A minimal model for T-cell vaccination

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SUMMARY

We have developed a mathematical model for the regulation of the growth of autoreactive T cells (the T cells responsible for autoimmunity). The model is very simple in that it is based only on the fundamental properties of T cells. However, despite this simplicity, it can account for a variety of phenomena referred to as T-cell vaccination. The purpose of T-cell vaccination is to create resistance to autoimmunity. This can be achieved by injecting either a subpathogenic quantity of autoreactive T cells, or attenuated autoreactive cells, or cells that recognize the autoreactive cells. The results of our model are based on the assumption that the self antigens involved in T-cell vaccination are normally not expressed; thus the autoreactive T lymphocytes are neither activated nor negatively selected. Self tolerance, therefore, corresponds to a 'passive' state. T-cell vaccination induces a transition from this passive state of tolerance to an active state of tolerance. In this state the autoreactive cells are controlled by regulator cells which recognize the autoreactive cells. The model predicts a qualitative difference between vaccination with normal autoreactive cells and vaccination with attenuated autoreactive cells. Normal cells may give rise to a permanent switch to the vaccinated state; attenuated cells, however, can provide only transient protection, which is dose dependent. Preliminary experimental data confirm this prediction. Finally, we propose a speculative explanation for relapsing autoimmune disease.

1. INTRODUCTION

Autoimmunity is an immune response to a self antigen. Although several self tolerance processes have been identified, autoimmunity is quite common. Experiments show that some autoimmune diseases can be prevented, or even cured, by injection with activated autoreactive T cells (i.e. the T cells responsible for the disease). To prevent these autoreactive T cells from inducing disease, they are either injected in a low concentration (Cohen 1986; Beraud *et al.* 1989), or they are 'attenuated'. Attenuation is achieved by exposing the cells to irradiation, mitomycin C, or hydrostatic pressure (Ben-Nun *et al.* 1981; Lider *et al.* 1986). This method is called 'T-cell vaccination' (TCV), and has been used in connection with a number of autoimmune diseases including experimental autoimmune encephalomyelitis (Ben-Nun *et al.* 1981), adjuvant arthritis (Holoshitz *et al.* 1983) and insulin-dependent diabetes mellitus (Formby & Shao 1993).

Experimenters have also been able to isolate and clone a second set of T cells, which appears after TCV and recognizes and possibly regulates the autoreactive T cells (Sun *et al.* 1988; Zhang *et al.* 1993). Acquired resistance can be transferred from vaccinated rats to naive recipient rats by injection of these cells (Lider *et al.* 1988; Sun *et al.* 1988; Cohen 1989).

TCV is a puzzling phenomenon: how can injection of the very cells that are responsible for a disease give protection against this disease? Several theorists have taken up the challenge to formulate a model of T-cell interactions to explain TCV. An interesting approach is that of Segel & Jäger (1994) who, by 'reverse engineering', devised a whole set of models compatible with TCV: however, none of these models is very realistic. The first modelling approach was the set of rather complicated automata models based upon a large number of cell types proposed by Weisbuch & Atlan (1988) and Cohen & Atlan (1989). Perelson & De Boer (1991) showed that one can account for TCV with the log bell-shaped network model that has become standard for studying B-cell network interactions. The main problem with this model is that it is based on symmetric interactions: symmetry is realistic for B cells but not for T cells, which recognize antigens in the form of peptides presented on major histocompatibility complex (MHC) molecules. The models that we propose here are simple and asymmetric. We model the interaction between an autoreactive clone and a clone that regulates it. Our simple model can explain TCV if we assume that the self antigens involved in TCV are normally not expressed in the body.

2. BASIC MODEL

The autoreactive T-cell response is probably composed of both cytotoxic and helper T cells, the former being restricted to class I MHC, the latter to class II MHC. For simplicity we consider only the helper T cells (which probably regulate the magnitude of the autoreactive response), and it is with respect to them that the aberrant expression of self antigens has been described (Bottazzo *et al.* 1983). We call these helper T cells the 'effector' cells; the T cells that recognize the

effector cells are called the 'regulator' cells. The experimental data show that the regulator cells are almost always MHC I restricted and inhibit the effector cells (Sun *et al.* 1988; Zhang *et al.* 1993).

We assume that both effectors and regulators are in a state of passive tolerance. They attain a population level that is determined by a normal influx of newborn cells from the thymus and by cell turnover: we call this level the 'normal' state. This assumption is quite reasonable in the case of MHC II restricted T cells as it is known that aberrant expression of class II MHC may lead to autoimmunity (Bottazzo *et al.* 1983). Because many cell types normally fail to express class II MHC, many potential self peptides will normally not be presented, thus the corresponding T cells will neither be activated nor be negatively selected. With respect to other self antigens and MHC class I restricted T cells, self tolerance processes are known to functionally inactivate autoreactive T cells (Blackman *et al.* 1990; Von Boehmer & Kisielow 1990).

(*a*) *Differential equations*

When properly stimulated, T cells proliferate. For our first model we propose as a proliferation function for the rate at which individual T cells divide

$$f(T, L) = L/(1+T+L), \tag{1}$$

where T is the total size of the T cell clone and L is the ligand for this clone. We derive this function $0 \leqslant f(T, L) < 1$ in Appendix 1.

T cell numbers also change because of the influx of cells from the thymus and because of inhibition and death. Thus we propose

$$\mathrm{d}E/\mathrm{d}t = m_{\mathrm{E}} + E[pf(E, L_{\mathrm{E}}) - cR - d], \tag{2a}$$

$$\mathrm{d}R/\mathrm{d}t = m_{\mathrm{R}} + R[pf(R, L_{\mathrm{R}}) - d], \tag{2b}$$

where E and R denote the sizes of the effector clone and the regulator clone, respectively, and L_{E} and L_{R} represent their ligands. The parameters m_{E} and m_{R} specify the influx from the thymus of effector and regulator cells. The maximum proliferation rate is p, d is the normal death rate and c is the strength at which regulators inhibit effectors.

(*b*) *Ligand*

We assume that the self antigen is normally not presented, and that its aberrant presentation leads to autoimmunity. Aberrant presentation may be evoked by a mimicking infection (Cohen 1984; Cohen *et al.* 1985; Holoshitz *et al.* 1986; Sinha *et al.* 1990). Once the self antigen is presented it also stimulates the effector T cells and subsequent lymphokine production by the effector cells (Bottazzo *et al.* 1983) will enhance the presentation of the self antigen. IFN-γ, for example, is known to upregulate MHC class II expression (Bottazzo *et al.* 1983). Thus the self antigen will sustain its own presentation and autoimmunity results.

Because the presentation of self antigen is enhanced by lymphokines produced by the effector cells, we model it as a linear function of the effector density. Furthermore, because the regulators are stimulated by the effectors we write

$$L_{\mathrm{E}} \equiv sE \tag{3a}$$

and

$$L_{\mathrm{R}} \equiv E, \tag{3b}$$

where s is a parameter for the concentration of the self antigen. Our basic model for TCV is obtained by substituting equations (3*a*) and (3*b*) into (2*a*) and (2*b*).

3. PROPERTIES OF THE BASIC MODEL

(*a*) *Nullclines*

In figure 1 we plot the phase plane of E and R. The nullclines intersect at three equilibrium points, of which two are stable. The 'normal state' (N) is a stable node. In this state the concentration of both effector and regulator cells is too low for significant proliferation or inhibition so that $E \approx m_{\mathrm{E}}/d$ and $R \approx m_{\mathrm{R}}/d$. We interpret this as a state of passive tolerance, in which an animal is healthy but susceptible to the autoimmune disease. Conversely, the 'vaccinated state' (V), which is a stable spiral, is interpreted as a state of active tolerance. In this state the animal is healthy and resistant to the autoimmune disease. The concentration of effector cells is high compared with the normal state, and the effector cells are controlled by the regulator cells.

Animals that suffer from an autoimmune disease often recover spontaneously and are subsequently resistant to another attempt to induce disease (Willenborg 1979; Ben-Nun & Cohen 1982). Therefore we model autoimmunity as a trajectory transiently having large effector populations and eventually attaining the vaccinated state. Thus autoimmune 'disease' (D) is represented by the shaded region in the phase plane, rather than by an equilibrium.

The separatrix defining the basins of attraction of the normal and the vaccinated state is depicted by the bold solid line in figure 1*b*. This line is the stable manifold of the saddle state (S).

(*b*) *T-cell vaccination*

First consider the introduction of activated effector cells into a system in the normal state. In the phase plane this initial condition corresponds to a point on the (broken) line $R = m_{\mathrm{R}}/d$. The state that will be attained from this initial condition is determined by the separatrix. Figure 1 shows that a trajectory corresponding to an intermediate dose of effector cells, i.e. $s_1 < E < s_2$, approaches the vaccinated state, whereas all other doses approach the normal state. Too small a dose of effectors fails to initiate proliferation. A large dose returning to the normal state resembles the 'overcure' phenomenon described by Segel & Jäger (1994). In our model overcure involves a transitory disease. Whether or not trajectories attaining the vaccinated state pass through the disease region depends on the dose of effectors. Thus the model

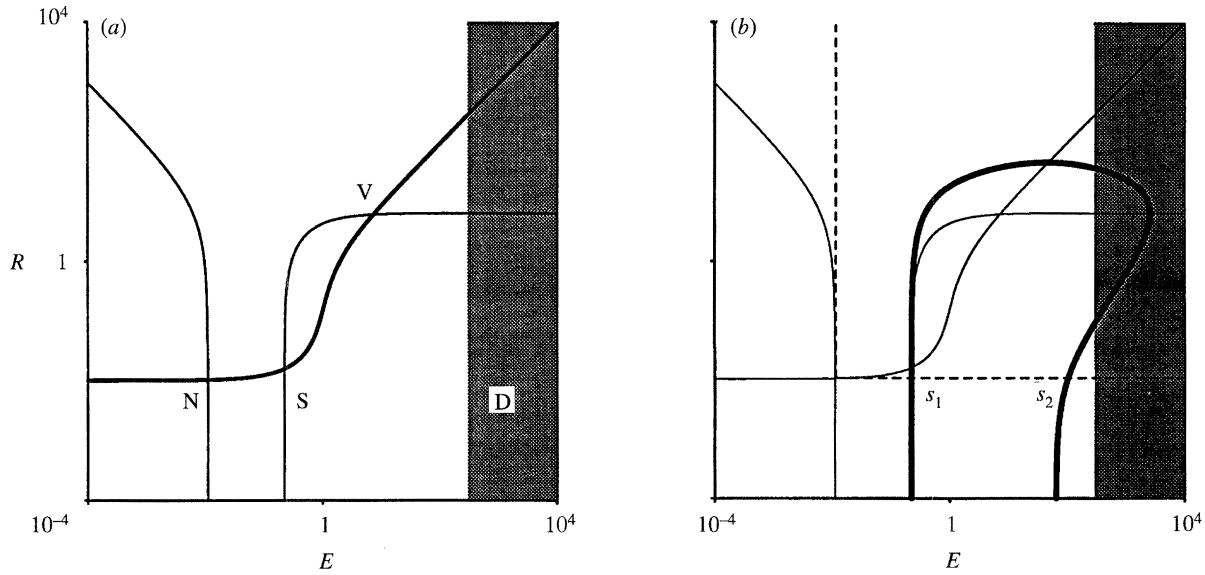

Figure 1. Nullclines, steady states and separatrix of the basic T cell model. (*a*) The thin lines denote the $dE/dt = 0$ nullclines; the thick line denotes the $dR/dt = 0$ nullcline. N represents the normal state, V the vaccinated state, and S the saddle point. The shaded region D represents disease. (*b*) The thick line denotes the stable manifold of the saddle point. The broken lines are the lines $E = m_E/d$ and $R = m_R/d$; s_1 and s_2 denote the intersections of the separatrix and the line $R = m_R/d$. See the text for interpretation. Parameters: $c = 0.1$, $d = 1$, $m_E = m_R = 0.01$, $p = 2$, $s = 5$.

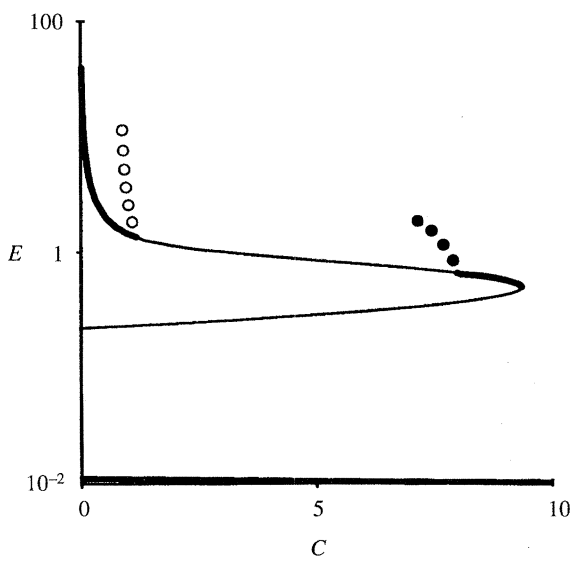

Figure 2. Bifurcation diagram with respect to *c*. Solid lines denote stable nodes and spirals; broken lines denote unstable equilibria. The open circles indicate unstable limit cycles; the filled circles represent stable limit cycles. Parameters as in figure 1.

demonstrates the possibility of successful vaccination with a subpathogenic dose of autoreactive cells (Cohen 1986; Beraud *et al.* 1989).

After the system has attained the vaccinated state, an attempt to induce autoimmunity (by introducing effector cells, for example) perturbs the system, but generally it will return to the vaccinated state. Because the effector cells are controlled by the regulator cells, the trajectory is unlikely to cross the region of disease.

Vaccination can also be achieved with attenuated effector cells (E_a) or with regulator cells (Ben-Nun *et al.* 1981; Lider *et al.* 1986; Lider *et al.* 1988; Sun *et al.* 1988; Cohen 1989). Attenuated cells have the same properties as normal effector cells except that they are unable to proliferate, and thus to sustain the presentation of the self antigen. Because attenuated cells stimulate the growth of regulator cells, both the introduction of regulator cells and the introduction of attenuated effectors corresponds to an initial condition on the line $E = m_E/d$. According to the separatrix this introduction can never result in a switch to the vaccinated state because the effectors are not stimulated by the regulators (the interactions are asymmetric). Thus the regulators decrease, and the system returns to the normal state.

Transiently, however, the elevated regulator levels do provide protection against disease; in experimental conditions this would be observed as transient vaccination. Thus, the model predicts a qualitative difference between vaccination with normal autoreactive cells and vaccination with attenuated autoreactive cells. Vaccination with normal cells results in a permanent switch. Attenuated cells, however, provide only transient protection which is dose dependent. Recent experiments by D. Elias (personal communication) confirm this prediction.

(*c*) *Bifurcations*

We study the robustness of our results by bifurcation analysis. As a principal bifurcation parameter we choose the rate of inhibition *c*. In figure 2, thick lines denote stable nodes and spirals, and thin lines denote unstable equilibria.

Figure 2 shows that the existence of our three equilibria requires $c < 9.4$. At this critical value of *c* the saddle equilibrium and the vaccinated state disappear through a saddle-node bifurcation: for $c > 9.4$ the model has only a normal state. Additionally we find two Hopf bifurcations around $c = 1.3$ and $c = 8.1$. At the lower (subcritical) bifurcation point an unstable limit cycle is born (open circles). This limit

cycle dies when it glues with the unstable manifold of the saddle state around $c = 0.9$. The upper Hopf bifurcation is supercritical, the stable limit cycle that is born here is depicted by the filled circles. The limit cycle dies by merging with the stable manifold of the saddle state around $c = 7$.

TCV is only possible if the vaccinated state exists and is stable. Figure 2 shows that this is not the case for $1.3 < c < 8.1$. The stable limit cycle that exists around the unstable vaccinated steady state for $7 < c < 8.1$, however, can also be interpreted as a 'state of vaccination'. On this limit cycle the effectors are controlled by the regulators.

A second requirement for TCV is that the state of vaccination is attainable by increasing the effectors on the line $R = M_R/d$. We investigate this by studying the global bifurcations of the stable manifold of the saddle state, using c as a bifurcation parameter. Before the first global bifurcation, i.e. for $c < 0.9$, the vaccinated state is stable and attainable. When $0.9 < c < 1.3$ the vaccinated state is stable but unattainable because the separatrix is formed by the unstable limit cycle (see figure 2). For $7 < c < 9.4$ there is again an attainable stable state of vaccination (see figure 2), which for $7 < c < 8.1$ corresponds to a stable limit cycle. Summarized TCV is possible for $c < 0.9$ and $7 < c < 9.4$.

Vaccination due to a stable limit cycle of E and R is a novel result; if the amplitude of the limit cycle is sufficiently large, the cycle will pass through the region of disease. This would be observed as a 'relapsing' disease. This is for instance typical for multiple sclerosis (Ironside 1992; Zhang *et al.* 1993). Thus the fact that animals recover from experimental autoimmune encephalomyelitis, whereas man typically contracts an oscillatory disease, can be accounted for by a simple parameter difference.

4. LOG BELL-SHAPED PROLIFERATION FUNCTION

In the basic T-cell model we considered T cells that proliferate according to a saturation function. Although this is in agreement with some experiments, others show humped T-cell proliferation functions (Matis *et al.* 1983; Knight 1987; Guttinger *et al.* 1988; Suzuki *et al.* 1988; Sebzda *et al.* 1994). In most of the work on B-cell network interactions we used phenomenological log bell-shaped proliferation functions (De Boer 1988; Weisbuch *et al.* 1990; De Boer *et al.* 1993). Using the same phenomenological function for T-cell proliferation we write

$$g(L) = \{L/[(1/\theta)+L]\}\,[\theta/(\theta+L)], \tag{4}$$

where L is again the ligand concentration. The function $0 \leqslant g(L) < 1$ is bell shaped with its maximum at $L = 1$, and its half maximum at $L = 1/\theta$ and $L = \theta$.

Although it is not necessary, we adapt the total ligand of E by saturating the presentation of self antigen as a function of E, so that

$$L_E = s[E/(\gamma+E)], \tag{5}$$

where γ represents a saturation constant. Our bell-shaped model is obtained by replacing the proliferation functions in equations (2*a*) and (2*b*) by equation (4), and substituting equations (3*b*) and (5) for the ligands.

Because the rising part of the bell-shaped function is a normal saturation function we can get a similar configuration of the normal, saddle and vaccinated steady state if we choose the right parameter combinations. This is shown in figure 3. The most important difference between this model and the previous one is that we get two new steady states. One is a stable 'disease' equilibrium (D), i.e. effectors are high and regulators low; the other one is a saddle point. As the separatrix through the new saddle point shows, the system no longer returns to the normal state when a large concentration of effector cells is introduced; instead disease is attained.

The basin of attraction of the vaccinated state can be such that a large dose of effectors leads to the normal state (i.e. overcure (cf. Segel & Jäger 1994)). This is determined by a heteroclinic bifurcation between the two saddles around $\theta_R = 2.14$. Figure 3*b* shows for $\theta_R = 2$ that the stable manifold of the first saddle bends upwards. Thus increasing the dose of effectors, we can get only: return to normal, vaccination and disease. Figure 3*c* shows for $\theta_R = 2.2$ that the stable manifold of the first saddle bends downwards. Thus increasing the

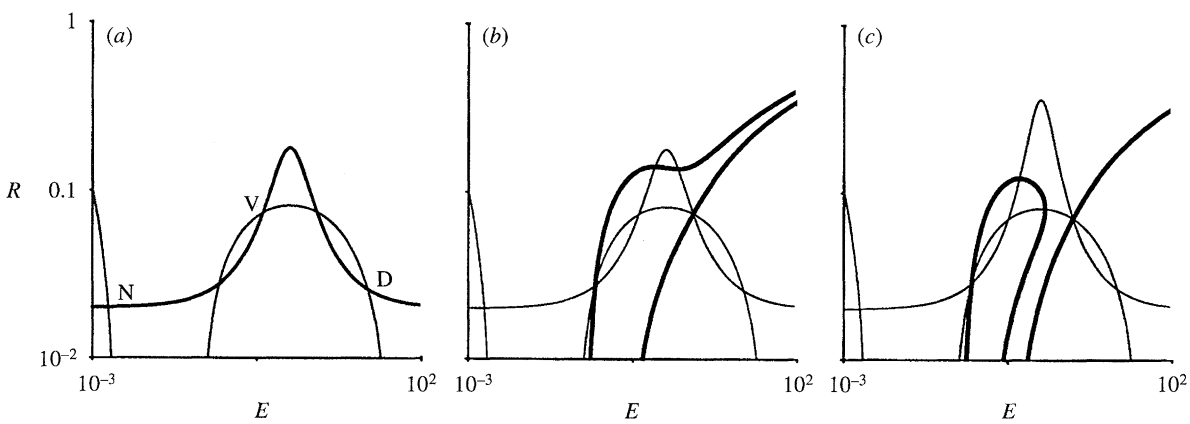

Figure 3. Nullclines, steady states and separatrix of the T-cell model with log bell-shaped proliferation function. (*a*) The thin lines denote the $dE/dt = 0$ nullclines; the thick line denotes the $dR/dt = 0$ nullcline. N represents the normal state, V the vaccinated state and D the diseased state. Parameters: $c = 10$, $d = 1$, $m_E = 0.002$, $m_R = 0.02$, $p = 2$, $\theta_E = 20$, $\theta_R = 2$, $\gamma = 50$, $s = 50$. (*b*) and (*c*) The thick lines denote the stable manifolds of the saddle states for $\theta_R = 2$ and $\theta_R = 2.2$, respectively.

dose of effectors, results in 'return to normal' between vaccination and disease.

5. DISCUSSION

Assuming that the antigens involved in TCV are normally not expressed on MHC class II, we have shown that TCV can be accounted for by extremely simple models. The simplicity of our models hinges upon this assumption because it gives us a normal state of passive tolerance with virtually no network interactions. In fact, we obtain similar results when the influx of effectors from the thymus is reduced due to self tolerance processes in the thymus, i.e. when $m_E < m_R$.

Alternative models in which the normal state is maintained by (suppressive) network interactions are necessarily more complex. An interesting possibility to study by a modelling approach is the Th1–Th2 switch that also seems to be involved in tolerance to autoimmune disease (Chen *et al.* 1994). Other experimental data have suggested that TCV fails to induce resistance to autoimmune diseases when there is no preformed network of autoreactive and regulator cells in the normal state (Jung *et al.* 1991; Zerubavel-Weiss *et al.* 1992). One possible interpretation of these data is that the regulators are positively selected by the effectors in the normal state. Hence the normal state would be a state with network interactions and a more complicated model would be required.

We think these issues call for a better empirical characterization of the normal (tolerant) state. This discussion also illustrates why the reverse engineering approach (Segel & Jäger 1994) is interesting. It is possible by reverse engineering to characterize the differences between the types of TCV models that have an active effector–regulator network in the normal state from those that have our passive form of tolerance.

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APPENDIX 1.

Here we show the derivation of the proliferation function in §2, equation (1). We assume that free T cells T_F and free ligands L_F form temporary complexes which dissociate and may result in T cell proliferation. Thus we propose the following reaction scheme:

$$T_F + L_F \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} 2T_F + L_F, \tag{A 1}$$

where k_1, k_{-1} and k_2 are the coefficients of binding, dissociation and proliferation, respectively.

With reference to Borghans *et al.* (1995) we make a change of variables, defining the 'total number of T cells' (T) as

$$T \equiv T_F + C. \tag{A 2}$$

Making the quasi-steady state assumption $dC/dt = 0$, and substituting equation (A 2) gives

$$dT/dt = k_2 C \tag{A 3a}$$

and

$$dC/dt = k_1[(L-C)(T-C) - K_m C], \tag{A 3b}$$

where

$$L \equiv C + L_F, \tag{A 4}$$

and

$$K_m = (k_{-1} + k_2)/k_1. \tag{A 5}$$

The initial conditions are

$$T(0) = T_0, \quad C(0) = 0, \quad L(0) = L_0. \tag{A 6}$$

We approximate the solution of $dC/dt = 0$ (equation (A 3*b*)) by a two-point Padé approximation (see Borghans *et al.* 1995) giving

$$C \simeq LT/(L + K_m + T). \tag{A 7}$$

Substitution of equation (A 7) into equation (A 3*a*) and rescaling yields our proliferation function. Thus equation (1) is based upon the total number of T cells, which means that we assume that both free T cells and T cells in a complex interact with regulator cells (see also Borghans *et al.* 1995).

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