta_2)}{\pi - \delta_1 + \delta_2} \Rightarrow \delta_2 > \frac{\delta_1(\delta_1 - 1)}{\delta_1 + \pi - 1}$
'chronic:Th1/Th2'	not existent if δ_2 small enough	not stable if δ_2 small enough

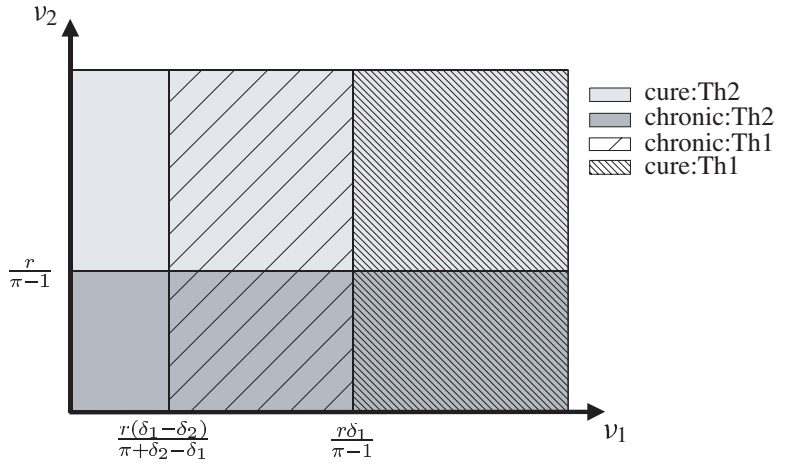

Figure 3. Existence and stability are marked by different shadings in the two-dimensional pathogen-elimination parameter plane (ν_1, ν_2) for $\delta_1 > 1, \pi > 1$, and $\delta_1 > \delta_2 > \delta_1(\delta_1 - 1)/(\delta_1 + \pi - 1)$.

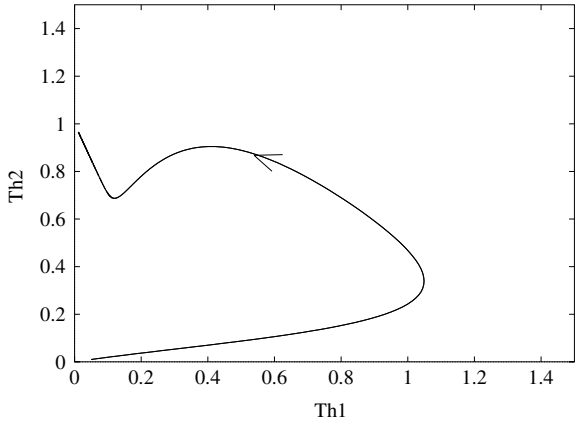

Figure 4. Transient coexistence of Th1/Th2 populations. Depicted is a trajectory in the Th1/Th2 state space with the initial condition $x_1(0) = 0.05, x_2(0) = 0.01, p(0) = 0.1$ with a bias towards Th1 because of the cell-cycle dependence of cytokine production. Transient Th1 dominance and coexistence is followed by Th2 dominance. Parameters are $\sigma = 2, \pi = 2, \delta_1 = 2, \delta_2 = 1, r = 1, \nu_1 = 0.1, \nu_2 = 2$. Here and in several figures below, for ease in interpretation we label curves Th1 and Th2, instead of x_1 and x_2.

The linear stability analysis shows what parameter domains are associated with suitable and interesting behaviour, i.e., $\delta_1 > 1, \pi > 1, \delta_1 > \delta_2, \delta_2 > \delta_1(\delta_1 - 1)$. Here we argue that these parameter choices are reasonable assumptions. Defects in either Fas or FasL can result in an autoimmune lymphoproliferative syndrome (Ju *et al*., 1999). Due to the importance of AICD in resolving immune responses we assume that removal by Fas-mediated AICD is more important than loss by other mechanisms; this means that $\delta_1 > 1$. Moreover we argue that—because of the importance of clonal expansion during an immune response—proliferation must be more important than T cell loss, i.e., $\pi > 1$. Experiments concerning AICD rates of Th2 cells (Varadhachary *et al*., 1999) showed that Th2 cells are more resistant to AICD than Th1 cells, i.e., $\delta_1 > \delta_2$, but not totally resistant ($\delta_2 > 0$). In our further analysis—if not stated otherwise—we take a representative set of parameters in the relevant domains.

3.3. ***Unequal proliferation and activation parameter.*** For simplicity we set the activation and proliferation parameters of both T helper subsets to equal values. Now we wish to discuss consequences of unequal parameter settings.

A detailed analysis of the steady states and their stability for unequal parameter settings of activation and proliferation parameters can be found in the Appendix. In summary, we find the following.

- Higher activation rates of one T helper type generally stabilize 'chronic' steady states dominated by the corresponding T helper subset, and destabilize chronic situations dominated by the competing T helper type. As a consequence, increasing σ_1 and σ_2 respectively enlarge and reduce the size of the parameter window for stability of 'chronic:Th1'. This is illustrated in Fig. 5.
- Higher efficiency of Th2 growth factors stabilizes Th2-dominated steady states and destabilizes Th1-dominated steady states and vice versa. With increasing π_2 the stability of 'chronic:Th1' is lost. Increasing π_1, however, decreases the lower boundary of the 'chronic:Th1' stability parameter window, which is given by the stability condition, but also decreases the upper boundary given by the existence condition. Effects on the size of the parameter window are illustrated in Fig. 6.
- The overall behaviour of the system is not affected by choices of activation and proliferation parameters.

4. INTERPRETATION

4.1. ***Obtaining a Th1-dominated response.*** In order to obtain a Th1-dominated immune response in our model, the presence of a Th1 bias is essential. This is particularly important if a Th1 response is the desired one ($\nu_1 > \nu_2$). In Fig. 7 we

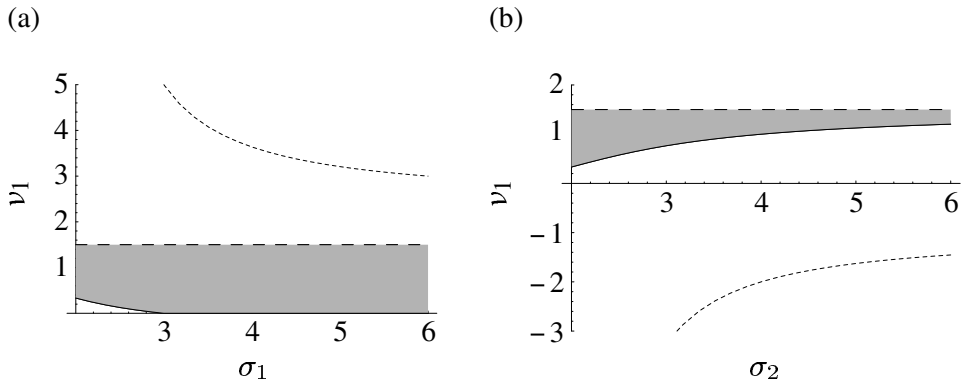

Figure 5. Upper and lower boundaries of the parameter window where 'chronic:Th1' is stable as a function of the activation parameters $\sigma_{1,2}$. Dashed lines represent the condition for existence, and dotted (solid) lines the condition for stability represented by B_1 (B_2), cf. the Appendix. For parameters that lie in the area between the solid and dashed line, 'chronic:Th1' is stable (shaded area). (a) $\sigma_1 > \sigma_2$. Increasing Th1-activation strength leads to extension of the parameter window where 'chronic:Th1' is stable. For Th1-activation strengths above a certain threshold the lower boundary is lost. (b) Higher Th2-activation parameters reduce the size of the parameter-window. The remaining parameters are $\sigma_i = 2$, $\pi = 2$, $\delta_1 = 1.5$, $\delta_2 = 0.5$, and $r = 1$.

show basins of attraction for a parameter setting where—depending on the initial conditions—the system can end up in a successful Th1-dominated immune response or in a chronic Th2-dominated disease state. We find that symmetrical initial conditions or symmetrical parameters for the two T helper subsets will always lead to the latter case. The important fact that initial antigen dose also influences the basins of attraction will be discussed in Section 4.2.

According to our model there are several alternatives for a Th1 bias. Theoretically, a Th1 bias can arise due to unequal initial concentrations (also see Section 3.1), higher efficiency of Th1 growth factors, higher Th1 activation or Th1-promoting APC-derived signals. If IL-2 were a more efficient inducer of Th1 proliferation than IL-4 is as an inducer of Th2 proliferation, leading to different proliferation parameters $\pi_1 > \pi_2$, we would find that a Th2-dominated state could never be attained. We therefore conclude that discrepancies in proliferation should be neglected as a possible source for the Th1 bias—for a well-working immune system must retain the option of a Th2 response. Which of the other possibilities might be relevant in nature, and under which circumstances, has still to be investigated. In summary, a Th1 bias is needed to attain Th1 dominance if this is the desired immune response. This bias, however, also increases the risk of chronic Th1 infections.

4.2. ***Influence of the initial antigen concentration.*** According to our model—as illustrated for an effective Th1-dominated situation in Fig. 7—increasing initial antigen levels promote the development of Th2 dominance whereas lower anti-

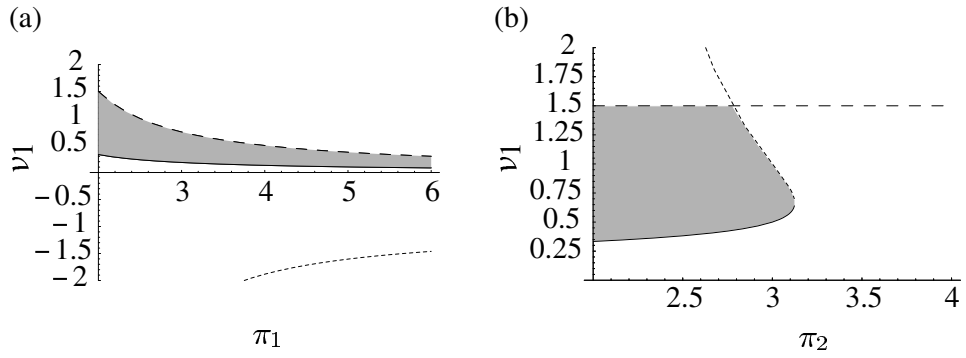

Figure 6. Upper and lower boundaries of the parameter window where 'chronic:Th1' is stable as a function of the proliferation parameters $\pi_{1,2}$. Dashed lines represent the condition for existence, and dotted (solid) lines the condition for stability represented by B_1 (B_2), cf. the Appendix. For parameters that lie in the shaded area, 'chronic:Th1' is stable. (a) $\pi_1 > \pi_2$. Increasing Th1-proliferation strength leads to extension of the lower boundary of the parameter window where 'chronic:Th1' is stable. (b) Higher Th2-activation parameters reduce the size of the parameter window. For values of π_2 above a certain threshold the stability of 'chronic:Th1' is lost. The remaining parameters are $\sigma_i = 2$, $\pi = 2$, $\delta_1 = 1.5$, $\delta_2 = 0.5$, and $r = 1$.

gen doses favour Th1. If Th2 cells instead of Th1 cells are effective in attacking the pathogen, the Th1 bias leads to a transient Th1 dominance, which—as Fig. 8 shows—is rapidly taken over by Th2 cells because of the high antigen levels.

The antigen dose dependence presented above is a consequence of asymmetries in cross-regulation and different susceptibilities of the two T helper subsets for AICD. Crucial for this effect is that IL-10 secreted by Th2 lymphocytes inhibits cytokine secretion of Th1 cells, which results in an indirect inhibition of proliferation and activation, whereas Th1 cytokines only inhibit Th2 proliferation. The inhibition of activation becomes more important with increasing intrinsic activation strength.

At first glance the fact that antigen dose *alone* can alter the Th1/Th2 ratio seems to make no sense in terms of a selection of a correct T helper response against a particular pathogen. When we look more closely, however, we find a built-in self-organizing mechanism for a decision-making process based on the occurrence of Th1 $\rightarrow$ Th2 switches when antigen concentrations increase sufficiently. In situations wherein initial Th1 responses are ineffective and thus antigen concentrations reach high levels—a situation that favours Th2 dominance—Th1 $\rightarrow$ Th2 switches are accelerated, leading to an appropriate Th2 response. However, if pathogens replicate rapidly then antigen concentrations sufficiently high to induce a Th1 $\rightarrow$ Th2 switch may be reached even when Th1-induced effectors are efficient in pathogen destruction. In such, dangerous, situations it would appear that additional Th1-promoting signals from other immune system components such as the innate immune system may be necessary in order to reinforce the Th1 response.

Experimentally, antigen dose has indeed been shown to influence the class of

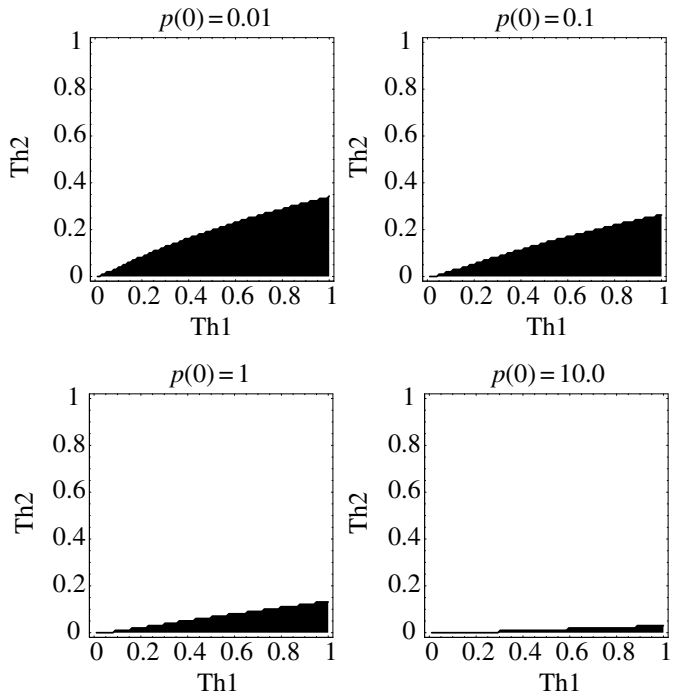

Figure 7. The dependence of Th1 dominance on a Th1 bias. For different values of initial antigen values, basins of attraction of the two stable steady states 'cure:Th1' (black areas) and 'chronic:Th2' (white areas) are plotted. In Section 3.1 we pointed out that initial conditions are represented by low and Th1-biased concentrations. Because absolute values are not known we study a whole range of possibilities. For equal initial conditions for the two T helper subsets 'cure:Th1', the appropriate T helper response for this setting of ν_1 and ν_2 is never reached. If Th1 is favoured initially, then for a sufficiently weak antigenic challenge a successful Th1 response can be attained. Parameters are $\sigma = 2$, $\pi = 2$, $\nu_1 = 2$, $\nu_2 = 0.1$, $\delta_1 = 1.5$, $\delta_2 = 0.5$ and $r = 1$.

immune response but the direction of influence is controversial. Some authors (Bretscher *et al*., 1992; Bancroft *et al*., 1994; Doherty and Coffman, 1996; Sarzotti *et al*., 1996; Menon and Bretschner, 1998) have found that low doses of antigen result in Th1 cells producing IFN-γ and undetectable levels of IL-4, whereas increasing the dose leads to disappearance of Th1 and development of IL-4-producing Th2 cells. Our findings support this relationship. In addition, Menon and Bretschner (1998) investigated time courses of cytokine production and found that at high antigen doses Th1 cytokines initially dominate but that the cytokine pattern switches to Th2, which correlates with our findings presented in Fig. 8. However, there is a report (Hosken *et al*., 1995) that at extremely low doses of antigen, IL-4 production is favoured, indicating Th2 dominance. Similarly, recent findings (Grakoui *et al*., 1999; Rogers and Croft, 1999) suggest that Th2 predominates at lower levels of initial signaling, whereas high doses of high affinity peptides lead to IFN-γ-secreting Th1 helper cells. With our present model we cannot explain these latter

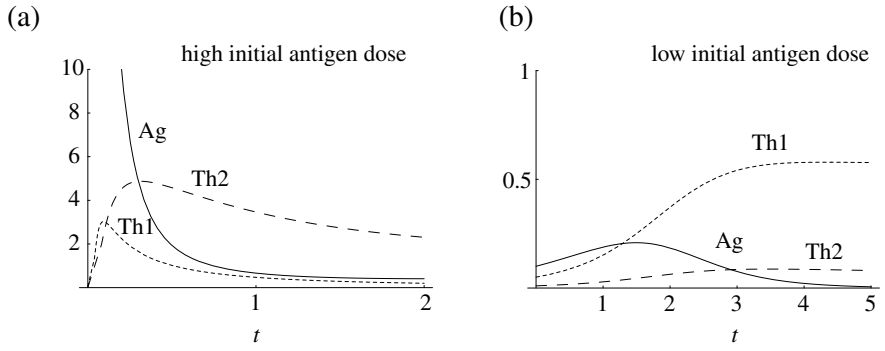

Figure 8. Time plots showing antigen (Ag) dose dependence. (a) The Th1 bias promotes Th1 but high antigen doses ($p(0) = 50$) induce a rapid shift to Th2 dominance. (b) At low initial antigen levels ($p(0) = 0.1$) Th1 eliminates the antigen and the initial Th1 bias is maintained. The remaining parameters are $\sigma = 2$, $\pi = 2$, $\delta_1 = 1.5$, $\delta_2 = 0.5$, $\nu_1 = 4$, $\nu_2 = 0.1$, and $r = 1$. Cell-cycle dependence of cytokine production leads to unequal initial T helper concentrations $x_1(0) = 0.05$, $x_2(0) = 0.01$.

findings. The defect may lie in our simplified representation of T helper cell–APC interactions. A more elaborate model might well need to incorporate the influences of co-stimulatory signals, APC-derived signals, time courses of cytokine production and spatial aspects in the antigen presentation. And of course the different experimental findings may lie in as yet unidentified differences in the experimental conditions.

4.3. ***Choice of the appropriate T helper response.*** We now examine more carefully the important result that in many circumstances the T helper system itself can select the appropriate T helper response that leads to successful antigen clearance. In Fig. 9 we show the temporal development of T helper and antigen concentrations for different types of pathogens (typically intracellular or extracellular) where different types of T helper responses are required. In both cases the system selects the efficient T helper type and clears the antigen. The strategy is

(1) try Th1 first,
(2) induce a Th1 $\rightarrow$ Th2 switch if Th1 has not been successful.

For fast replicating intracellular pathogens the above strategy fails. Because pathogens cannot be cleared sufficiently rapidly a Th1 $\rightarrow$ Th2 shift is induced *before* antigen has been eliminated (see Fig. 10). In that case an appropriate response requires further reinforcement of the appropriate T helper response.

4.4. ***Role of the susceptibility for Fas-mediated AICD.*** We now show that for our model the important findings of Section 4.3 rely on the asymmetry in susceptibility to AICD of Th1 and Th2 lymphocytes.

Let us first assume that Th2 cells are totally resistant to AICD, i.e., $\delta_2 = 0$. Only the two Th1-dominated steady states are affected by δ_2. As a necessary condition

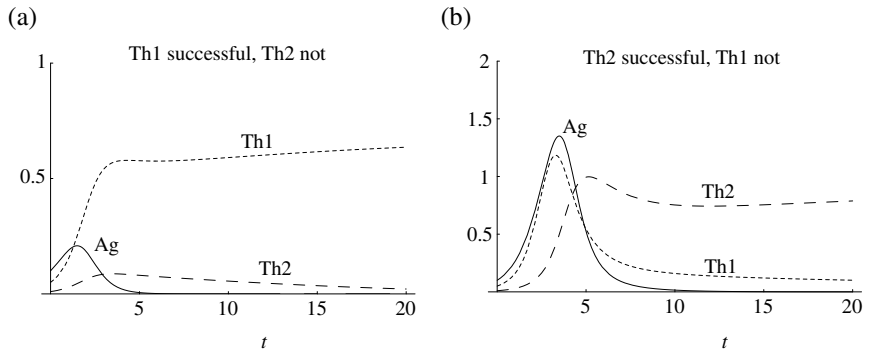

Figure 9. Time plots showing the self-organized selection of the appropriate T helper response. (a) Th1-responsive antigen is successfully cleared by Th1: $\nu_1 = 2$, $\nu_2 = 0.01$. (b) For a Th2-responsive antigen ($\nu_1 = 0.01$, $\nu_2 = 2$) a Th1 $\rightarrow$ Th2 switch is induced by early antigen proliferation; then the humoral response leads to pathogen destruction. The remaining parameters are $\sigma = 2$, $\pi = 2$, $\delta_1 = 1.5$, $\delta_2 = 0.5$, and $r = 1$. The initial concentrations for T helper cells are asymmetric: $x_1(0) = 0.05$, $x_2(0) = 0.01$.

for stability for these steady states we found that $\delta_2 > \frac{\delta_1(\delta_1-1)}{\delta_1+\pi-1}$. Recall from Section 3.2 that due to the importance of AICD in T cell homeostasis we assume that $\delta_1 > 1$, which implies that stability requires δ_2 to be sufficiently large. Therefore sufficiently high susceptibility of Th2 for AICD is essential for the accessibility of Th1-dominated immune responses. If δ_2 is too small then bistability of 'cure:Th1' and 'chronic:Th2' or 'chronic:Th1' and 'cure:Th2' is lost (see Fig. 3). This phenomenon is illustrated in Fig. 11(b).

On the other hand, comparable susceptibilities for the Fas-mediated apoptotic signal of Th1 and Th2 cells ($\delta_1 \approx \delta_2$) lead to the loss of Th1 $\rightarrow$ Th2 switches (as demonstrated in Fig. 12), which is crucial for the ability to select the appropriate T helper response. High δ_2 values strongly stabilize both Th1-dominated steady states and extend their basins of attraction. If purely Th2-induced effectors lead to pathogen destruction this favours the development of chronic Th1-dominated T helper responses with very high transient antigen load. Additionally, as illustrated in Fig. 11(b), the parameter window in the (ν_1, ν_2)-space where 'chronic:Th1' is stable is expanded, leading to bistability of 'cure:Th2' and 'chronic:Th1' even for very low efficiency of Th1-induced effectors ($\nu_1 \approx 0$). That increases the risk of chronic Th1-dominated situations.

In the case of inefficient Th1 effectors ($\nu_1 \approx 0$) we also find that elevating the susceptibility of Th2 for Fas-mediated apoptosis not only increases the risk of Th1-dominated chronic diseases but also increases the risk of chronic infections with coexisting T helper populations. This is illustrated in the Appendix.

In Section 3.2 we cited experimental support for our assumption that susceptibility of Th2 lymphocytes for AICD is less than that of Th1 cells but greater than zero. According to our model, a well-balanced susceptibility of Th2 for AICD leads to the selection of the appropriate T helper response while minimizing the risk of

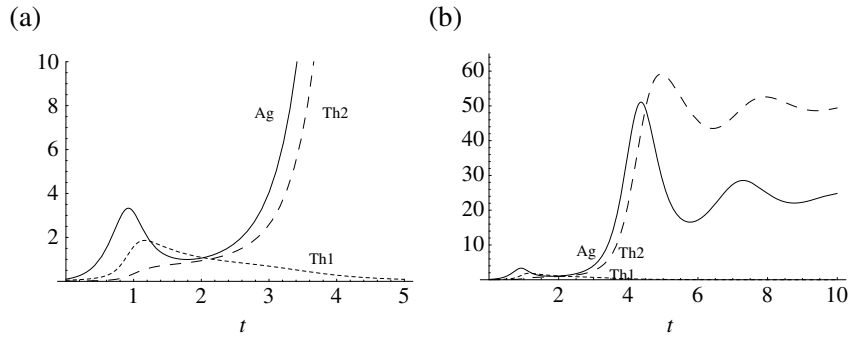

Figure 10. Time plots showing failure of the default strategy for fast replicating pathogens. The correct Th1-dominated response is switched into a Th2-dominated response (a) because antigen cannot be eliminated sufficiently rapidly, owing to its high rate of replication. The antigen and Th2 concentrations reach high levels before the system settles into a chronic Th2-dominated state (b). The remaining parameters are $\sigma = 2$, $\pi = 3$, $\delta_1 = 1.5$, $\delta_2 = 0.5$, $\nu_1 = 4$, $\nu_2 = 0.1$, and $r = 5$. The initial concentrations for T helper cells are asymmetric: $x_1(0) = 0.05$, $x_2(0) = 0.01$.

chronic Th1-dominated diseases. We therefore suggest that evolutionary pressure has selected the Fas-mediated AICD rate of Th2 cells in order to minimize damage to the host. Additionally, we predict that—when we leave aside autoimmune diseases, which we assume to be importantly affected by influences that we did not consider here—chronic infections are more likely to be Th2 dominated than Th1 dominated.

5. SUMMARY AND DISCUSSION

The importance of the balance between Th1 and Th2 cell subsets and their influence on the development of different immune responses has been well established. However, the influences that guide the initial activation of one particular T helper type are not clearly understood. A number of potentially important elements have been proposed, among them the overall cytokine milieu, the presence of co-stimulatory molecules, the dose of antigen, the nature of the early antigen-presenting cell, and influences of components of the innate immune system arising from pattern recognition of infectious agents. One approach to Th1/Th2 selection is to search for some sort of dominant controller that is responsible for the decision-making process. Yet it has proved difficult to single out a single dominant factor, since all the different factors interact. Accordingly, we view the T helper cells as a self-organizing system that is able to make the decision itself by means of regulatory mechanisms from within the system that influence the activation and differentiation step (see Fig. 13).

Recently we presented a model of cytokine-modulated regulation of helper T cell populations under a constant antigenic stimulus (Yates *et al.*, 2000). This model

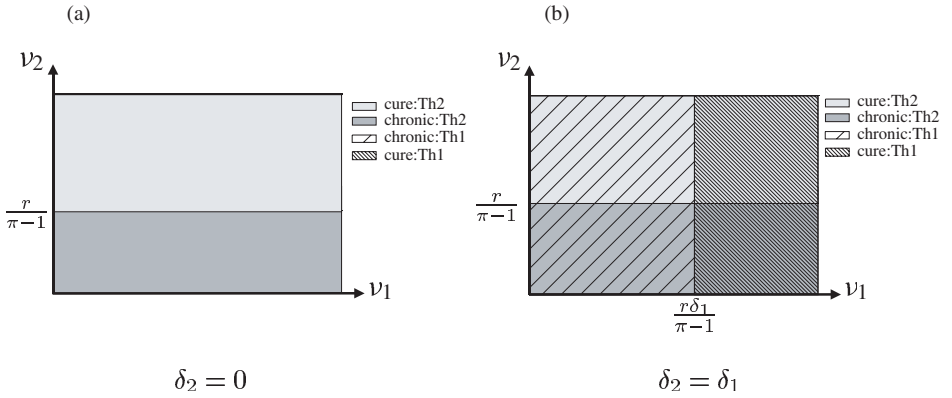

Figure 11. Stability diagram for the relevant steady states in the pathogen-elimination parameter space (ν_1, ν_2). For AICD-resistant Th2 cells, i.e., $\delta_2 = 0$ (a) the stability of the Th1-dominated steady states is lost. For high values of δ_2 (b) the risk of chronic Th1-dominated infections is increased.

did not consider pathogen removal and growth but concentrated instead on the evolution of the T helper response under antigen exposure controlled by cytokine and Fas/FasL interactions. We concluded from this model that the dominant T helper subset of an immune response with persistent antigen is determined by the strengths of activation signals, which are correlated with the antigen concentration. Low antigen levels lead to Th1 dominance whereas higher levels favour Th2 dominance. This is due to asymmetries in the cross-regulation of the two T helper subsets: Th2 cytokines inhibit (directly or indirectly) activation of Th1 but there is no corresponding inhibition of Th2 activation by Th1 cytokines. Moreover, switches from Th1 to Th2 dominance are a common feature for wide parameter ranges and arise from unequal Fas-meditated apoptosis for the two T helper subsets and from asymmetries in the nature of cross-suppression. These conclusions still held if we assumed that growth factors act in an autocrine rather than systemic way (unpublished observations).

In the context of how the immune system can select the appropriate T helper response we interpreted these results in the following way.

- Failure in antigen clearance is a sign of an insufficient T helper response.
- Shifts from Th1 to Th2 predominance under these circumstances could mean that there are mechanisms within the T helper system that somehow allow a switch to a different type of T helper response if the one triggered first did not lead to pathogen elimination.

The present model is based on a simple mathematical model, which explicitly (albeit with considerable approximation) incorporates most of the known regulatory cytokine interactions within the T helper system and the interplay between the immune system—initiated by T helper subsets—and pathogens. Here is a summary of our conclusions.

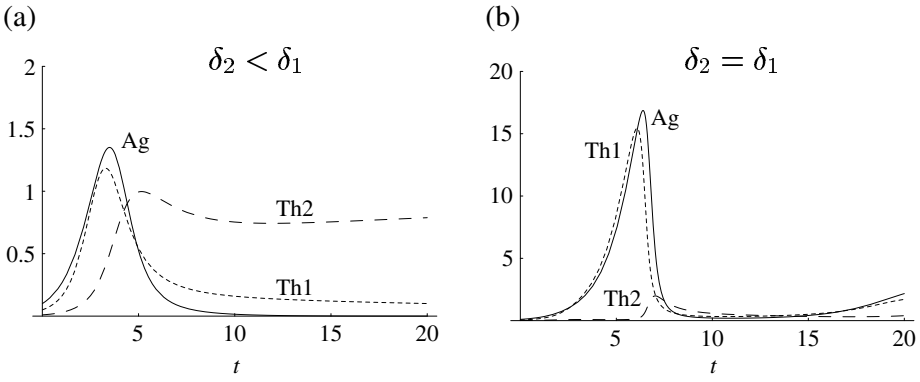

Figure 12. Time plots showing presence and absence of a Th1 → Th2 switch, depending on the resistance of Th2 cells to AICD. (a) If Th2 are more resistant to AICD than Th1 ($\delta_2 = \delta_1/3$) then a Th1 → Th2 switch is induced if Th1 is not effective; after this switch the humoral response leads to pathogen destruction. (b) Comparable susceptibility of Th1 and Th2 to AICD ($\delta_2 = \delta_1$). Antigen and Th1 concentrations reach very high values before Th2 effectors diminish the antigen load. The remaining parameters are $\nu_1 = 0.01$, $\nu_2 = 2$, $\sigma = 2$, $\pi = 2$, $\delta_1 = 1.5$, and $r = 1$. The initial concentrations for T helper cells are unequal: $x_1(0) = 0.05$, $x_2(0) = 0.01$.

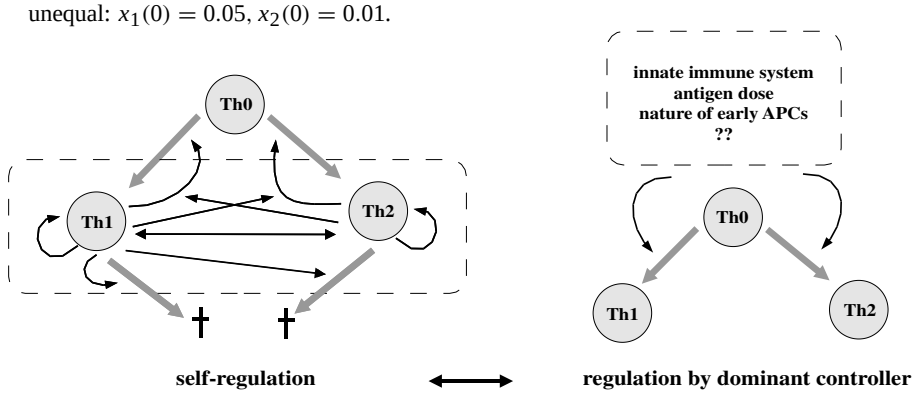

Figure 13. Contraposition of different regulation concepts.

(i) Cytokine interactions within the T helper system itself provide a built-in self-organizing mechanism for the selection of the appropriate T helper response. The selection is appropriate for many circumstances but not all [see (iii)].
(ii) The immune system's default response to pathogen is a primary Th1 response followed by a Th1 → Th2 switch in case of a failure of the Th1 response.
(iii) For fast replicating Th1-susceptible pathogens this built-in mechanism fails to destroy the pathogen; additional stimuli provided by other immune system components are necessary in order to induce an effective immune response.
(iv) Crucial for the function of the selection process is antigen dose dependence of the T helper ratio (high antigen levels promote a Th1 → Th2 switch) and an initial Th1 bias, which stems from cell-cycle dependence of cytokine

production. Therefore, we show here that these dependences, which could be considered as artefacts of the system without functional significance, play important roles for the function of the T helper system.

(v) The rate with which Th2 undergo AICD must be suitably balanced to enable this selection mechanism and to reduce the risk of chronic Th1-dominated disease.

(vi) As a consequence of (v) infections are more likely to become Th2 dominated than Th1 dominated. This may be part of effects of evolutionary pressure to minimize damage to the host.

In the present paper we have restricted ourselves to events that influence the decision-making process within the T helper system only. As we have pointed out, the proposed mechanisms lead to appropriate T helper responses for most pathogens and could therefore be seen as the default decision-making process. The essence of the idea for the proposed decision-making process is that an early advantage for Th1 leads to the induction of a Th1-dominated immune response, whereas the tendency of high antigen doses—potentially indicating failure of the present immune response—to favour Th2 initiates a shift towards Th2. Clearly, any other model with the same essence will give the same result.

Other authors have also modelled the response of the T helper system to pathogens (Fishman and Perelson, 1994; Carneiro *et al*., 1995; Muraille *et al*., 1995; Fishman and Perelson, 1999; Behn *et al*., 2000). To our knowledge, there is no detailed study on implications of the regulatory mechanisms within the T helper system on the decision-making process. Behn *et al*. (2000) incorporated cross-regulation of T helper subsets and feedback of cytokines of the existing T helper pool on differentiation of naive T helper cells, as we do here, but they did not consider different efficiencies of T helper subsets in pathogen clearance and AICD. This article provides a mechanism for hyposensitization that is based on antigen dose dependence of Th1/Th2 ratios, along the lines of our findings. Fishman and Perelson (1993) concentrated on consequences of asymmetries in cross-regulation. Their predictions concerning antigen dose dependence of the immune response are in agreement with those presented in Section 4.2, which is based on similar implementations of the cross-regulation. Fishman and Perelson (1999) focused on T helper differentiation upon interaction with antigen-bearing accessory cells and account for multi-clonality. They found that T helper responses are polarized towards one phenotype, Th1 or Th2,—owing to autocatalytic Th1/Th2 cross-suppressive processes, similar to our findings—and towards one receptor specificity due to competition for re-stimulation of different clones. Carneiro *et al*. (1995) found that the key feature underlying the regulation of Th differentiation pathways is the population dynamics of the lymphocytes themselves. According to their model the regulation of T helper differentiation is not driven by an APC-dominated selection process—where certain types of antigen are preferentially taken up and presented by particular types of APCs, which activate a certain type of lymphocyte subset. They pointed to the alternative that the major decisional events in the immune sys-

tem are determined by its own intrinsic dynamics but they did not provide concrete mechanisms as to how correct decisions are made. Muraille *et al*. (1995) considered cytokine interactions that are similar to those analysed here but they did not consider AICD. They also found Th1 $\rightarrow$ Th2 shifts and an association between chronicity and Th2 responses. They argued that chronicity and Th2 responses have been linked together evolutionarily because helminth infections, where protective immunity depends upon Th2 responses, tend to be long and chronic. In agreement with our results they proposed that persistence of the pathogen can represent a positive signal for the induction of a Th2 response. Our results, however, indicate an important role of differences of T helper subsets in AICD and provide a mechanism for the selection of appropriate and protective T helper responses for both intercellular and intracellular pathogens.

Other *external* influences from outside of the T helper system—such as signals from the innate immune system, the nature of early antigen-presenting cells, etc.—are likely to play greater or lesser roles in different circumstances. For cases of fast replicating Th1-sensitive pathogens (as we have seen), or pathogens that have found other ways to evade the immune response, additional mechanisms such as pattern recognition and pathogen destruction feedback might be necessary. These issues will be the subject of forthcoming work.

ACKNOWLEDGEMENTS

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APPENDIX A: UNEQUAL ACTIVATION PARAMETER

We find that the location and stability of Th1- or Th2-dominated 'cure' steady states is unaffected by unequal activation rates ($\sigma_1 \neq \sigma_2$), as is the stability but not the location of the 'chronic' steady states. Higher activation rates of one T helper type generally stabilize 'chronic' steady states dominated by the corresponding T helper subset and destabilize chronic situations dominated by the competing T helper type. This becomes clear if we look at the relevant eigenvalues

$$\lambda_1 = -1 + \frac{\pi \nu_2}{r + \nu_2} + \frac{\sigma_1}{\sigma_2} \frac{\nu_2[r + \nu_2(1 - \pi)]}{(r + \nu_2)^2}$$

for 'chronic:Th2' and

$$\lambda_1 = -1 - \frac{\delta_2 r}{\nu_1} - \frac{\pi \nu_1}{r + \nu_1} + \frac{\sigma_2}{\sigma_1}\left(1 - \pi + \frac{\delta_1 r}{\nu_1}\right)$$

for 'chronic:Th1'. The parameter regions in the (ν_1, ν_2)-space (pathogen-elimination efficiency) where 'chronic' steady states are stable are the following.

- If $\sigma_1 > \sigma_2$ then 'chronic:Th2' is stable if $\nu_2 < \frac{r}{\pi-1}$ and $\nu_2 < \frac{r}{(\sigma_1/\sigma_2)-1}$, or if $\nu_2 > \frac{r}{\pi-1}$ and $\nu_2 > \frac{r}{(\sigma_1/\sigma_2)-1}$. If $\frac{\sigma_1}{\sigma_2} > \pi$, conditions for the first case are even more restrictive than the conditions for equal activation parameters. The latter case can never be fulfilled because of the conditions for existence. If $\sigma_1 < \sigma_2$ then 'chronic:Th2' is stable if $\nu_2 < \frac{r}{\pi-1}$ and $\nu_2 > 0$, as in the case $\sigma_1 = \sigma_2$.
- Different activation strengths affect 'chronic:Th1' in the following way. We define

$$B_{1;2} = \frac{[r(1-\delta_2)\sigma_1 + (\pi - 1 - \delta_1)\sigma_2]}{2(\pi-1)(\sigma_2-\sigma_1)}$$

$$\pm\sqrt{r[(1-\delta_2)\sigma_1+(\pi-1-\delta_1)\sigma_2]^2+4(\pi-1)r^2(\sigma_2-\sigma_1)(\delta_2\sigma_1-\delta_1\sigma_2)}.$$

  Then 'chronic:Th1' becomes stable if:

  (1) for $\sigma_1 > \sigma_2$, $B_1 < \nu_1 < B_2$ if $B_1 < B_2$ and $B_2 < \nu_1 < B_1$ if $B_2 < B_1$
  (2) and, for $\sigma_1 < \sigma_2$, $\nu_1 < \min(B_1, B_2)$ or $\nu_1 > \max(B_1, B_2)$.

  In Fig. 5 we illustrate that the activation parameters affect the lower boundary of the parameter window where 'chronic:Th1' becomes stable. Higher Th2-activation strengths reduce the risk of chronic Th1-dominated situations, whereas higher Th1-activation parameters increase it.

APPENDIX B: UNEQUAL PROLIFERATION PARAMETERS

Unequal proliferation parameters ($\pi_1 \neq \pi_2$) lead to the following changes in the stability of the steady states.

- 'cure:Th2' becomes unstable when Th1 proliferation is higher than Th2 proliferation because of the eigenvalue $\lambda_2 = -1 + \pi_1/\pi_2$. This occurs via a transcritical bifurcation with the steady state 'Th1/2-chronic', which represents a chronic situation with coexisting T helper populations.
- 'cure:Th1', however, is stabilized by higher Th1 proliferation. The corresponding eigenvalue has the form

$$\lambda_2 = -1 - \frac{(\pi_1 - 1)\delta_2}{\delta_1} + \frac{\delta_1\pi_2}{\pi_1 - 1 + \delta_1}.$$

- In contrast, 'chronic:Th2', with relevant eigenvalue

$$-1 + \frac{\pi_1\nu_1}{r+\nu_2} + \frac{\nu_2(r+\nu_2-\pi_2\nu_2)}{r+\nu_2}$$

  is destabilized by higher Th1 proliferation (not shown).

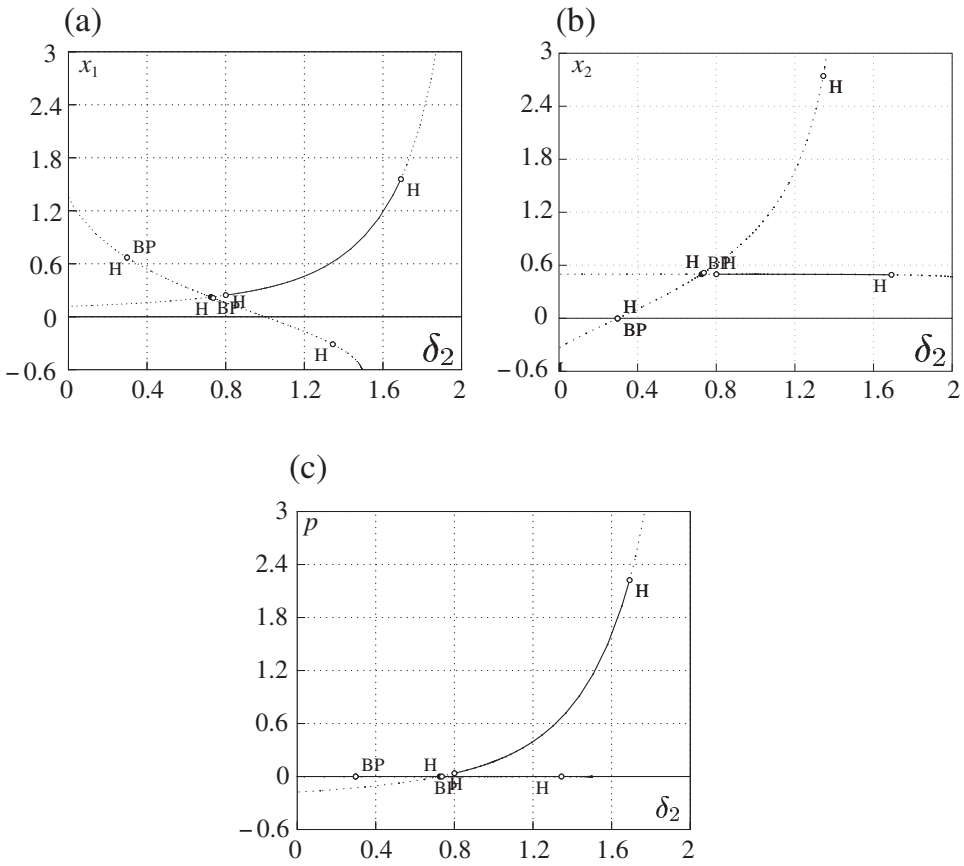

Figure 14. Bifurcation diagram with δ_2 as the bifurcation parameter (horizontal axis). Increasing values of δ_2 stabilize the steady state that represents chronic disease with coexisting T helper population. (a), (b) and (c) show the corresponding Th1, Th2 and pathogen concentrations, respectively. Stable steady states are shown as thick lines, unstable steady states as dotted lines. Hopf bifurcation points and branching points are represented by H and BP. The other parameters are $\sigma = 2, \pi = 2, \delta_1 = 1.5, \nu_1 = 0.1, \nu_2 = 2$.

- For 'chronic:Th1' the relevant eigenvalue for the stability analysis has the form $-\pi_1 + \pi_2\nu_1 + \frac{r(\delta_1-\delta_2)}{\nu_1}$. Higher Th1 proliferation and Th2 proliferation, respectively, increase and decrease stability of this fixed point. Effects of different proliferation parameters on boundary conditions for ν_1 on the stability are illustrated in Fig. 6. We define

$$B_{1,2} = \frac{r[\delta_1 - \delta_2 - \pi_1 \pm \sqrt{\delta_1^2 + \delta_2^2 - 2\delta_2\pi_1 + \pi_1^2 + 4\delta_2\pi_2 - 2\delta_1(\delta_2 - \pi_1 + 2\pi_2)}]}{2(\pi_1 - \pi_2)}.$$

'chronic:Th1' becomes stable for values of ν_1 between B_1 and B_2 if $\pi_2 > \pi_1$ and greater than the maximum of both B_1 and B_2 otherwise. We find that

increasing π_2 diminishes the ν_1-parameter window. For values of ν_1 close to zero and close to $\frac{r\delta_1}{\pi_1 - 1}$ 'chronic:Th1' is unstable.

APPENDIX C: HIGH SUSCEPTIBILITY OF Th2 FOR AICD STABILIZE CHRONIC STATES WITH MIXED T HELPER POPULATIONS

Steady states with both T helper subsets cannot be analysed analytically. Therefore, we show results of numerical calculations in the bifurcation diagram of Fig. 14, with typical choices of the other parameters; beyond a certain threshold increasing δ_2 stabilizes the steady state that represents chronic disease with coexisting T helper populations. For values of δ_2 beyond the Hopf bifurcation value, 'chronic:Th1/Th2' becomes unstable again and instead the steady state 'chronic:Th1' is attained.

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