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Optimal number of regulatory T cells

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ABSTRACT

The adaptive immune system of a vertebrate may attack its own body, causing autoimmune diseases. Regulatory T cells suppress the activity of the autoreactive effector T cells, but they also interrupt normal immune reactions against foreign antigens. In this paper, we discuss the optimal number of regulatory T cells that should be produced. We make the assumptions that some self-reactive immature T cells may fail to interact with their target antigens during the limited training period and later become effector T cells causing autoimmunity, and that regulatory T cells exist that recognize self-antigens. When a regulatory T cell is stimulated by its target self-antigen on an antigen-presenting cell (APC), it stays there and suppresses the activation of other naive T cells on the same APC. Analysis of the benefit and the harm of having regulatory T cells suggests that the optimal number of regulatory T cells depends on the number of self-antigens, the severity of the autoimmunity, the abundance of pathogenic foreign antigens, and the spatial distribution of self-antigens in the body. For multiple types of self-antigen, we discuss the optimal number of regulatory T cells when the self-antigens are localized in different parts of the body and when they are co-localized. We also examine the separate regulation of the abundances of regulatory T cells for different self-antigens, comparing it with the situation in which they are constrained to be equal.

1. Introduction

In vertebrates, self-reactive naive T cells are mostly eliminated by negative selection in the thymus (Kappler et al., 1987), but this process is not perfect and some remain in our bodies (Sakaguchi and Sakaguchi, 1990; Seddon and Mason, 1999; Jordan et al., 2001; Abbas and Lichtman, 2007). These autoreactive T cells are prevented from being activated by T-cell ignorance (Ohashi et al., 1991), T cell anergy (Schwartz, 1997), or regulatory T cells (Sakaguchi, 2004). In particular, naturally arising regulatory T cells play an important role in preventing autoimmunity—the depletion of $CD25^+CD4^+$ regulatory T cells produces autoimmune diseases, and their reconstitution prevents them (Sakaguchi et al., 1995). Activated regulatory T cells can suppress the immune reactions of any conventional effector T cells, including both those reactive to foreign antigens and those reactive to self-antigens (Thornton and Shevach, 2000). As a result, they can potentially interrupt normal immune reactions against foreign antigens (Cools et al., 2007).

Theoretical studies of regulatory T cells have addressed the question of how this non-specific regulatory mechanism achieves a proper balance between tolerance to self-antigens and immunity to foreign antigens by focusing on T cell population dynamics. Leon et al. (2000, 2003) and Carneiro et al. (2007) considered the interaction of regulatory T cells and effector T cells on antigen-presenting cells (APCs), and Burroughs et al. (2006, 2008) modeled the cytokine-dependent growth of T cells and the inhibition of IL-2 secretion by regulatory T cells. These studies concluded that the bistability of T cell population dynamics allowed achievement of a balance between tolerance and immunity. Effector T cell populations are usually kept small under the control of regulatory T cells, but when a pathogen invades, the equilibrium state changes to one with a high abundance of effector T cells. After pathogen clearance, the effector T cell population is again controlled at a lower level. These findings suggest that immune responses to pathogens might trigger autoimmune diseases (Benoist and Mathis, 2001).

In a previous paper (Saeki and Iwasa, 2009), we studied the costs and benefits of immune reactions, including those of regulatory T cells, by extending theoretical studies on the adaptive significance of immune system design (e.g., Perelson and Oster, 1979; De Boer and Perelson, 1993; Borghans et al., 1999; Shudo and Iwasa, 2001, 2002, 2004; Shudo et al., 2003). In that paper, we developed a mathematical model to determine under what conditions it is advantageous to have regulatory T cells by evaluating the benefit of suppressing autoimmune diseases against the cost of jeopardizing the immune reactions that enable the organism to cope with foreign antigens. The analysis results

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indicated that having regulatory T cells is not advantageous if activated regulatory T cells suppress effector T cells everywhere in the body. In contrast, the production of regulatory T cells can be beneficial when a body is composed of many compartments and regulatory T cells suppress immune reactions only within the compartment that they exist (localized suppression). We also examined several extensions of the basic model and found that localized suppression is always necessary for having regulatory T cells to be advantageous (Saeki and Iwasa, 2009).

In this paper, we model one example of localized suppression, suppression by regulatory T cells on APCs (Cobbold et al., 1996; Davies et al., 1996; Frasca et al., 1997; Wise et al., 1998; Miyara and Sakaguchi, 2007). We consider the optimal number of regulatory T cells, taking into account both the benefit and harm to the host of immune reactions, and the maintenance cost of regulatory T cells. We assume that when a regulatory T cell is stimulated by its target self-antigen on an APC, it stays on the APC and starts suppressing the activation of other naive T cells there. We find that the optimal number of regulatory T cells to maximize the benefit depends on the number of self-antigens, the severity of the autoimmunity, the abundance of pathogenic foreign antigens, and the spatial distribution of self-antigens in the body. In addition, we investigate two different distributions of multiple types of self-antigens, either localized in different parts of the body, or in the same part. We also contrast the separate regulation of the abundances of regulatory T cells for different self-antigens with the situation in which they are constrained to be equal.

2. Model

In our previous study of the adaptive significance of having regulatory T cells (Saeki and Iwasa, 2009), we defined fitness as follows:

$$\Phi = \Lambda + v[\text{abundance of effector T cells reactive to foreign antigens}] - \mu[\text{abundance of effector T cells reactive to self} - \text{antigens}], \quad (1)$$

where Λ is the basic fitness without T cells, v is the benefit of having effector T cells reactive to foreign antigens, and μ is the severity of the disadvantage of having effector T cells attacking the self. The function of regulatory T cells is to reduce both the second and the third term of Eq. (1) by suppressing the activation of naive T cells.

In that study (Saeki and Iwasa, 2009), we concluded that having regulatory T cells confers an advantage only when the suppression by regulatory T cells is limited in a small part of the body (localized suppression). Here we focus on one possible mode of realizing localized suppression of immune reactions, namely, localization of the suppression of T cell activation on the APCs on which the regulatory T cell is located. APCs collect various antigens from the peripheral regions of the body, and these antigens are digested into peptides, which are presented on the cell surface. Suppose that each APC has k sites, estimated to be about 10 (Yata, 2007), for antigen presentation, and that a regulatory T cell can suppress the activation of naive T cells only on the same APC that it occupies (Fig. 1). We assume that each site presents either a self-antigen or a non-self-antigen with some probability. Let A_i be the fraction of APCs on which exactly i sites present self-antigens. Then, A_i is a function of the abundance of self-antigens, u, and it follows a binomial distribution:

$$A_i = \binom{k}{i} u^i (1-u)^{k-i}, \quad (2)$$

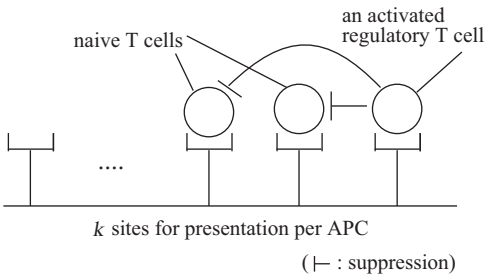

Fig. 1. Basic scheme of our model. Each antigen-presenting cell (APC) has k sites for antigen presentation, which are occupied by self- or non-self-antigens. If a regulatory T cell recognizes its own reactive self-antigen on the APC it occupies, the activation of all naive T cells on the same APC is prevented regardless of their antigen specificity. However, the regulatory T cell cannot prevent naive T cell activation on different APCs.

We assume that the other $(k-i)$ sites present non-self-antigens. (Later, we modify this assumption.)

A naive T cell becomes activated when it recognizes a site presenting its corresponding peptide on an APC. We assume that an activated naive T cell then leaves the APC and explores the body in search of sites where it can work as an effector T cell. In contrast, when a regulatory T cell recognizes its peptide, it stays on the APC and prevents other naive T cells from being activated.

Let T_N be the number of non-self-reactive naive T cells, T_S the number of self-reactive naive T cells, T_R the number of regulatory T cells, h the encounter rate between an APC and a T cell, and ε the mortality of APCs. The expected life time of an APC is $1/\varepsilon$, and the expected number of times that an APC encounters a regulatory T cell during its life time is about hT_R/ε, which we assume to be much >1. From this assumption, we can derive the fitness as follows (see Appendix A):

$$\Phi \approx \Lambda + A_0 \frac{khvT_N}{\varepsilon} - \frac{1}{T_R}\sum_{i=1}^{k} A_i \left[\mu T_S - \frac{(k-i)vT_N}{i}\right] - \gamma T_R. \quad (3)$$

The last term on the right-hand side is the maintenance cost of regulatory T cells, where γ is the cost per cell. Fitness can increase with the number of regulatory T cells only when the sum in Eq. (3) is positive. This condition can be written as

$$\frac{\mu T_S}{vT_N} > \frac{1}{1-A_0}\sum_{i=1}^{k} \frac{k-i}{i} A_i. \quad (4)$$

The value of the right-hand side of Eq. (4) depends on the abundance of self-antigens u because A_i depends on u. $A_i/(1-A_0)$ with i=1, 2, 3,…,k, has a binomial distribution without a zero term. Hence, the mean of this truncated binomial distribution increases as the mean of the original binomial distribution ku increases. In contrast, with this truncated binomial distribution, the mean of $1/i$ should decrease as ku increases. Consequently, the right-hand side of Eq. (4) decreases as u increases (Fig. 2a), and Eq. (4) is more likely to be satisfied when the abundance of self-antigens u is large.

2.1. Optimal number of regulatory T cells

The optimal value of T_R that maximizes the fitness given by Eq. (3) is

$$\hat{T}_R = \sqrt{\frac{1}{\gamma}\sum_{i=1}^{k} A_i \left[\mu T_S - \frac{(k-i)vT_N}{i}\right]}. \quad (5)$$

Note that when Eq. (4) holds, the sum under the square root symbol is positive. When Eq. (4) is not true, no regulatory T cells should be produced.