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ORIGINAL ARTICLE

A Theory of Immunodominance and Adaptive Regulation

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Abstract Immunodominance refers to the phenomenon in which simultaneous T cell responses against multiple target epitopes organize themselves into distinct and reproducible hierarchies. In many cases, eliminating the response to the most dominant epitope allows responses to subdominant epitopes to expand more fully. The mechanism that drives immunodominance is still not well understood, although various hypotheses have been proposed. One of the more prevalent views is that immunodominance is driven by *passive* T cell competition for space on antigen presenting cells (APCs) or for access to specific MHC:epitope complexes on the surface of APCs. However, several experimental studies suggest that passive competition alone may not fully explain the robustness of immunodominance under physiological conditions or varying proportions of antigen-specific precursor T cells and APCs. These studies propose that a mechanism of *active* suppression among T cells gives rise to immunodominance.

In this work, we present the novel hypothesis that mutual suppression of simultaneous T cell responses results from the appearance of adaptive regulatory T cells (iTregs) during the course of the overall T cell expansion. We extend the mathematical model of T cell expansion proposed in Kim et al. (Bull. Math. Biol. 2009, doi:10.1007/s11538-009-9463-1) to consider multiple, concurrent T cell responses.

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The model is formulated as a system of independent feedback loops, in which antigen-specific T cell population produces a nonspecific feedback response. Our simulations show that the fastest response to expand gives rise to a *de novo* generated population of iTregs that induces a premature contraction in slower or weaker T cell responses, leading to a hierarchical expansion as observed in immunodominance. Furthermore, in some cases, removing the dominant T cell response allows previously subdominant responses to develop more fully.

Keywords Immunodominance · T cell response · Adaptive regulatory T cells · Delay differential equations · Competition model

1 Introduction

Pathogens contain many different epitopes to which the adaptive immune system may respond. T cell responses against multiple epitopes self-organize into consistent hierarchies; a phenomenon known as *immunodominance*. When the most dominant response is removed, the second most dominant response may expand to compensate. Likewise, if the two most dominant epitopes are removed, then the third most dominant response may expand. This hierarchy of compensation may continue up to several layers of T cell responses. For example, the CD8+ T cell response to murine influenza A virus consists of concurrent T cell responses against two immunodominant epitopes and a smaller response against a third epitope. Under normal circumstances, the response to the third epitope is hardly detectable. However, when mice are infected with viruses that do not present the immunodominant epitopes, a significant response to the third epitope emerges (Thomas et al. 2007).

In addition, immunodominance hierarchies generated during the primary response may rearrange upon reinfection. During primary infection by murine influenza A, the two immunodominant epitopes elicit comparable CD8+ responses, but upon secondary challenge, only one of the epitopes dominates, producing a CD8+ response that is approximately 10 times higher than that of the second one (Thomas et al. 2007).

The nature of immunodominance and compensation varies, however, from target to target. For example, in the case of the immune response to *Listeria monocytogenes*, a consistent hierarchy of dominance and subdominance develops, but elimination of the two dominant epitopes does not lead to compensation by subdominant responses (Vijh et al. 1999). These and other experimental studies show that the degree of competition among concurrent T cell responses may be minimal for some targets as in Vijh et al. (1999) or almost complete as in Weidt et al. (1998).

How do simultaneous T cell responses rapidly organize during an acute immune response? While the precise mechanisms of immunodominance are not well understood, the majority of experimental and theoretical works agree on some form of T cell competition, and set forth the following two theories (Borghans et al. 1999; Grufman et al. 1999; Kedl et al. 2000, 2003; Probst et al. 2002; Roy-Proulx et al. 2001):

Theory 1. T cells *passively* compete for a limited resource, most likely access to antigen-presenting cells (APCs),

Theory 2. T cells *actively* suppress the development of other T cells.

In this paper, we take a dynamical systems perspective to argue in favor of the theory of active suppression. We then consider a recent mathematical theory that models the dynamics of a T cell response as a self-regulating feedback loop involving adaptive regulatory T cells (iTregs) (Kim et al. 2009). We extend this model to consider the case of multiple, simultaneous T cell responses and conclude that the phenomenon of immunodominance might occur as a natural result of the iTreg-mediated contraction of the T cell response proposed in Kim et al. (2009). In this manner, immunodominance may not only be the result of passive competition for limited resources, but may also be viewed as a consequence of active suppression that functions to limit the extent and duration of the overall T cell response. In closing, we propose possible experimental studies that could distinguish between theories of passive competition and active suppression and that could also determine whether iTregs play an significant role in immunodominance.

The paper is organized as follows. Background material is provided in Sect. 2: In Sect. 2.1, we overview various experimental works on immunodominance. In Sect. 2.2, we present an argument supporting active suppression as the main mechanism of T cell competition. In Sect. 2.3, we discuss various mathematical models of immunodominance. In Sect. 3, we extend the model of T cell expansion from (Kim et al. 2009) to include separate CD4+ and CD8+ T cell subpopulations and polyclonal T cell responses. In Sect. 4, we conduct numerical simulations of our model, while considering several different scenarios of mutually competing T cell responses. In Sect. 5, we provide a closing discussion and propose some experimental studies that could corroborate or falsify the hypothesis presented in the paper.

2 Background

2.1 Experimental Background

One prevalent theory for immunodominance is that T cells passively compete for access to APCs (Borghans et al. 1999; Grufman et al. 1999; Kedl et al. 2000, 2003). Nevertheless, Grufman et al. remark that active suppression via T cells cannot be entirely excluded, since the experiments of Taams et al. (1998) show that anergic T cells actively mediate T cell suppression via APCs and such suppression is not simply mediated by passive competition for ligands on the APC surface or by soluble factors secreted by anergic T cells (Grufman et al. 1999). Kedl et al. also put forward the possibility that regulatory T cells might compete against conventional T cells for access to APC binding sites (Kedl et al. 2000).

Regardless of the precise mechanism, these works concur that T cell interference only occurs when different epitopes are presented on the same APC (Grufman et al. 1999; Kedl et al. 2000, 2003; Roy-Proulx et al. 2001). These studies stress that T cell inhibition happens both when T cells of the same specificity compete for the same antigen and when T cells of different specificity compete for different antigen presented on the same APC, i.e., cross-competition. On the contrary, Probst et al. claim,

based on another experimental study, that cross-competition is not of functional relevance in antiviral immune responses (Probst et al. 2002). In response, Kedl et al. agree that cross-competition is difficult to demonstrate and may not be observable in all circumstances (Kedl et al. 2003). Nonetheless, they maintain that cross-competition is a key factor in immunodominance, because immunodominance has been observed primarily in the context of cross-competition among responses against different (i.e., dominant and subdominant) epitopes. The experimental studies above also show that the effects of immunodominance can be overcome by immunizing mice with large numbers of APCs, lending further evidence to the notion that competition occurs at the level of APCs (Borghans et al. 1999, Grufman et al. 1999; Kedl et al. 2000, 2003).

With regard to secondary challenge, Grufman et al. show that repeated reinfections may result in emerging responses against previously subdominant epitopes (Grufman et al. 1999). However, Kedl et al. observe that after reinfection, the average T cell affinity to target antigen increases as higher affinity clones become more prevalent (Kedl et al. 2000), and by extension, multiple stimulations by the same antigen eventually select T cell clones with the highest affinity (Kedl et al. 2003). These observations can be reconciled by the realization that precursor frequency plays a prominent role in determining immunodominance during a primary response, whereas affinity plays a major role in determining whether the hierarchy shifts during a secondary response (Kedl et al. 2003).

Despite the current view that T cells passively compete for access to space on APCs, Probst et al. present a significant counterargument. They note that their experiments could not reproduce the results of (Kedl et al. 2000). Specifically, in their experiments, T cells of one specificity did not inhibit the priming of T cells of other specificities, even if all epitopes were presented on the same APC (Probst et al. 2002). This observation implies that differences in dominant and subdominant clones might emerge from differences in expansion rather than in priming. Probst et al. note that experimental differences may have arisen because Kedl et al. used peptide-loaded dendritic cells (Kedl et al. 2000), while their dendritic cells produced antigen endogenously, resulting in more physiological levels of antigen presentation (Probst et al. 2002).

Probst et al. also point out that antigen-specific CD8+ T cell precursors normally comprise a small population that disperses over numerous lymphoid organs, making it hard to see how crowding could operate under physiological circumstances (Probst et al. 2002). In conclusion, they reject the hypothesis that passive competition for APC space plays a major role in immunodominance and put forward the alternative hypothesis that immunodominant T cell clones actively inhibit the development (i.e., priming and/or expansion) of subdominant clones by eliminating APCs, either through killing or by active suppression. Roy-Proulx et al. also support the idea of active elimination and propose that CD8+ T cells may kill APCs or exhaust them through repeated stimulation (Roy-Proulx et al. 2001).

The remark that crowding may not play a functional role in T cell stimulation is independently corroborated by recent observations. Using real-time two-photon microscopy, Busso et al. indicate that dendritic cells (DCs) interact efficiently with T cells and that one DC could potentially be scanned by 500 T cells in one hour (Bousso and Robey 2003). In addition, they conclude that if enough antigen is

present, the limiting factor in the number of T cells that a DC can engage simultaneously is the surface area of the DC (Bousso and Robey 2003). In a separate study, Miller et al. conclude based on surface area estimates that a single DC could interact with as many as 300 T cells simultaneously, and they estimate from observed scanning rates that each DC routinely contacts an average of 250 T cells at any instant (Miller et al. 2004a). Furthermore, they estimate a T cell precursor frequency of 1 in 10^5 to 10^6, from which they conclude that even a few DCs could recruit nearly all antigen-specific precursors in a lymph node with high probability (Miller et al. 2004a). In another study focusing on T cell clustering around APCs, Miller et al. observe that a rapid turnover of T cell contacts with APCs allows many T cells to be primed at once (Miller et al. 2004b).

2.2 The Main Argument for Active Suppression

Along the lines of the experimental observations and reasoning of Grufman et al. (1999), Probst et al. (2002), Roy-Proulx et al. (2001), we argue that active suppression among T cell responses cannot be entirely excluded as a mechanism driving immunodominance. In fact, we argue that some form of active suppression could play a significant role in producing this phenomenon. Our main line of reasoning is based on the notion of antigen-independent T cell proliferation and contraction during the primary T cell response. Various experimental studies *in vivo* and *in vitro* have developed this notion that CD4+ and CD8+ T cells function autonomously after activation and can complete their phases of expansion and differentiation without further antigen stimulation (Kaech and Ahmed 2001; Mercado et al. 2000; Razvi et al. 1995; Renno et al. 1999; van Stipdonk et al. 2003; Yang et al. 1998). Moreover, experiments of Mercado et al. show that removing antigen stimulation 24 hours after infection by *L. monocytogenes* does not affect the expansion and contraction kinetics of the T cell response to the dominant or to the subdominant epitope (Mercado et al. 2000). This evidence implies that primed T cells only depend on interaction with APCs during initial stimulation (approximately 24 hours after antigen exposure), and as demonstrated in Bousso and Robey (2003), Miller et al. (2004a, 2004b), overcrowding of APCs does not occur during this period, when DCs scan the lymph node efficiently.

On the other hand, APC crowding and competition for resources may play a significant role during the latter phases of the primary T cell response. At this point, remaining T cells compete for survival signals from IL-7 and IL-15 (and/or MHC complexes on APCs) during the transition from effector cells to long-lived memory cells (Surh and Sprent 2008). However, in this paper, we concentrate on immunodominance during the primary T cell response when T cell kinetics are predominantly governed by antigen-independent mechanisms. Based on the arguments above, *we hypothesize that T cell competition during the primary response involves a significant level of active suppression rather than only passive interference.*

2.3 Mathematical Models of Immunodominance

Several mathematical models have associated immunodominance with the concept of competitive exclusion, an ecological principle that states that when two species (e.g.,

T cells) compete for the same resources (e.g., antigen) one will overpower the other one and eliminate it. For example, De Boer and Perelson show that for each target epitope only the T cell clone with the highest affinity will survive long-term T cell competition (De Boer and Perelson 1994, 1995).

In another study of long-term immunodominance, Nowak develops a mathematical model and predicts that for an antigenically homogeneous virus population, the immune response will ultimately be directed against only one epitope, a situation known as *complete immunodominance* (Nowak 1996). In this case, the epitope with the highest immunogeneity becomes immunodominant. On the other hand, the model predicts that for a heterogeneous virus population, multiple immune responses against different epitopes may coexist. In addition, interactions between the immune response and the heterogeneous viral population can lead to oscillating antigen levels and fluctuating immune responses. Nowak remarks that competitive exclusion applies only to long-term immunodominance and not to acute infections, when multiple responses to different epitopes may arise temporarily.

De Boer et al. formulate a mathematical model to analyze experimental measurements of the CD8+ T cell response to lymphocytic choriomeningitis virus (De Boer et al. 2001). The response consists of one immunodominant response and one subdominant response against different epitopes. De Boer et al. propose that differences in growth rate and recruitment times of different T cell populations can account for immunodominance. Antia et al. also formulate a model in which multiple epitope-specific T cell populations undergo a brief period of expansion in response to antigen, followed by a period of antigen-independent proliferation and contraction (Antia et al. 2003). The dynamics of their model are consistent with the results of De Boer et al. (2001) that immunodominance is affected by differences in precursor frequency and time of initiation of different epitope-specific T cell responses.

Scherer et al. present an alternative mathematical model in which the downmodulation of antigen-presentation leads to long-term coexistence of T cell responses (Scherer and Bonhoeffer 2005). Their hypothesis operates independently of viral heterogeneity and does not imply the necessity of a high mutation rate or even any mutation rate for the viral population. In their model, APCs that have stimulated T cells of a certain specificity are no longer able to stimulate T cells of the same specificity. This assumption is based on an experimental study of Manca, who proposes that interactions with T cells induce APCs to internalize affected MHC complexes (Manca 1992). Under this assumption, the model of Scherer et al. gives rise to long-term persistence of broad T cell responses against multiple epitopes.

In another study, Scherer et al. devise an agent-based model to understand whether T cells compete for nonspecific stimuli, such as access to the surface of APCs, or for specific stimuli, such as MHC:epitope complexes (Scherer et al. 2006). Their model shows that the density of target epitopes per APC influences whether the competition is mainly for specific or nonspecific stimuli. Specifically, for low epitope density, T cells mostly compete for specific epitopes, thus allowing T cells of different epitope-specificity to coexist. On the other hand, for high epitope density, T cell competition becomes more nonspecific, leading to strong competitive exclusion between different epitope-specific T cell populations, leading to a narrower response.

Handel and Antia develop a mathematical model to explain the shift in the immunodominance hierarchy between the primary and secondary responses to influenza A

(Handel and Antia 2008). They conclude that during primary infection, antigen-specific precursor concentrations are low, allowing all reactive T cells to be fully activated. However, upon reinfection, precursor concentrations are high, allowing only one T cell clone to expand significantly due to competition for APCs.

3 Mathematical Model of Adaptive Regulatory T Cell-Mediated Contraction

In this section, we extend our model for a monoclonal T cell response, introduced in Kim et al. (2009), to a polyclonal T cell response. The original model is based on the hypothesis that primary response may be governed by a feedback control system involving adaptive regulatory cells (iTregs) rather than by intrinsic, intracellular feedback mechanisms. In summary, iTregs differentiate *de novo* from nonregulatory (CD4+CD25-FOXP3-) T cells in the periphery during an immune response (Walker et al. 2005), and the appearance of regulatory T cells produces a negative feedback loop that controls the size of the immune response. Our simulations show that this feedback loop (either in conjunction with or independently of intracellular feedback) responds robustly over a range of four orders of magnitude of precursor concentrations, a result that cannot be reproduced by a purely intracellular feedback mechanism (Kim et al. 2009). We extend the work in Kim et al. (2009) by explicitly modeling the interactions between CD4+ and CD8+ T cells and by considering polyclonal T cell populations. Through this extended model, we show that the suppression of effector T cells by iTregs recreates elements of the behavior associated with immunodominance. In this way, we show that immunodominance may occur as a natural result of iTreg-mediated self-regulation of polyclonal T cell responses.

The mathematical model presented in this paper is an extension of the model from Kim et al. (2009). The key extensions of the model are to separate the nonregulatory T cell population into CD4+ and CD8+ T cells and to consider polyclonal T cell responses. The model can be summarized in six steps (illustrated in Fig. 1):

1. APCs mature, present relevant target antigen, and migrate from the site of infection to the draining lymph node.
2. In the lymph node, APCs activate naïve CD4+ and CD8+ T cells that enter a minimal developmental program of m_1 or m_2 cell divisions, respectively.
3. Effector CD4+ and CD8+ T cells both secrete positive growth signal at different rates.
4. CD4+ and CD8+ T cells that have completed the minimal developmental program become effector cells that keep dividing as long as they are not suppressed by iTregs.
   - CD4+ T cells proliferate in response to interactions with APCs. (It is assumed that CD4+ T cells produce enough IL-2 to stimulate their own growth in an autocrine loop. Hence, we do not explicitly model the secretion and consumption of IL-2 by CD4+ T cells.)
   - CD8+ T cells proliferate after consuming free positive growth signal.
5. Effector CD4+ cells differentiate into iTregs at a constant rate.

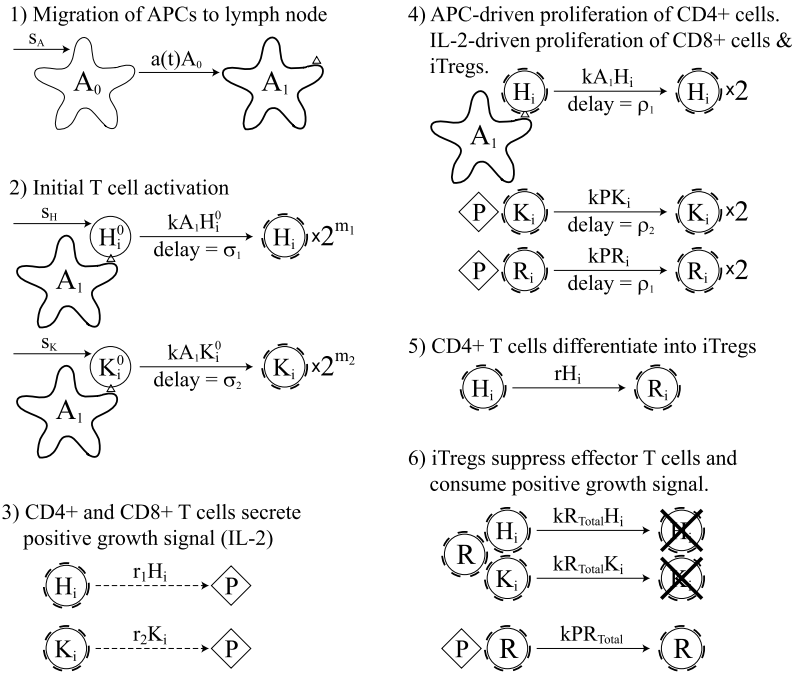

Fig. 1 Diagram of polyclonal T cell response model. (*1*) Immature APCs pick up antigen at the site of infection at a time-dependent rate $a(t)$. These APCs mature and migrate to the lymph node. (*2*) Mature antigen-bearing APCs present antigen to naïve CD4+ and CD8+ T cells causing them to activate and enter the minimal developmental program of m_1 or m_2 divisions, respectively. (*3*) Effector CD4+ and CD8+ T cells secrete positive growth signal at rates r_1 and r_2, respectively. (*4*) CD4+ and CD8+ T cells that have completed the minimal program continue to divide upon further stimulation. CD4+ cells divide in response to interactions with APCs, and CD8+ cells divide after consuming positive growth signal. (*5*) Effector CD4+ cells differentiate into iTregs at rate r. (*6*) The iTregs suppress effector CD4+ and CD8+ cells in a contact-dependent manner and divide after consuming positive growth signal. Although not indicated, each cell in the diagram has an associated natural death rate

6. The iTregs suppress effector CD4+ and CD8+ cells in a contact-dependent manner and proliferate after consuming free positive growth signal.

The T cell dynamics in the model are based on the concept of antigen-independent T cell proliferation and contraction. Various experiments have shown that the during a primary CD8+ T cell response, T cell kinetics are determined early on (after approximately 24 h of stimulation) (Mercado et al. 2000), T cell expansion and differentiation are antigen-independent after initial exposure (approximately 20 h of stimulation) (van Stipdonk et al. 2003), and T cells divide at least 7–10 times after stimulation even if antigen is removed (Kaech and Ahmed 2001). Similar results have been found for CD4+ T cells (Yang et al. 1998). These results along with other related studies have led to the notion of *antigen-independent T cell program*. The main principle is that following initial stimulation, the primary T cell response is governed as if by an independent *program* that is highly insensitive to the nature and duration of subsequent antigen stimulation. The implication is that T cells somehow regulate them-

selves during a primary response without feedback from the antigen source. Since in this paper we only consider immunodominance during a primary T cell response, we model T cell dynamics from the perspective of an antigen-independent, self-regulating process. Other examples of mathematical models of antigen-independent primary T cell response dynamics can be found in Antia et al. (2003), Wodarz and Thomsen (2005).

The mathematical model corresponding to Fig. 1 is formulated as the following system of delayed differential equations (DDEs):

$$\dot{A}_0(t) = s_{\mathrm{A}} - d_0 A_0(t) - a(t)A_0(t), \tag{1}$$

$$\dot{A}_1(t) = a(t)A_0(t) - d_1 A_1(t), \tag{2}$$

$$\dot{H}_i^0(t) = s_{\mathrm{H,i}} - \delta_0 H_i^0(t) - k_i A_1(t) H_i^0(t), \tag{3}$$

$$\begin{aligned}\dot{H}_i(t) = {} & 2^{m_1} k_i A_1(t-\sigma_1) H_i^0(t-\sigma_1) - k_i A_1(t) H_i(t) + 2k_i A_1(t-\rho_1) H_i(t-\rho_1) \\ & - (\delta_H + r) H_i(t) - k R_{\mathrm{total}}(t) H_i(t),\end{aligned} \tag{4}$$

$$\dot{K}_i^0(t) = s_{\mathrm{K,i}} - \delta_0 K_i^0(t) - k_i A_1(t) K_i^0(t), \tag{5}$$

$$\begin{aligned}\dot{K}_i(t) = {} & 2^{m_2} k_i A_1(t-\sigma_2) K_i^0(t-\sigma_2) - k P(t) K_i(t) + 2k P(t-\rho_2) K_i(t-\rho_2) \\ & - \delta_K K_i(t) - k R_{\mathrm{total}}(t) K_i(t),\end{aligned} \tag{6}$$

$$\dot{P}(t) = r_1 H_{\mathrm{total}}(t) + r_2 K_{\mathrm{total}}(t) - \delta_P P(t) - k P(t) K_{\mathrm{total}}(t) - k P(t) R_{\mathrm{total}}(t), \tag{7}$$

$$\dot{R}_i(t) = r H_i(t) - k P(t) R_i(t) + 2k P(t-\rho_1) R_i(t-\rho_1) - \delta_H R_i(t), \tag{8}$$

where $H_{\mathrm{total}} = \sum H_i$, $K_{\mathrm{total}} = \sum K_i$, and $R_{\mathrm{total}} = \sum R_i$ for $i = 1, \ldots, n$. The variable A_0 is the concentration of APCs at the site of infection and A_1 is the concentration of APCs that have matured, started to present target antigen, and migrated to the lymph node. For each clone i, the variable H_i^0 is the concentration of naïve CD4+ (helper) T cells, H_i is the concentration of effector CD4+ cells, K_i^0 is the concentration of naïve CD8+ (helper) T cells, and K_i is the concentration of effector CD8+ cells, and R_i is the concentration of iTregs. In addition, P is the concentration of positive growth signal (e.g., IL-2).

Equation (1) pertains to APCs waiting at the site of infection. These cells are supplied at a constant rate s_{A} and die at a proportional rate d_0. Without stimulation, the population remains at its equilibrium level, s_{A}/d_0. The time-dependent coefficient $a(t)$ is the rate of APC stimulation from antigen at the site of infection. Equation (2) pertains to APCs that have matured, started to present relevant antigen, and migrated to the lymph node. The first term of the equation corresponds to the rate at which these APCs enter the lymph node. The second term is the natural death rate of this population.

Equations (3) and (5) pertain to naïve CD4+ and CD8+ T cells, respectively. For each clone i, the CD4+ and CD8+ populations are replenished at constant rates $s_{\mathrm{H,i}}$ and $s_{\mathrm{K,i}}$, respectively, and die at a proportional rate δ_0. Without stimulation, the populations remain at their equilibrium levels, $s_{\mathrm{H,i}}/\delta_0$ and $s_{\mathrm{K,i}}/\delta_0$. The third terms in these equation are the rates of stimulation of naïve CD4+ and CD8+ T cells by mature APCs. The bilinear form of this term follows the law of mass action where

k is the proportionality constant (or kinetic coefficient). We assume all cell-cell or cell-signal interactions follow the same law of mass action.

Equation (4) pertains to effector CD4+ cells. The first term gives the rate at which activated naïve CD4+ T cells enter the effector state after finishing the minimal developmental program of m_1 cell divisions. The coefficient 2^{m_1} accounts for the increase in population after m_1 divisions, and the time delay σ_1 is the duration of the minimal developmental program. The second term is the rate at which effector CD4+ cells are stimulated by mature APCs for further division, and the third term is the rate in which cells reenter the effector CD4+ population after having divided once. The time delay ρ_1 is the duration of one CD4+ cell division. The fourth term is the rate at which effector CD4+ cells exit the population through death at rate δ_H or differentiation into iTregs at rate r. The final term is the rate at which effector CD4+ cells are suppressed by iTregs.

Equation (6) pertains to effector CD8+ cells. The first term gives the rate at which activated naïve CD8+ T cells enter the effector state after finishing the minimal developmental program of m_2 cell divisions. The coefficient 2^{m_2} accounts for the increase in population after m_2 divisions, and the time delay σ_2 is the duration of the minimal developmental program. The second term is the rate at which effector CD8+ cells are stimulated by positive growth signal for further division, and the third term is the rate at which cells reenter the effector CD8+ population after having divided once. The time delay ρ_2 is the duration of one CD8+ cell division. The fourth term is the rate at which effector CD8+ cells die at rate δ_K. The final term is the rate at which effector CD8+ cells are suppressed by iTregs.

Equation (7) pertains to positive growth signal. The first two terms are the rates at which positive growth signal is secreted by effector CD4+ and CD8+ cells, respectively. The third term is the decay rate of positive growth signal. The fourth and fifth terms are the rates at which positive growth signal is consumed by effector CD8+ cells and iTregs, respectively.

Equation (8) pertains to iTregs. The first term is the rate at which effector CD4+ cells differentiate into iTregs. The second term is the rate at which iTregs are stimulated by positive growth signal for further division, and the third term is the rate at which cells reenter the iTreg population after having divided once. The time delay ρ_1 is the duration of one CD4+ cell division. The fourth term is the rate at which iTregs die. We assume that iTregs have the same division time and death rate as CD4+ cells.

The parameter estimates used for this model are mostly taken from (Kim et al. 2009), where applicable. For parameters pertaining to CD4+ and CD8+ populations, we assume CD4+ and CD8+ cells have a half-life of 3 days and 41 hours, respectively, yielding death rates of $\delta_H = 0.23$ and $\delta_K = 0.4$/day (De Boer et al. 2003). In addition, we assume CD4+ and CD8+ populations have doubling times of 11 hours and 8 hours, respectively, yielding cell division rates of $\rho_H = 11/24$ and $\rho_K = 1/3$ day (De Boer et al. 2003). For the minimal developmental programs, we take the value of $m_2 = 7$ divisions for CD8+ cells used in Kim et al. (2009), and assume that $m_1 = 2$ divisions for CD4+ cells, since CD4+ cells do not proliferate as extensively as CD8+ cells (De Boer et al. 2003). We assume that the total initial concentration, $\sum K_i^0(0)$, of CD8+ cells is around 0.04 k/μL as estimated in Kim et al. (2009), and we assume that the total initial concentration, $\sum H_i^0(0)$, of CD4+ cells is around

Table 1 Estimates for model parameters. Concentrations are in units of k/μL, and time is measured in days

Parameter	Description	Estimate
$A_0(0)$	Initial concentration of immature APCs	10
$H_i^0(0)$	Initial naïve CD4+ T cell concentration for clone i	$\sum H_i^0(0) = 0.06$
$K_i^0(0)$	Initial naïve CD8+ T cell concentration for clone i	$\sum K_i^0(0) = 0.04$
d_0	Death/turnover rate of immature APCs	0.03
d_1	Death/turnover rate of mature APCs	0.8
δ_0	Death/turnover rate of naïve CD4+ and CD8+ T cells	0.03
δ_H	Death/turnover rate of effector CD4+ T cells	0.23
δ_K	Death/turnover rate of effector CD8+ T cells	0.4
s_A	Supply rate of immature APCs	$d_0 A_0(0) = 0.3$
$s_{\mathrm{i,H}}$	Supply rate of naïve CD4+ T cells from clone i	$\delta_0 H_i^0(0)$
$s_{\mathrm{i,K}}$	Supply rate of naïve CD8+ T cells from clone i	$\delta_0 K_i^0(0)$
k	Kinetic coefficient	20
m_1	# of divisions in minimal CD4+ developmental program	2
m_2	# of divisions in minimal CD8+ developmental program	7
ρ_H	Duration of one T cell division	11/24
ρ_K	Duration of one T cell division	1/3
σ_H	Duration of minimal developmental program	$1 + (m_1 - 1)\rho_H = 1.46$
σ_K	Duration of minimal developmental program	$1 + (m_2 - 1)\rho_K = 3$
r_1	Rate of secretion of positive growth signal by CD4+ cells	100
r_2	Rate of secretion of positive growth signal by CD8+ cells	1
δ_P	Decay rate of free positive growth signal	5.5
r	Rate of differentiation of effector CD4+ cells into iTregs	0.02
$a(t)$	Rate of APC stimulation	Equation (9)
b	Duration of antigen availability	10
c	Level of APC stimulation	1

$1.5 \sum K_i^0(0) = 0.06$ k/μL, which is the typically observed proportion of CD4+ and CD8+ T cells (Catron et al. 2004).

We do not have good estimates of the secretion rates of positive growth signal by effector T cells, hence we estimate that CD4+ and CD8+ T cells secrete positive growth signal at rates $r_1 = 100$ and $r_2 = 1$/day, respectively. We assume free positive growth signal decays with a half-life of 3 hours, yielding an estimate of $\delta_P = 5.5$/day. In this model, only effector CD4+ cells can differentiate into iTregs, so the new estimate of the iTreg differentiation rate, r, must be higher than the estimate of $r = 0.01$/day from Kim et al. (2009) to maintain similar dynamics. Hence, in this model, we assume $r = 0.02$/day. These parameter values are summarized in Table 1.

The function $a(t)$ represents the rate of antigen stimulation, and we assume that the function starts at 0, remains positive for some time, and eventually returns to 0.

To generate a smooth function for $a(t)$, we let

$$\phi(x) = \begin{cases} e^{-1/x^2}, & \text{if } x \geq 0, \\ 0, & \text{if } x < 0, \end{cases}$$

and set

$$a(t) = c\frac{\phi(t)\phi(b-t)}{\phi(b)^2}, \tag{9}$$

where $b, c > 0$. The variable t is defined such that mature APCs begin appearing in the lymph node at $t = 0$, although the infection may have begun slightly earlier. We estimate that the duration of antigen availability, b, is about 10 days. Furthermore, we estimate that the level of APC stimulation, c, is around 1. (See Fig. 2 for graphs of $a(t)$ for $b = 3$ and $b = 10$ when $c = 1$.)

Notice from (1)–(2) that the APC populations are independent of the T cell populations. Hence, we can evaluate the APC dynamics separately. Figure 3 shows the time evolution of the APC populations with parameters taken from Table 1. We numerically simulate the solution to (1)–(2) using the DDE solver "dde23" in MATLAB R2008a.

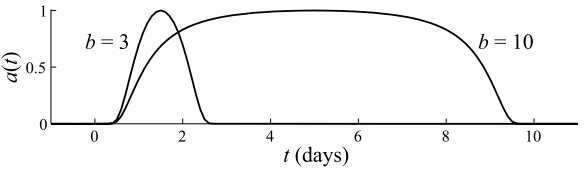

Fig. 2 Graphs of the antigen function $a(t)$ given by (9) for $b = 3$ and $b = 10$ when $c = 1$. The function $a(t)$ represents the time-dependent rate that immature APCs pick up antigen and are stimulated

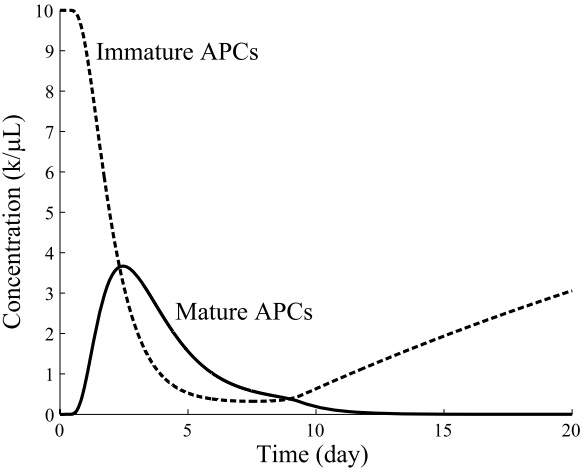

Fig. 3 Time evolution of immature and mature APCs. The mature APC population stimulates CD4+ and CD8+ naïve T cell activation and further CD4+ T cell proliferation

4 Results

We consider several scenarios of multiple T cell clones responding to the same target at once. Each T cell clone is characterized by its reactivity, p_i, to target antigen and its initial concentration, $N_i(0)$. We numerically simulate solutions to (1)–(8) using the DDE solver "dde23" in MATLAB R2008a.

Scenario 1 (Five T cell clones, different reactivities) For the first scenario, we consider five T cell clones with the same initial concentrations that only differ in terms of their reactivities to the target antigen. For $i = 1, \ldots, 5$ we set the reactivities $p_i = 2^{-i}$. The initial concentrations of naïve CD8+ cells are set to be $K_i(0) = 0.01$ k/μL, $\forall i$. In addition, the initial concentrations of naïve CD4+ cells are set to be $H_i^0(0) = 1.5K_i^0(0)$, which is the typically observed proportion of CD4+ and CD8+ T cells (Catron et al. 2004). We also consider cases of single knockout (SKO), double knockout (DKO), and triple knockout (TKO) experiments in which the T cell responses mediated by one, two, or three immunodominant T cell clones are removed. Our simulations are as follows:

(a) Control: No T cells are removed. Clones 1–5 all respond.
(b) Single knockout (SKO): Clone 1 is removed. Only clones 2–5 respond.
(c) Double knockout (DKO): Clones 1 and 2 are removed. Only clones 3–5 respond.
(d) Triple knockout (TKO): Clones 1–3 are removed. Only clones 4 and 5 respond.

We see from Fig. 4(a) that the CD8+ responses and the CD4+ responses of the five clones fall into hierarchies based on their initial concentrations. However, the removal of the immunodominant clone 1 does not lead to any compensation by clone 2 (see Fig. 4(b)). In fact, the response of clone 2 actually diminishes very slightly in the absence of clone 1. This phenomenon results because the feed forward loop of involving CD4+ cells and positive growth signal from clone 1, partially drives the expansion of the immune response from the less reactive clone 2. In the same manner, clone 3 does not compensate when clones 1 and 2 are removed, and clone 4 does not compensate when clones 1–3 are removed (see Fig. 4(c) and (d)). As a result, the five T cell clones in Scenario 1 exist in a hierarchy resembling codominance more than immunodominance.

Scenario 2 (Four clones, different initial concentrations) For the second scenario, we consider four T cell clones with the same reactivities that only differ in terms of their initial concentrations. In this case, all reactivities are assumed to be identical: $p_i = 1/2$, $i = 1, \ldots, 4$. The initial concentrations of naïve CD8+ cells are set to be $K_1^0(0) = 0.04$ k/μL, $K_2^0(0) = 0.01$ k/μL and $K_3^0(0) = 2.5 \times 10^{-3}$ k/μL, $K_4^0(0) = 6.25 \times 10^{-4}$ k/μL. In addition, the initial concentrations of naïve CD4+ cells are taken to be $H_i^0(0) = 1.5K_i^0(0)$. As before, we consider single knockout (SKO), double knockout (DKO), and triple knockout (TKO) experiments. Figure 5 shows numerical solutions for the control and knockout experiments of Scenario 2.

Figure 5(a) shows that the four T cell clones in Scenario 2 fall into a hierarchy based on their initial concentrations. However, unlike Scenario 1, when the dominant clone is removed, the second most frequent clone compensates effectively, even

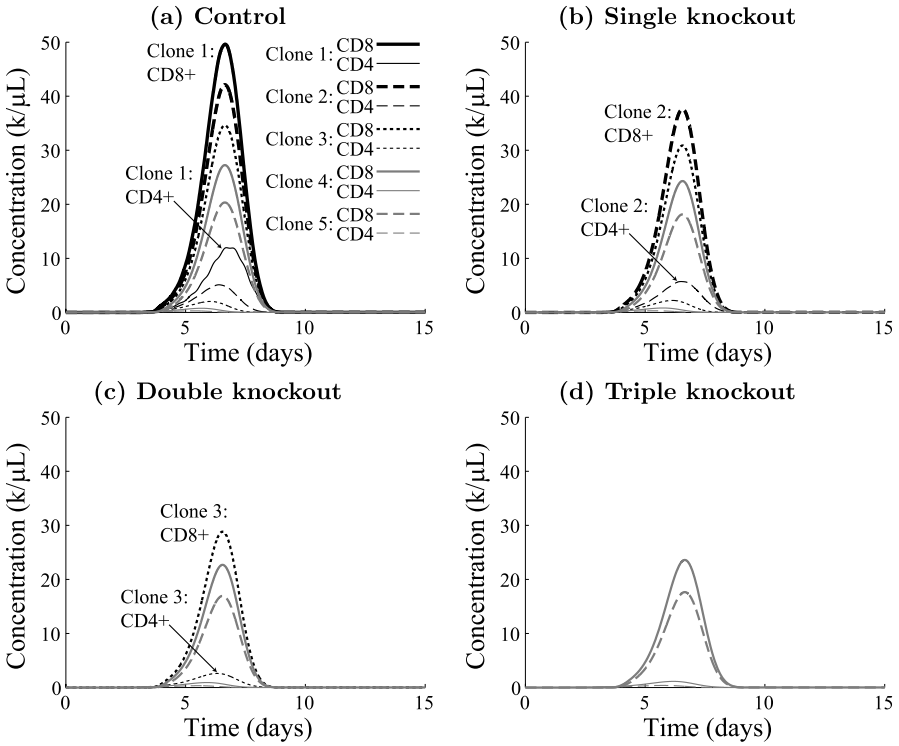

Fig. 4 Time evolution of CD4+ and CD8+ T cell populations for Scenario 1. Five T cell clones are present at the same initial concentration $K_i(0) = 0.01$ k/μL and $H_i(0) = 0.015$ k/μL with reactivities $p_1 = 1/2$, $p_2 = 1/4$, $p_3 = 1/8$, $p_4 = 1/16$, and $p_5 = 1/32$. All other parameters are taken from Table 1. (**a**) Control experiment: Clones 1–5 all respond. (**b**) SKO: Clone 1 is removed. Only clones 2–5 respond. (**c**) DKO: Clones 1 and 2 are removed. Only clones 3–5 respond. (**d**) TKO: Clones 1–3 are removed. Only clones 4 and 5 respond

though it starts with an initial concentration that is four time less than that of clone 1 (see Fig. 5(b)). In addition, when the two most dominant clones are removed the third most frequent clone also compensates effectively, and so on (see Figs. 5(c) and (d)).

Comparing Scenarios 1 and 2, we observe that clones that occur at similar concentrations, but with different reactivities (Scenario 1) are more likely to have little or no ability to compensate for immunodominant responses. On the other hand, clones that have similar reactivities, but occur at different concentrations (Scenario 2) are more likely to effectively compensate when immunodominant responses are removed.

The phenomenon of compensation was observed experimentally by van der Most et at. who showed that loss of epitope-specific responses was associated with compensatory responses against subdominant epitopes. In addition, their experiments showed that noticeable compensation by a subdominant response depended on the removal of all or most of the more dominant epitopes, creating room for subdominant epitopes to emerge (van der Most et al. 2003). In the same manner, our simulations of Scenario 2 show that a response from clone 2 does not substantially emerge until clone

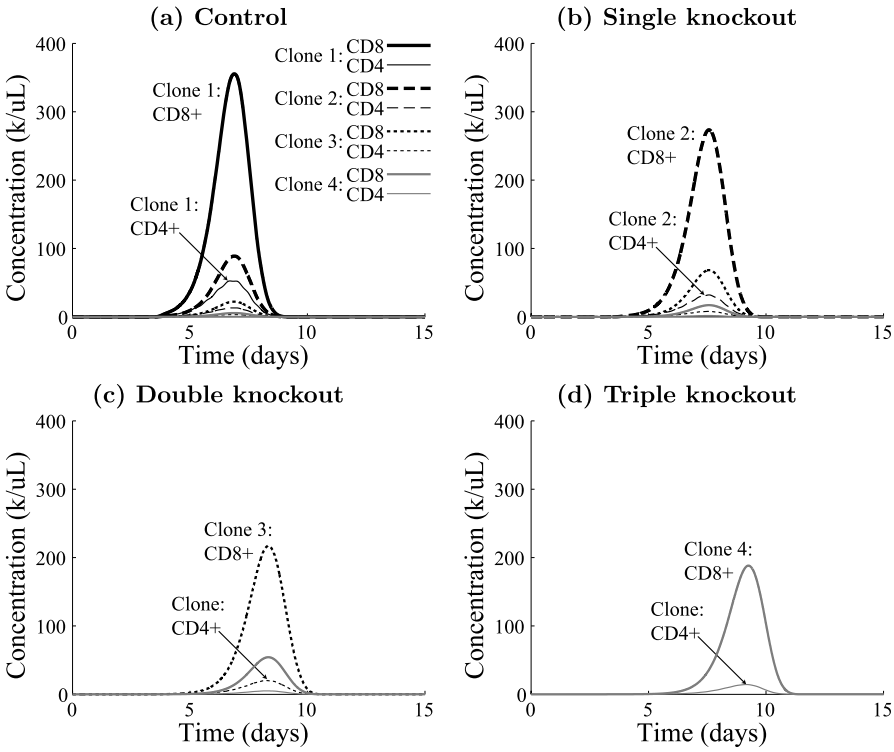

Fig. 5 Time evolution of CD4+ and CD8+ T cell populations for Scenario 2. Four T cell clones are present with the same reactivity $p_i = 1/2$ and initial naïve CD8+ concentrations $K_1^0(0) = 0.04$, $K_2^0(0) = 0.01$, $K_3^0(0) = 2.5 \times 10^{-3}$, and $K_4^0(0) = 6.25 \times 10^{-4}$ k/μL. Initial naïve CD4+ concentrations are given by $H_i^0(0) = 1.5K_i^0(0)$. All other parameters are taken from Table 1. (**a**) Control experiment: Clones 1–4 all respond. (**b**) SKO: Clone 1 is removed. Only clones 2–4 respond. (**c**) DKO: Clones 1 and 2 are removed. Only clones 3 and 4 respond. (**d**) TKO: Clones 1–3 are removed. Only clone 4 responds

1 is removed and that a response from clone 3 does not emerge until clones 1 and 2 are removed, and so on. By extension, a response against a subdominant epitope is likely not to emerge until all or most T cell clones that are specific for the dominant epitope (or epitopes) are removed. On the other extreme, Vihj et al. observed that the elimination of two dominant epitopes to *Listeria monocytogenes* does not lead to noticeable compensation by subdominant responses (Vijh et al. 1999). These different results show that compensation does not occur in all circumstances or in the same manner. Some key differences must occur in the immune responses to different targets that causes compensation to either effectively or almost not at all. From our results, we hypothesize that compensation occurs if subdominant T cell clones are nearly as reactive or even more reactive than immunodominant clones.

Scenario 3 (Two clones, one with a higher reactivity and one with a higher precursor concentration) In Scenarios 1 and 2, we examined the effects of varying reactivities and initial concentrations separately. For the third scenario, we vary both parame-

ters and consider two clones. We start by considering a possible primary response in which the more reactive clone starts at a lower concentration than the less reactive clone. For our hypothetical secondary response, the initial concentrations are reversed.

1. Reactivity: $p_1 = 1/2$. Initial CD8+ concentrations: $K_1(0) = 0.004$ (primary), 0.04 (secondary) k/μL.
2. Reactivity: $p_2 = 1/4$. Initial CD8+ concentrations: $K_2(0) = 0.04$ (primary), 0.004 (secondary) k/μL.

As before, in all cases, initial CD4+ concentrations are set by the relation $H_i(0) = 1.5K_i(0)$.

Figure 6 shows numerical solutions for Scenario 3. From Fig. 6(a), we see that the clone with the higher initial concentration dominates during the primary response. Indeed, clone 2 produces a response that is about three times as high as the response of clone 1. However, by day 10, the population of clone 1 persists whereas the population of clone 2 has nearly vanished. The more reactive clone, clone 1, ends up producing a more long-lived T cell response than clone 2, and so it follows that this clone might also end up producing a greater number of memory T cells and hence a stronger secondary response.

Figure 6 shows numerical solutions for Scenario 3. From Fig. 6(a), we see that the more frequent clone dominates the primary response. Indeed, clone 2 produces significantly stronger CD4+ and CD8+ responses than clone 1. However, the more reactive clone, clone 1, ends up producing a more long-lived CD4+ T cell response than clone 2, so it follows that clone 1 might also end up producing a greater number of memory CD4+ T cells than clone 2. For now, we leave the explicit modeling of memory T cell formation for a future work. Nonetheless, we see from Fig. 6(a) that iTreg-mediated contraction could give rise to a natural process of "collective affinity

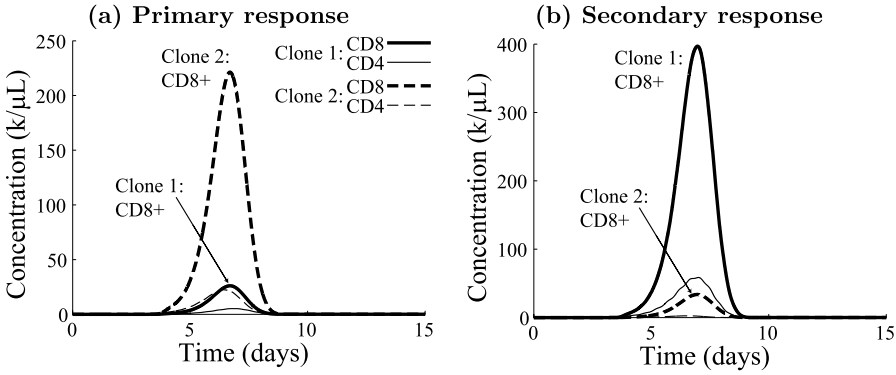

Fig. 6 Time evolution of CD4+ and CD8+ T cell populations for Scenario 3. Reactivities of the two clones to target antigen are $p_1 = 1/2$ and $p_2 = 1/4$. (**a**) Primary response. The less reactive clone is more common. Initial concentrations for the two clones are $(K_1(0), H_1(0)) = (0.004, 0.006)$ and $(K_2(0), H_2(0)) = (0.04, 0.06)$ k/μL. (**b**) Secondary response. The two clones have switched places, and now the more reactive clone is more common. Initial concentrations for the two clones are $(K_1(0), H_1(0)) = (0.04, 0.06)$ and $(K_2(0), H_2(0)) = (0.004, 0.006)$ k/μL. All other parameters are taken from Table 1

maturation" that enables the CD4+ memory repertoire to select for highly reactive clones even when these clones do not produce the most dominant primary responses.

On the other hand, unlike the CD4+ T cell response, the CD8+ T cell response from clone 1 does not outlast the CD8+ T cell response from clone 2, since CD8+ proliferation during the latter part of the immune response is driven by interaction with the positive growth signal rather than by antigen-specific interaction with APCs. According to these results, it seems that any "collective affinity maturation" of the CD8+ T cell memory pool would have to be predetermined by interactions early in the T cell response, whereas the composition of the CD4+ memory pool could be continually adjusted from feedback during the course of the immune response.

Without explicitly modeling memory T cell formation, let us suppose that between primary and secondary responses, the composition of the T cell repertoire shifts in favor of the more reactive T cell clone. In particular, suppose that for the hypothetical secondary response, the initial concentrations are reversed. Then Fig. 6(b) shows that clone 1 clearly dominates the secondary response. Furthermore, both primary and secondary responses start with the same total initial concentration of T cells, but a much stronger response from clone 1 causes the combined secondary response to peak at twice the height of the combined primary response.

For simplicity, we generated a hypothetical secondary response by switching the initial concentrations of the two T cell populations, but there is no reason to assume that initial concentrations must switch or that the total initial population must stay the same. In fact, the memory pool generated after a primary response is probably larger than the original naïve T cell pool. Yet even with this simplified view of collective affinity maturation, we see that simple shifts in the relative distribution of T cell clones may result in large differences in subsequent responses. Hence, a mechanism of immunodominance mediated by iTregs may serve as a global, self-organizing phenomenon among simultaneous T cell responses that serves to improve the overall quality (rather than just the quantity) of the T cell repertoire.

5 Discussion

In this paper, we formulate a novel mathematical model to address the phenomenon of immunodominance. In particular, we propose that immunodominance may occur as a natural consequence of iTreg-mediated T cell contraction. The notion that short-lived iTregs, generated in the periphery, may induce a timely T cell contraction during an acute T cell response was proposed in Kim et al. (2009). Here, we propose that the self-regulating mechanism induced by individual effector cells also functions to control the extent of the global T cell response.

The model in this paper is formulated as a system of interdependent feedback loops, in which each *antigen-specific* T cell population produces a *nonspecific* feedback response that inhibits itself and simultaneous T cell responses. This system falls into the general category of mutual competition models. However, prevalent models for immunodominance have focused on passive competition for some external resource (e.g., antigen, De Boer and Perelson 1994, 1995; Nowak 1996 or access to APCs and MHC:epitope complexes, Handel and Antia 2008; Scherer et al. 2006) rather than active suppression between competing populations.

Hence, our mathematical model falls more along the lines of the hypothesis proposed by Probst et al. and Roy-Proulx et al. that immunodominant T cell clones actively inhibit the expansion of other clones, in particular by suppressing or eliminating APCs (Probst et al. 2002; Roy-Proulx et al. 2001). Our hypothesis differs, however, in that we propose iTregs as the primary agents of inhibition.

We develop a mathematical model of T cell dynamics in which nonregulatory T cells are actively suppressed by iTregs that appear later in the immune response. From this study, we hypothesize that the nature of immunodominance and compensation depends on the precursor frequencies and reactivities of competing T cell clones. Specifically, we propose that precursor frequency plays the primary role in determining the initial immunodominance hierarchy, but that reactivity plays a significant role in determining the ability of subdominant clones to compensate when immunodominant clones are removed.

In the current paper, we have not taken into account the suppression of APCs by iTregs, although it is a known function of regulatory T cells (Chang et al. 2002). Incorporating suppression of APCs is a direction for a future work and may partly explain why competition is only observed for epitopes presented on the same APC. In this light, considering spatial elements is another relevant extension, since regulatory T cells locally suppress cells in a contact-dependent manner, but no longer inhibit cells that have moved out of the vicinity (Trimble and Lieberman 1998). Specifically in the context of immunodominance, regulatory (or suppressor) T cells give rise to highly localized inhibition that operates only in the context of one or a few common APCs (Sercarz et al. 1993). Also, in their mathematical models, León et al. assume that regulatory and effector cells need to be activated by APCs that are close in space and time in order to interact (León et al. 2007a, 2007b). Indeed, such localization may be necessary to prevent a regulatory response from shutting down the whole immune system.

What determines rates of different T cell responses, and hence immunodominance? According to the model, when precursor frequencies are equal, T cells that are more reactive to the target antigen produce the dominant responses (see Scenario 1 in Sect. 4). Similarly, when reactivities are equal, T cell populations that have higher precursor frequencies produce the dominant responses (see Scenario 2 in Sect. 4). With regard to the relative influences of reactivity and precursor frequency, we find that during a primary response, T cells with higher precursor frequencies tend to initiate faster, and hence produce the dominant immune responses initially, whereas T cells with higher reactivities to the target antigen persist longer, and thus are likely to produce larger memory populations (see Scenario 3 in Sect. 4). Therefore, more reactive T cell populations are likely to become progressively more dominant upon repeated reinfection, even if they had been subdominant initially. In this way, the interaction between T cell reactivity and precursor frequency in our model agrees with the experimental results of Grufman et al. (1999), Kedl et al. (2000, 2003), discussed in Sect. 2.1.

The principal claim of this paper is that iTregs not only contribute to the timely contraction of a T cell response to pathogen (Kim et al. 2009), but also to a focused response that hones the memory repertoire toward the most reactive clones. In other words, immunodominance provides a means of peripheral positive selection that may

be optimal in most circumstances, since it generates highly adapted responses against specifically targeted antigen. However, this phenomenon is disadvantageous against rapidly evolving pathogens such as HIV or cancer that can evade narrow T cell responses. Hence, our model of iTreg-mediated immunodominance may have implications for improving therapy via T cell vaccinations. In particular, our model suggests that temporarily suppressing the generation of *de novo*-generated iTregs following a T cell vaccination may result in a broader T cell response than normal against multiple target epitopes, which will then make it more likely for the immune system to eliminate rapidly evolving targets that would otherwise escape immune detection. In this light, a relevant study would be to obstruct the development of iTregs during infection and to see whether this difference results in greater breadth of the overall T cell response.

As discussed in Sect. 2.1, various experimental studies have shown that the immunodominance can be overcome by immunizing mice with large numbers of dendritic cells, suggesting that competition occurs at the level of APCs (Borghans et al. 1999; Grufman et al. 1999; Kedl et al. 2000, 2003). However, in these studies, wide ranges of dendritic cells were used, spanning at least one order of magnitude (Kedl et al. 2000). These results seem to suggest that T cells do not passively compete for access to space on APCs. For if competition were only passive, one could overcome the effects of immunodominance by merely doubling the number of dendritic cells, which would then provide sufficient free space on APCs to stimulate the subdominant response. Therefore, one possible experiment to test the plausibility of passive versus active competition for APCs would be to measure the expansion levels of dominant and subdominant T cell responses if 2, 3, 4, or 10 times the normal population of dendritic cells were introduced. It is, in fact, possible that this data is already available from the experimental studies mentioned above.

As mentioned above, another experiment that may have application to developing T cell vaccines is to inhibit the development of iTregs in the periphery. Our model predicts that such a knockout would lead to reduced immunodominance, resulting in a heightened multiepitope immune response. In this case, another competitive regulatory mechanism with different dynamical behavior would likely come into play. Observing how the nature of T cell competition and regulation changes with or without iTregs would indicate whether or not iTregs play a significant role in maintaining immunodominance.

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