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Autoimmunity arising from bystander proliferation of T cells in an immune response model

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ABSTRACT

We study a mathematical model of immune response by T cells where the regulatory T cells (Treg) inhibit interleukin 2 secretion. The bystander proliferation to an immune response is modelled. We consider an asymmetry reflecting that the difference between the growth and death rates can be higher for the active T cells and Tregs than for the inactive. This asymmetry leads to a better understanding of the bystander proliferation. An exposure to a pathogen results in an increased proliferation rate of the bystander T cells. If the population of the bystander T cells becomes large enough, autoimmunity can arise, eventually after a long transient period.

1. Introduction

The primary function of the immune system is the protection of the host from pathogen invasion. During such an invasion, T cells specific to the antigen proliferate and under most circumstances successfully remove the pathogen. However, the immune system can also target self-antigens (autoimmunity) and cause tissue damage and death. Tregs clearly function to limit such autoimmune responses with a delicate balance between appropriate immune activation and immune response suppression being achieved. Part of this growth inhibition is the inhibition of secretion by T cells as studied in [1,2]. How such a balance is established and controlled is the central focus of [3,4]. In [5], we studied an asymmetry in the death rates caused for example by the presence of memory cells. This asymmetry reflects the fact that the difference between the growth and death rates can be higher for the active T cells than for the inactive T cells, with a similar asymmetry present for Tregs.

Under exposure to their specific antigen, conventional T cells are activated leading to secretion of growth cytokines (predominantly interleukin 2, denoted IL-2), and expression of the interleukin 2 receptor which triggers cytokine driven proliferation [6,7]. T cell proliferation through cytokines has a control structure, since cytokine driven growth exhibits a quorum population size threshold [8–10]. In [3], we proposed that Tregs locally adjust these thresholds by inhibiting IL-2 secretion. The immune response–suppression axis is then a balance between the local numbers of activated T cells (e.g. from a pathogen encounter) and activated Tregs.

In this paper, we study the effect of asymmetry for both the T cells and Tregs in cases where a bystander proliferation of T cells occurs. We consider different lines of T cells that respond to different antigens. The presence of a pathogen can

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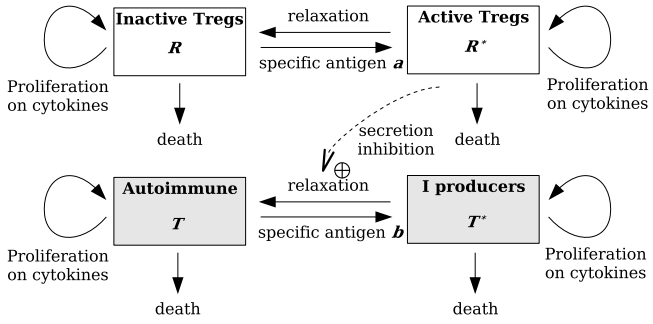

Fig. 1. Model schematic showing growth, death and phenotype transitions of the Treg populations R, R^*, and conventional T cell T, T^* populations. Cytokine dynamics are not shown: IL-2 is secreted by activated T cells T^*, adsorbed by all the T cell populations equally.

increase the antigenic stimulation of one of these lines of T cells, to values enough to trigger an immune response. As a result, that line of T cells will secrete IL-2 cytokine. The presence of IL-2 cytokine will increase the proliferation rate of the lines of T cells, responding to the pathogen, as well as it will increase the proliferation rate of all other lines of T cells. Therefore, the population size of the non responding lines of T cells will increase as a consequence of their bystander proliferation. However, under the asymmetric assumption, the number of bystander T cells is lower than the number of responding T cells. An (auto)immune response caused by a bystander proliferation can occur, which is mathematically justified by the presence of the IL-2 cytokine that moves the current state of the dynamical system, through the unstable equilibria manifold of the hysteresis, to the basin of attraction of the autoimmune response stable equilibria.

2. Theory

There are a number of different (CD4) T cell regulatory phenotypes reported; we use a model of Tregs that are currently identified as $CD25^+$ T cells, although this is not a definitive molecular marker. At a genetic level, these Tregs express Foxp3, a master regulator of the Treg phenotype inducing CD25, CTLA-4 and GITR expression, all correlating with a suppressive phenotype [11].

The model uses a population of Tregs (denoted R, R^*) and conventional T cells (T, T^*) with processes shown schematically in Fig. 1 (see [3,5] for further details).

Both populations require antigenic stimulation for activation, Tregs being activated by self-antigens. Levels of antigenic stimulation are denoted a and b for Tregs and conventional T cells respectively. On activation, conventional T cells secrete IL-2 and acquire proliferative capacity in the presence of IL-2, while Tregs proliferate in the presence of IL-2, although less efficiently than normal T cells [2], and they do not secrete IL-2. Activated Tregs suppress IL-2 secretion [2] thereby inhibiting T cell growth. The model, as in [3], assumes that T cells activated by exposure to their specific antigen have a cytokine secreting state (a normal activated state T^*) and a nonsecreting state (denoted by T) to which they revert at a constant rate k; thus in absence of antigen growth halts. The regulatory T cells can be active (denoted by R^*) or inactive (denoted by R). Activated Tregs R^* also induce a transition in the T cells to the (inhibited) nonsecreting state, this transition rate is assumed proportional to the Treg population density. T cells regain secretion status on coreceptor stimulation (CD28, [12]), which we assume correlates with antigen exposure through an increased conjugate formation rate. Thus in the presence of costimulation and Tregs, the T cell population would be a mixture of partially inhibited, and normal T cells.

Regulatory T cells are assumed to be in homeostasis, thus Treg density is controlled through some type of (nonlinear) competition. We also include a growth limitation mechanism; we use a (quadratic) Fas-FasL death mechanism that is assumed to act on all T cells equally [13]. Results will be similar with any saturation mechanism. We include an influx of (auto) immune T cells into the tissue (T_{input} in cells per ml/day), which can represent T cell circulation or naive T cell input from the thymus.

We consider an influx of Tregs into the tissue (R_{input} in cells per ml/day), similar to the influx T_{input} of T cells for the Tregs.

The model has a controlled stable steady state (with low concentration of T cells) and an immune response stable steady state (with high concentration of T cells), depending of the antigenic stimulation b of T cells and the initial conditions. If the antigenic stimulation b of T cells rises above the threshold b_H control is lost and autoimmunity arises. After an autoimmune response, the control state is recovered when the stimulation falls below a lower threshold b_L. This phenomena is due to the equilibria manifold being an hysteresis. The presence of Tregs increases the thresholds b_L and b_H. We assume that the local tissues activate the Tregs by a probably tissue specific profile of self-antigens, thereby controlling the size of the local population of Tregs.

In the simulations of a bystander proliferation, we considered two lines of T cells T_b, T_b^* and T_c, T_c^* that have, respectively, pathogen stimulation b and autoimmune antigen stimulation c. We study this model considering three cases: (A) the symmetric case, as in [3]; (B) a partially asymmetric case where the asymmetry is present for the T cells but not for the Tregs; (C) the asymmetric case, as in [5]. The model consists of a set of ordinary differential equations (see [3,5] for further

details) and is employed to study the dynamics, with a compartment for each T cell population (inactive Tregs R, active Tregs R^*, non secreting T cells T_b and T_c, secreting activated T cells T_b^* and T_c^*) and interleukin 2 density I:

$$\begin{aligned}
\frac{dR}{dt} &= (\epsilon\rho I - \beta N - d_R)R + \hat{k}(R^* - aR) + R_{\text{input}},\\
\frac{dR^*}{dt} &= (\epsilon\rho I - \beta N - d_{R^*})R^* - \hat{k}(R^* - aR),\\
\frac{dT_b}{dt} &= (\rho I - \beta N - d_T)T_b + k(T_b^* - bT_b + \gamma R^* T_b^*) + T_{\text{input}},\\
\frac{dT_b^*}{dt} &= (\rho I - \beta N - d_{T^*})T_b^* - k(T_b^* - bT_b + \gamma R^* T_b^*),\\
\frac{dT_c}{dt} &= (\rho I - \beta N - d_T)T_c + k(T_c^* - bT_c + \gamma R^* T_c^*) + T_{\text{input}},\\
\frac{dT_c^*}{dt} &= (\rho I - \beta N - d_{T^*})T_c^* - k(T_c^* - bT_c + \gamma R^* T_c^*),\\
\frac{dI}{dt} &= \sigma(T_b^* + T_c^* - (\alpha N + \delta)I),
\end{aligned}$$

with $N = R + R^* + T_b + T_b^* + T_c + T_c^*$. We chose the following values for the parameters $R_{\text{input}} = T_{\text{input}} = 100$ cells/ml/day, $d_R = d_T = 0.1$/day, $d_{R^*} = d_{T^*} = 0.01$ or 0.1/day and the values of the other parameters are equal to the ones presented in Table 1 in [3]. The important aspects of this model are a mechanism to sustain a population of Tregs, secretion inhibition of T cells with a rate that correlates with Treg population size, and growth and competition for IL-2 with a higher growth rate of T cells relative to Tregs.

3. Dynamics of bystander proliferation

We compare the dynamics of the bystander proliferation between the model with symmetric death rates [3] and the model with asymmetric death rates [5]. The asymmetry reflects that the difference between the growth and death rates can be higher for the active T cells and the active Tregs than for the inactive T cells and inactive Tregs. The asymmetry in the difference between the growth and death rates brings up of the relevance of the antigenic stimulation of Tregs in the control of the local Treg population size [5]. This asymmetry can be due to the presence of memory T cells and memory regulatory T cells.

We observe that the asymmetry in the model provokes slightly faster growth rate of the T cells, in particular for high antigenic stimulations b of T cells due to the lower average death rate of T cells.

In the case of the cross reactive direct stimulation, the results are analogous to the immune response model [3]: the final state of the model is either a controlled state or an immune response state, the last one being achieved if the stimulation of the autoimmune antigen b is between b_L and b_H and the duration of the immune response is of sufficient duration (about 5 days in the simulations in [3]).

The simulations of the bystander proliferation present differences between the symmetric case and the asymmetric case.

In our simulations, we consider a tissue with initial controlled state of both T cells lines and we simulate a pathogen infection as a step increase in b from 0 to 1000 between days 0 and 7 (other choices of suitable pathogen dynamics give analogous results). If the autoimmune stimulation of T cells was too low ($c < c_L$) the autoimmune T cells could not sustain autoimmunity after pathogen clearance and Tregs would be able to regain control. On the other hand, if the autoimmune stimulation of T cells was too high ($c > c_H$) it would be impossible to have an initial controlled autoimmune state. In the simulations in Fig. 2, we choose the autoimmune antigenic stimulation $c = 0.1$ to be a constant value between the thresholds c_L and c_H of antigen stimulation. In the three simulations presented in Fig. 2, we observe that the concentrations of the autoimmune line of T cells T_c, T_c^* increases between days 0 and 7, since during this period of time there is an increase of the concentration of I cytokine secreted by the line of T cells T_b, T_b^* that respond to the pathogen. There is also a transient increase in the population of Tregs due to the I cytokine followed by suppression of Tregs due to the Fas-FasL mediated apoptosis. In the end of the pathogen exposure (after 7 days) the secreting autoimmune T cells T_c^* generate enough I cytokine to sustain the population of autoimmune T cells T_c, T_c^* in high concentrations, thus developing an autoimmune response.

The onset of autoimmunity depends both of the duration of the pathogen exposure and of the model considered. In the symmetric case with two lines of T cells (with $d_{R^*} = d_{T^*} = 0.1$/day), we observe that the autoimmune response stabilizes around 10 weeks after the pathogen exposure (see Fig. 2A). In the asymmetric case, with lower death rate of secreting T cells and active Tregs ($d_{R^*} = d_{T^*} = 0.01$/day), the autoimmunity arises approximately 8 weeks after the pathogen exposure (see Fig. 2C). We also consider an intermediate choice of death rates (see Fig. 2B), where the asymmetry of the death rates is present only for the T cells ($d_{R^*} = 0.1$/day and $d_{T^*} = 0.01$/day). In this case, the autoimmunity appears after about 6 weeks. The comparison of the Tregs concentrations, presented in Fig. 2B and C, show that the asymmetry in the growth and death rates between the active and inactive regulatory T cells have implications in the concentration of the regulatory T

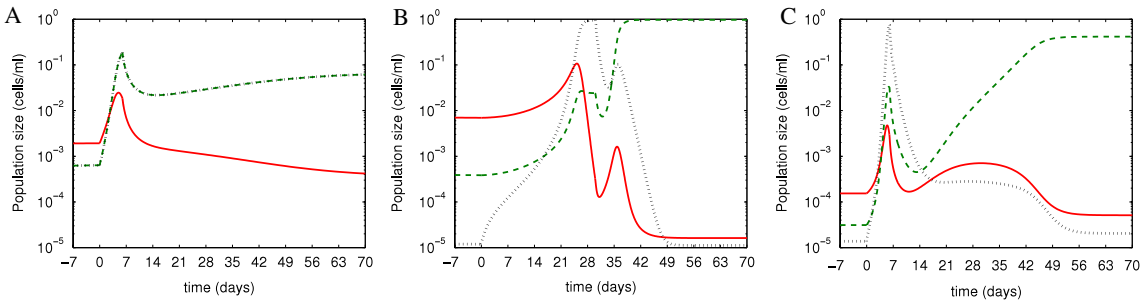

Fig. 2. Bystander proliferation for different models. A. The symmetric case: The T cells not responding to the pathogen have equal concentration to the T cells responding to the pathogen. B. Only the secreting T cells T^* die slower: The T cells not responding to the pathogen have lower concentration than the T cells responding to the pathogen. C. The asymmetric case: The T cells not responding to the pathogen have lower concentration than the T cells responding to the pathogen and take more time than in case B to achieve an immune response. Black dots: Concentration of T cells responding to the pathogen ($T_b + T_b^*$); Green dashes: Concentration of T cells not responding to the pathogen ($T_c + T_c^*$); Red line: Concentration of the Tregs ($R + R_*$).

cells after the pathogen removal. As we can see, in Fig. 2B and C, the concentration of the regulatory T cells is higher in the presence of the asymmetry.

In the case of an autoimmune response of T cells T_c, T_c^*, we observed that the concentration of both lines of T cells are always equal in the symmetric case where $T_b + T_b^* = T_c + T_c^*$ (see Fig. 2A), because the growth rates and the death rates of the two types of T cells are equal. However, in the asymmetric case (see Fig. 2C), the line of T cells T_b, T_b^* that responds to the pathogen stimulation b has higher concentration than the other line of T cells T_c, T_c^* during the infection period (between 0 and 7 days) due to the lower average death rate of the line of T cells that respond to the pathogen T_b, T_b^*. For the same reason, when we consider the asymmetry of the death rates only for the T cells (see Fig. 2B), the concentration of the line of T cells T_b, T_b^* that responds to the pathogen is also higher than the other concentration of the other line of T cells T_c, T_c^* during the infection period. After the infection period, the T cells T_b, T_b^* decrease to the initial homeostatic levels. However, the autoimmune response for the T cells T_c, T_c^* appear because the antigenic stimulation c is between c_L and c_H and, also, because the IL-2 cytokine concentration is high enough to move their state, through the hysteresis unstable manifold, to the basin of attraction of the autoimmune response equilibrium state.

4. Discussion

Treg induced secretion inhibition can protect different tissues from immune responses by adjusting (possibly through evolutionary selection) the size and activity of the local Treg population. These mechanisms allow tissues that are frequently exposed to antigen, e.g. the gut, to have the balance more in favour of inhibition, while other tissues may not need a local Treg population.

Since regulation is non specific, an immune response, and the associated proliferative cytokine production can induce bystander proliferation of autoimmune T cells (and Tregs), whilst enhanced levels of costimulation can abrogate inhibition which undermines control of autoimmunity. The asymmetry is an improvement of the immune response model, in the simulation of the bystander proliferation, because it allows the T cells T_b stimulated by the pathogen to have higher concentrations than the other lines of T cells T_c. Because of the hysteresis implicit in the dynamics, the high proliferation of these bystanders during the immune response may lead to the escape of T cells T_c from Treg control and thereby establish chronic autoimmunity.

The load threshold behaviour observed in adoptive transfer experiments [1] is also explained by this quorum growth mechanism, whilst we predict a cytokine (principally IL-2) dependence of this threshold and thus its modulation under alteration of the IL-2 environment. The reverse switch from autoimmune to controlled state can be achieved if the autoimmune T cell population can be lowered sufficiently, or Treg density increased. However, because of the hysteresis in this system high levels of suppression may be needed.

The comparison of the Tregs concentrations presented in Fig. 2B and C show that the asymmetry of the growth and death rates between the active and inactive regulatory T cells have implications in the concentration of the regulatory T cells after the pathogen removal. If experimental results confirm the concentrations presented in Fig. 2C, then the asymmetry in the regulatory T cells give evidence that the regulatory T cells, like the T cells, also differentiate to memory T cells. Hence, we propose such a laboratory experiment to be done.

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