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A mathematical model for a T cell fate decision algorithm during immune response

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AUTHOR-HIGHLIGHTS

- We suggest a deterministic molecular algorithm for individual T cell fate choice in immune response.
- We model a simple version of such algorithm in mathematical terms.
- We show that collective patterns can emerge from individual T cell decisions.

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ABSTRACT

We formulate and analyze an algorithm of cell fate decision that describes the way in which division vs. apoptosis choices are made by individual T cells during an infection. Such model involves a minimal number of known biochemical mechanisms: it basically relies on the interplay between cell division and cell death inhibitors on one hand, and membrane receptors on the other. In spite of its simplicity, the proposed decision algorithm is able to account for some significant facts in immune response. At the individual level, the existence of T cells that continue to replicate in the absence of antigen and the possible occurrence of T cell apoptosis in the presence of antigen are predicted by the model. Moreover, the latter is shown to yield an emergent collective behavior, the observed delay in clonal contraction with respect to the end of antigen stimulation, which is shown to arise just from individual T cell decisions made according to the proposed mechanism.

1. Introduction

Cytotoxic T cells (henceforth referred to as T lymphocytes or T cells) play a major role in the immune response against pathogens. As soon as pathogenic agents are detected, naïve T cells activate and differentiate into effector cells that mediate pathogen removal. To that end, T cells must undergo massive proliferation in order to offset the high growth rates characteristic of many infectious microorganisms. In a few days they can go through 15–20 rounds of cell division, thus increasing the population of activated T cells by up to 10^6 times, a process known as clonal expansion. Following pathogen clearance, massive apoptosis of activated T cells restores initial population levels, a phenomenon which is termed clonal contraction. Some activated T cells (around 5–10% of the cells present at the peak of the expansion) are spared, though, and revert to a resting state, thus generating an immune memory that provides rapid response potential in case of a new infection by the same agent (Grayson et al., 2002). Interestingly, a delay in time is observed between the onset of clonal contraction and the sharp drop in antigenic stimulation that precedes it (Williams and Bevan, 2007).

Clonal expansion and contraction, and the formation of an immune memory can be viewed as the global, population-scale manifestation of many individual choices taken by activated T cells between dividing, becoming a memory cell or dying. Experimental evidence reveals that antigenic stimulation by itself is not enough to account for such individual choices. Actually, in the course of acute infections, activated T cells continue to divide even when that stimulus is absent (Badovinac et al., 2002) (see Fig. 1). On the other hand, effector T cells may undergo apoptosis even if antigenic stimulation is still available (Badovinac et al., 2002).

To explain the diversity of individual fates and the emergence of such collective behavior, several hypotheses have been formulated (Buchholz et al., 2013). For instance, it has been suggested that activation could trigger a developmental program in naïve

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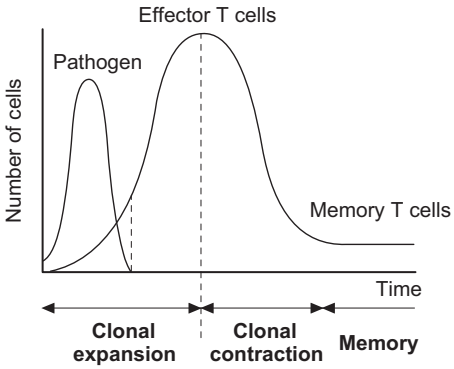

Fig. 1. Dynamics of T cell populations during acute infections. The observed delay between pathogen clearance and the onset of clonal contraction implies that T cells continue to divide in the absence of pathogens.

T cells whose subsequent execution would be largely independent of antigen stimulation (Kaech and Ahmed, 2001; van Stipdonk and et al., 2003; Mercado et al., 2000). According to this scenario, effector T cells would initiate the apoptosis program, thus causing the onset of clonal contraction, after a number of rounds of cell division ranging from a fixed minimum (7–10) to a variable maximum (related to the level of antigenic stimulation in individual naïve T cells), referred to as "division destiny" (Hawkins et al., 2007). Under such assumption, the antigenic stimulation perceived by a naïve T cell during activation would determine the fate of its whole progeny. In particular, sibling T cells would share the same fate, regardless of incidental differences in their encounters with antigen. To make the previous mechanism more flexible, it has been proposed that such developmental program might in part be modulated by antigenic stimulation or cytokines (van Stipdonk and et al., 2003). However, the precise cellular and molecular mechanisms responsible for the execution of such programs have not been elucidated as yet.

As an alternative to the previous scenario, some models of T cell cycle and apoptosis (reviewed in Miao et al., 2012) assume instead that T cell fate and lifespan result from stochastic processes. More precisely, T cell fate would be determined by the competition of two independent stochastic clocks controlling cell division and apoptosis (Duffy and Hodgkin, 2012; Subramanian et al., 2008). However, as in the previous case, the precise cellular and molecular mechanisms accounting for a stochastic T cell cycling and lifespan remain currently unknown.

In this work we propose an alternative theoretical framework to explain the choice between division and apoptosis in T cells in the course of an immune response as well as the emerging properties thereby resulting. Importantly, our model makes use of well-known biological facts and needs no additional hypothetical mechanisms. We suggest that a simple deterministic cellular algorithm, independently run in each T cell, allows any such cell to decide both its fate and lifespan, depending on its own level of antigen encounters. Furthermore, we show that such algorithm can be mathematically formulated in a particularly simple form. Analysis of the resulting mathematical model is shown to account for both a variety of individual cell behaviors, as well as for emergent properties as is the case of clonal contraction.

At this juncture, it is worth pointing out that the use of mathematical models to analyze particular aspects of the immune response has deserved considerable interest. For instance, the dynamics of membrane receptor binding to ligands has been studied in Alarcón and Page (2006, 2007) and the specific manner in which T cells check intracellular pathogens has been described in Regoes et al. (2007). The recruitment of specialized subpopulations to better fight raging microbial infections has been modeled and discussed in Day et al. (2009). On the other hand, models to estimate T cells turnover have been recently reviewed in De Boer and Perelson (2013) and the dependence on the magnitude of activated T cells in terms of the initial number of naïve precursors has been studied in Bocharov et al. (2011). The role of T cells in checking tumor progression has attracted considerable attention (see Matzavinos et al., 2004; Joshi et al., 2009; Kogan et al., 2010); a general mathematical framework to model competition between tumor progression and immune response has been proposed and discussed in Bellomo et al. (2004). However, none of the previous works seems to have been concerned with the nature of the decision-making process that leads each individual T cell to divide or die during an infection. This is precisely the subject we address here.

Specifically, the plan of this paper is as follows. To begin with, in Section 2 we briefly review some known facts about cell cycle and apoptosis in T cells that provide the foundations of our general mathematical model, which is formulated at the end of that section. Specifically, we build it up around two key ingredients. These are the roles of Retinoblastoma (Rb) and B-cell lymphoma-2 (Bcl-2) proteins as inhibitors of cell cycle progression and apoptosis respectively, and their functional link with cytokine receptors. A major assumption in the model is that the commitment of the cell to divide or die emerges from the competition between Rb and Bcl-2 to reach a certain threshold. Such competing behavior is in itself not new (see e.g. Duffy and Hodgkin, 2012; Subramanian et al., 2008). However, to the best of our knowledge, no attempt has been made to explicitly model the kinetics of Rb and Bcl-2 and their interplay with membrane receptors to explain T cell fate determination during immune response.

In Section 3 of this paper we discuss in some detail a simplified version of our mathematical model. As a matter of fact, given that current knowledge on T cell biology is only partial (for instance, the catalogue of cytokines that might be related to T cell division and apoptosis is not fully characterized yet), a complete description of the cell algorithm cannot be presently formulated. Interestingly enough, the simplified model therein discussed suffices to show that both T cell division in the absence of antigen, and T cell apoptosis in the presence of antigenic stimulus can be explained as alternative outcomes of a common deterministic cellular mechanism, when executed in individual T cells exposed to different environmental conditions.

Finally, by modeling the simultaneous performance of such algorithm in coexisting T cells during an immune response, we are able to show that the coherent collective behavior displayed by T cells during an acute infection, and in particular the delay in clonal contraction represented in Fig. 1, can be explained as an emergent property of the same algorithm that determines the choice between cell division and cell death in individual cells. Our results are then summarized in a concluding Section 4.

2. A cell fate algorithm: biological assumptions and mathematical model

In this section we describe in detail the cell fate algorithm we propose to account for each individual T cell choice between dividing and undergoing apoptosis during immune response to acute infection. To this end, we begin by stating the biological assumptions our model relies upon.

2.1. Biological assumptions

2.1.1. Assumption 1. Competition between two inhibitory molecules determines the fate of each T cell, as well as its lifespan

Cell division and the onset of the cell death program are initially blocked in newly formed T cells by the action of two inhibitory proteins. On the one hand, active Rb proteins arrest cell cycle

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progression at an early stage (G1 phase) by preventing the expression of genes needed for the cell to enter the S phase of the cycle (Yoon et al., 2010). Since Rb must be phosphorylated in order to inactivate its function as transcriptional repressor, the phosphorylation of a sufficient number of Rb molecules is needed for the cell cycle to progress and, consequently, for the T cell to eventually divide (Quelle, 2007). On the other hand, Bcl-2 proteins block the pathway of effector T cell death during acute infections (Activated T Cell Autonomous Death or ACAD) by restraining the action of pro-apoptotic proteins such as Bax or Bim (Strasser et al., 2008, 2009).

We postulate that T cells can only exit G1 phase once the number of either active Rb or Bcl-2 molecules falls below a certain threshold. In the former case, the T cell passes through the so-called Restriction Point that determines the transition from phase G1 to S and marks the commitment of the cell to divide (Weinberg, 1995; Knudsen and Knudsen, 2006). On the contrary, if the amount of Bcl-2 proteins falls beyond a given limit, the T cell exits G1 to initiate the ACAD program that irreversibly leads to cell death (Fletcher et al., 2008; Arnold et al., 2006) (see Fig. 2A).

Other than deciding T cell fate, the dynamics of active Rb and Bcl-2 also provides an explanation for the observed variability in the duration of G1 phase in T cell populations. In fact, differences among individual T cells in the time it takes for inhibitory proteins to reach their critical threshold could explain the observed heterogeneity in G1 length (Smith, 2005) and, consequently, in T cell lifespan (see Fig. 2B).

2.1.2. Assumption 2. Feedback with membrane receptors regulates the dynamics of Rb and Bcl-2, and thus determines the choice between cell division and cell death

Fluctuations in the amount of inhibitory proteins leading to cell division or cell death result from the action of cytokines during G1 phase (Migliaccio et al., 2006; Song et al., 2007). However, once the T cell exits G1, its commitment to divide or die cannot be reverted by cytokines stimulation (Knudsen and Knudsen, 2006; Smith, 2005). According to our previous remarks, cytokines that induce the phosphorylation of Rb molecules, such as interleukin-2 (IL-2), IL-4, IL-15 or IL-21 (Migliaccio et al., 2006), move the T cell towards the Restriction Point, and can be defined as *proliferation cytokines*. Similarly, other cytokines can be described as *survival* (such as IL-6, IL-7, IL-15) or *death cytokines* (for instance, Fas or TNF) (Plas et al., 2002; Scaffidi et al., 1999) depending on their effect, positive or negative respectively, on the amount of Bcl-2 molecules.

A key point to be stressed is that action induced by cytokines takes place through their interactions with specific membrane receptors (Wardle, 2009). Thus the corresponding effect perceived by a T cell depends both on cytokines concentrations in the surroundings of the cell and on the number of receptors existing in the cell membrane. It should be noticed that IL-2 has basically an autocrine character, since it acts on the T cells that actually produce it (Lezzi et al., 1998), whereas IL-7 is produced by non-immune cells and its concentration remains basically constant during clonal expansion and contraction (Sun et al., 2006).

We assume that similar behaviors hold true for other cytokines involved, which in turn leads to the following working hypothesis: the dynamics of cytokines concentration and receptor expression proceed at substantially different time scales during immune responses, the former being much faster than the second. For instance, a rapid IL-2 production, leading to high local concentrations in the surroundings of activated T cells, is accompanied by a much slower up-regulation of IL-2 receptor (IL-2R) (Stahl and et al., 2002; Schluns and Lefrancois, 2003). In this situation, the number of IL-2 signals perceived by an activated T cell can be assumed to be proportional to the amount of receptors in its membrane (Phillips et al., 2009). Similarly, the effect of IL-7 on

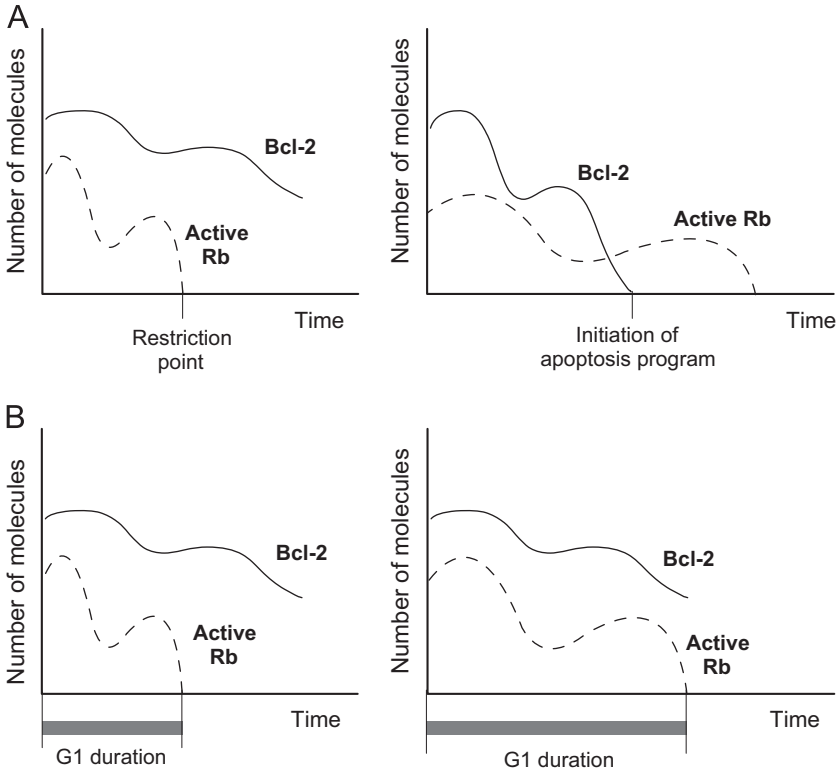

Fig. 2. (A) Cell cycle and apoptosis program are blocked in T cells by two inhibitory molecules, Rb and Bcl-2. The first of these proteins to drop below a critical threshold irreversibly determines T cell fate. In particular, the Restriction Point is marked by the deactivation of Rb (left), while the apoptosis program is initiated upon Bcl-2 reaching a corresponding threshold (right). (B) Dynamics of inhibitory molecules are shown in two different cases. Since active Rb is neutralized while Bcl-2 continues to block apoptosis, both cells will divide. However, differences in the time it takes for Rb to be deactivated result in different lifespans.

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activated T cells survival during clonal contraction is determined by the presence or absence of IL-7R in their membrane, and is not significantly augmented by externally increasing IL-7 concentration (Tripathi et al., 2007).

These observations indicate that it is the number of specific membrane receptors and not the amount of available cytokine molecules that constrains the precise number of cytokine/receptor signals perceived by a T cell at any given moment. On the other hand, the number of membrane receptors in activated T cells populations is far from remaining constant during an immune response (Schluns and Lefrancois, 2003; Wherry and et al., 2007), and seems to be controlled by complex feedback relations involving cytokine receptors and the T Cell Receptor (TCR) (Fig. 3; see e.g. Stahl and et al., 2002; Xue and et al., 2002; Smith and Cantrell, 1985; Swainson et al., 2006; Fluur and et al., 2007; Brenner et al., 2008; Dai et al., 1999; Singer and et al., 2004; Hammerbeck and Mescher, 2008).

Thus, cytokine receptors control active Rb and Bcl-2 dynamics and simultaneously modulate the expression or inhibition of other receptors in the T cell surface. From these facts, the pattern of activated membrane receptors at any given moment can be viewed as the input of a cellular algorithm that produces as output both a new combination of receptors and a change in the number of inhibitory proteins, eventually deciding T cell fate and lifespan. We postulate that this algorithm suffices to account for individual T cell fate determination during immune response. Such algorithm allows for neighbor T cells to take divergent fate decisions, even if they share a common cytokine environment, by simply expressing different patterns of membrane receptors.

For instance, differences in IL-7R expression account for the presence of two alternative T cell types during the final stages of an immune response: apoptosis-susceptible cells, that will die during clonal contraction, and apoptosis-resistant cells, that will survive as memory T cells (Rocha and Tanchot, 2006; Tuma and Pamer, 2002). Alternative IL-7R dynamics seem to be determined in the early stage of the immune response due to naïve T cells asymmetric division (Gerlach et al., 2010; Chang et al., 2007), which leads to our next assumption.

2.1.3. *Assumption 3. Naïve T cells divide asymmetrically after activation. Differences in membrane feedback relations in daughter cells account for different apoptosis susceptibilities during clonal contraction*

It has been shown in Chang et al. (2007) that the immune synapse induces a polarization of the naïve T cell membrane, which results in signaling pathways involved in cell fate being asymmetrically distributed in daughter cells. In particular, it has been observed in Chang et al. (2007) that the distal daughter cell showed a higher predisposition to IL-7R expression than the proximal daughter cell.

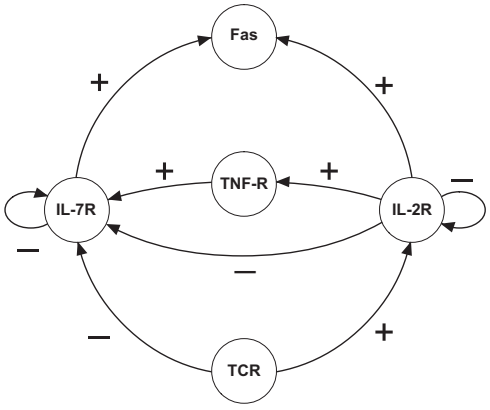

Fig. 3. Feedback relations between some of the membrane receptors in T cells as described in the literature (see references in the text). TCR signals down-regulate the expression of *survival receptors* (IL-7R) and simultaneously up-regulate the production of *proliferation receptors* (IL-2R). *Proliferation receptors*, in turn, stimulate the expression of *death receptors* in the T cell membrane (TNF-R and Fas), while inhibiting the production of *survival* and *proliferation signals*.

Bearing these facts in mind, we postulate that apoptosis-sensitive and apoptosis-resistant cell phenotypes are determined during the immune synapse and emerge from differences in the fine-tuning of the cell fate decision algorithm between the daughter cells appeared after the asymmetric division of activated naïve T cells. Cytokine/receptor signals are actually known to activate alternative intracellular pathways in different subpopulations of T cells, so that the same signal shows divergent effects on both activation and deactivation of cell cycle and cell death inhibitory molecules (Osborne and Abraham, 2010), and the expression of other membrane receptors (Swainson et al., 2006).

Furthermore, we assume that both the apoptosis-susceptible and the apoptosis-resistant T cells can subsequently proliferate in case of further antigenic stimulation. Actually, both cell types divide symmetrically in the sequel, which implies that the cell type is inherited in the ensuing rounds of cell division.

Notice that, although the asymmetry in the division of naïve T cells may initially give rise to effector (proximal daughter cell) versus memory (distal daughter cell) phenotypes (Chang et al., 2007), both cell types may acquire effector functions and be externally indistinguishable in the course of the immune response. Only after pathogen clearance, surviving apoptosis-resistant lymphocytes will lose their effector function and eventually revert to a memory phenotype. Thus, seemingly contradictory data supporting memory T cells differentiation from effector and naïve T cells are compatible under this assumption: depending on the activation of apoptosis-resistant daughter cells, memory phenotype can appear directly after naïve asymmetric division, or, alternatively, from effector-like lymphocytes (Sprent and Surh, 2002; Harrington et al., 2008).

2.2. *A mathematical model. General framework*

In this section we formulate in mathematical terms an algorithm of T cell fate determination based in our previous assumptions. We will denote by $c(t)$ and $a(t)$ the amounts of active Rb and Bcl-2 at time t respectively. Without loss of generality we will set the respective thresholds that determine the decision to progress into cell cycle or launch the apoptosis program at the values $c(t)=0$ or $a(t)=0$ respectively.

According to Assumption 1, we can define the following discrete states in the life of a T cell:

- *Decision*: It extends from the birth of the T cell until one of the inhibitory molecules reaches its critical threshold.
- *Cycle*: It spans between the Restriction Point (determined by the deactivation of Rb) and cell division.
- *Apoptosis*: It is the part of the T cell life ranging between the deactivation of Bcl-2 and the completion of the ACAD program of cell death.
- *Division*: Final state in the life of a T cell that has entered *cycle* phase.
- *Death*: Final state in T cell life after completion of the *apoptosis* phase.

Entering *cycle* and *apoptosis* phases are mutually exclusive events. The first of the inhibitors to vanish in *decision* phase irreversibly determines the choice between both cell fates. We assume that in case of simultaneous cancelation of both inhibitors, T cells enter *apoptosis* phase.

Suppose that k different types of cytokines are involved in the control of inhibitory molecules Bcl-2 and active Rb. Let us denote

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by R_i the receptor of i-th cytokine, and by $r_i(t)$ the amount of receptor R_i at time t. Inhibitory molecules will be modeled as continuous variables whose evolution, as stated above, is a function of the number of receptors:

$$\begin{cases} \dot{c}(t) = f_c(r_T, r_1, \ldots, r_k) \\ \dot{a}(t) = f_a(r_T, r_1, \ldots, r_k), \end{cases} \tag{1}$$

where r_T is the number of TCR/antigen signals perceived by the T cell under consideration. On the other hand, the amount of receptors will be represented by continuous variables evolving according to feedback relations as described in the previous section:

$$\dot{r}_i(t) = f_i(r_T, r_1, \ldots, r_k) \quad \text{for } i = 1, \ldots, k. \tag{2}$$

To proceed further, we now postulate the following particular form to Eq. (1):

$$\begin{cases} \dot{c}(t) = \mu_{Tc} r_T(t) + \sum_{j=1}^{k} \mu_{jc} r_j(t) \\ \dot{a}(t) = \mu_{Ta} r_T(t) + \sum_{j=1}^{k} \mu_{ja} r_j(t), \end{cases} \tag{3}$$

where μ_{Tc} (respectively μ_{Ta}) and μ_{ic} (respectively μ_{ia}) represent the rate of change in cell cycle (respectively apoptosis) inhibitor induced by TCR or membrane receptor R_i (for $i = 1, \ldots, k$). Analogously, Eq. (2) are selected as follows:

$$\dot{r}_i(t) = \lambda_{Ti} r_T(t) + \sum_{j=1}^{k} \lambda_{ji} r_j(t) \quad \text{for } i = 1, \ldots, k, \tag{4}$$

where λ_{Ti} and λ_{ji} denote the change in membrane receptor R_i due to TCR and R_j signals respectively.

The basic assumption leading to linearity in Eqs. (3) and (4) is that membrane receptors involved in the T cell fate decision algorithm are independent and have cumulative effects. Under this assumption, there is a linear relation between the input of the algorithm (number of membrane receptors) and its output (change in active Rb, Bcl-2 and membrane receptors). It has been observed that the effect of IL-2R on cell cycle progression is, in fact, cumulative: T cells count the number of IL-2/IL-2R signals during G1 phase, so that when the number attains a fixed threshold, the cell is committed to divide (Smith, 2005, 2010). It should be noted that linear input–output relations, described in both bacteria and eukaryote cells (Nevozhay et al., 2009; Yu and et al., 2008), reduce the amplification of stochastic noise during signal transmission (Becskei, 2009). Accordingly, linear relations would increase feedback accuracy and robustness by ensuring that similar configurations of membrane receptors lead to similar cell decisions (see Fig. 4).

The conditions $a(t) \geq 0$, $c(t) \geq 0$ and $r_i(t) \geq 0$, for $i = 1, \ldots, k$, define the range of validity of Eqs. (3) and (4) during *decision* phase. Any receptor reaching a negative value (condition $r_i(t) \leq 0$) is reset to 0 without changing cell life phase. Conversely, conditions $a(t) = 0$ and $c(t) = 0$ trigger instantaneous transitions from *decision* to *apoptosis* and *cycle* phases respectively. The duration of *decision* phase (denoted by t_{dec}) is variable and depends on the time it takes for one of the inhibitory proteins to reach its critical threshold, i.e, it is given by the conditions $c(t_{dec}) = 0$ or $a(t_{dec}) = 0$. On the other hand, both *cycle* and *apoptosis* phases have constant lengths (Evan et al., 1995; Rehm et al., 2006) that will be denoted by t_{cycle} and t_{apo} respectively.

The exit of *decision* phase determines the choice between two separate and mutually exclusive cell fates: *cycle* and *apoptosis*. From this moment, the commitment of the cell to divide or die is irreversible and cannot be changed by cytokines stimulation (Knudsen and Knudsen, 2006; Smith, 2005). This fact implies that, once the T cell exits *decision* phase, the evolution of cell cycle and cell death inhibitors becomes independent of cytokine receptors. Furthermore, if the T cell progresses into the cell cycle, initial values of active Rb and Bcl-2 must be reset during *cycle* in order for daughter cells to restart at *decision* phase. Although we have not found empirical evidence to support or dismiss this assumption for Bcl-2, this behavior has been described for active Rb molecules (Weinberg, 1995; Knudsen and Knudsen, 2006). Since the particular details of inhibitory molecules dynamics during *cycle* and *apoptosis* phases are not relevant for T cell fate determination, they will not be explicitly modeled. Instead, we will only consider the evolution of membrane receptors which, as for *decision* phase, is governed by Eq. (4).

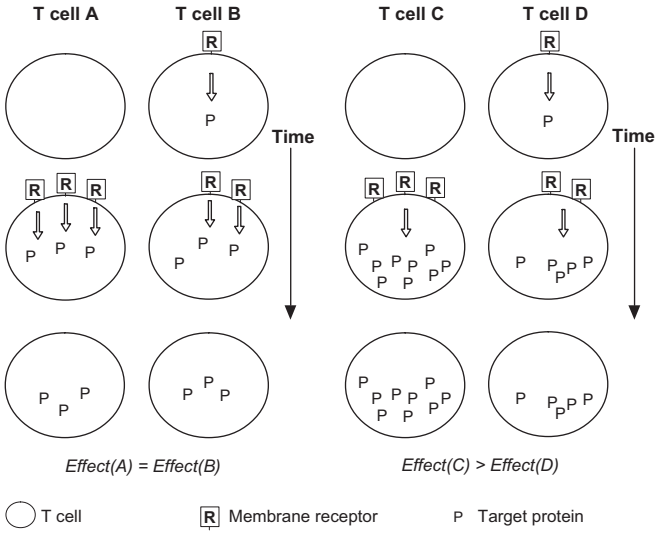

Fig. 4. Influence of temporal pattern of membrane receptors expression on its induced effect. Membrane receptors of type R are independent in T cells A and B, that is, every receptor leads to the production of one molecule of protein P, regardless of the presence of other membrane receptors. In this case the final output is the same if receptors are simultaneously (T cell A) or sequentially (T cell B) expressed in the cell membrane. Conversely, in T cells C and D receptors are not independent, but interact, producing different outputs depending on the membrane configuration. In this case simultaneous expression (T cell C) may lead to a greater effect than sequential expression (T cell D).

In both *cycle* and *apoptosis* phases, receptors reaching a negative value are reset to 0 and do not induce any change in discrete state. Once cell cycle or apoptosis program is completed (conditions $t = t_{cycle}$ or $t = t_{apo}$ respectively), a T cell exits *cycle* or *apoptosis* phase to enter a final state (*division* or *death*), which marks the end of T cell life (see Fig. 5).

Parameters λ_{ji}, μ_{ic}, μ_{ia} (for i and $j = 1, \ldots, k$), λ_{Ti} (for $i = 1, \ldots, k$), μ_{Tc}, μ_{Tc}, t_{cycle}, t_{apo}, $c(0)$ and $a(0)$ are structural parameters, that is, they refer to explicit biological mechanisms assumed to remain unchanged in the course of the immune response. Accordingly, they are assumed to have the same value in clonal T cells.

On the other hand, parameters related to the initial composition of membrane receptors in a particular T cell (r_{i0}, for $i = 1, \ldots, k$) depend on the history of antigenic encounters of its mother cell and are expected to differ among clonal T cells.

2.2.1. Linking pathogen dynamics and individual T cell fate

We model here the interaction between T cells and pathogen populations. The precise details of pathogen spreading and removal in host tissues greatly vary between infectious agents. However, in this work we will not refer to any particular case of pathogen proliferation and clearance. Instead, we will use a simple phenomenological model that reproduces the observed pathogen dynamics:

$$\dot{y}(t) = \alpha y(t) - \beta n(t) y(t), \tag{5}$$

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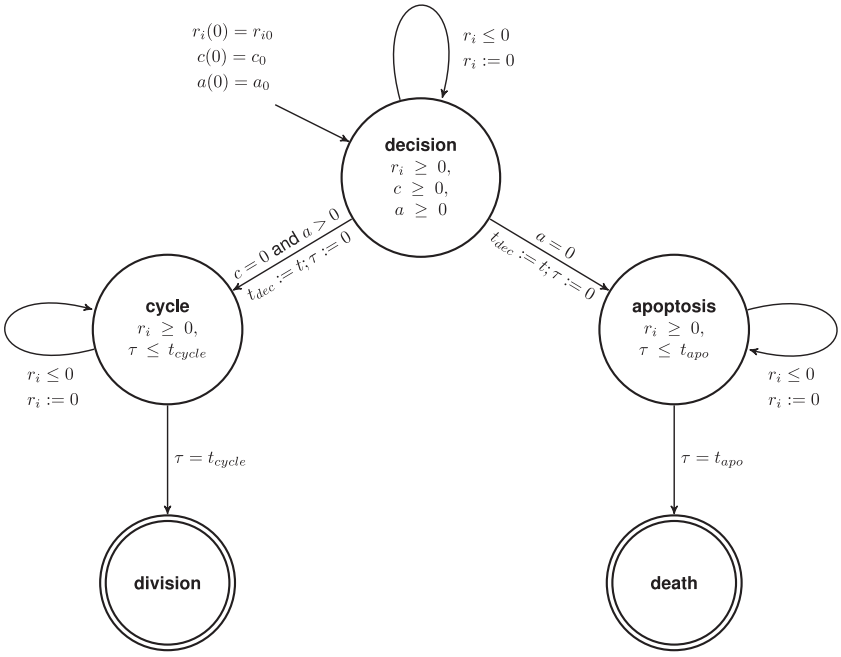

Fig. 5. Diagram of the algorithm of T cell fate and lifespan determination. The nodes of the graph represent the discrete states in the life of a T cell. Inequalities inside the nodes specify the range of validity for the equations describing the dynamics of each state. If one of these conditions is violated during the numerical simulations, the model jumps to a new discrete state (arrows symbolize jumps between states). Each arrow of the diagram is labeled with the conditions that determine the corresponding transition (denoted generically by expressions like $x \le 0$ or $x = 0$) and the reset values for the variables involved in the transition (denoted by the symbol $:=$).

where $y(t)$ and $n(t)$ are the number of pathogen cells and the number of T cells at time t respectively and α and β are positive parameters that depend on the specific infectious agent.

According to this model, pathogens proliferate until activated T cells reach a critical population threshold. Subsequently, the rate of growth of the pathogen becomes negative and its population declines.

We will assume that TCR signals perceived by a T cell are proportional to its encounter with antigens, which in turn depends on the number of infectious cells and on the T cell population size. Denoting by $r_T^x(t)$ the number of TCR signals of T cell x and by n the number of T cells at time t, we can write

$$r_T^x(t) = \gamma \rho_n^x y(t). \tag{6}$$

Parameter γ is antigen-specific and it denotes the probability of a single TCR activation in T cell x due to antigen molecules present in the pathogen. On the other hand, ρ_n^x is a T cell-specific parameter representing the amount of total antigen that is available for a single effector T cell x when the size of the effector cells population is n. Hence, we have

$$\sum_{x=1}^{n} \rho_n^x \le 1. \tag{7}$$

Eqs. (6) and (7) summarize all the events that mediate between pathogen detection by immune cells and TCR/antigen interactions in the membranes of T cells.

Finally, we need to determine the initial number of membrane receptors in daughter cells after T cell division. Unlike naïve T cells, apoptosis-sensitive and apoptosis-resistant T cells are assumed to divide symmetrically (see previous section) sharing their membrane receptors between both daughter cells after division according to the following equation:

$$\begin{cases} r_{i0}^1 = \delta_i^x r_i^x \\ r_{i0}^2 = (1 - \delta_i^x) r_i^x, \end{cases} \tag{8}$$

where δ_i^x represents the ratio of membrane receptors of type R_i between daughter cells, r_{i0}^1, r_{i0}^2 denote initial values of receptor R_i in daughter cells 1 and 2 respectively and r_i^x denotes the number of R_i receptors in T cell x membrane at the time of cell division.

The mechanism of activation is not explicitly considered in the model. Simulations start with an initial number y_0 of infectious cells and an initial population of memory and effector T cells resulting from asymmetric division of n_0 specific naïve T cells. The state of both pathogen population and individual T cells is recalculated in every step of the numerical simulations of the model. The new value for pathogen population is stated by Eq. (5) and the number of TCR signals received by any T cell x, specified by Eq. (6), is used as input to Eqs. (3) and (4) to compute new discrete and continuous states of the model. If a T cell reaches the final state it is removed from the population. Conversely, if a T cell ends in *division* phase, it is replaced by two new cells of the same type, whose initial conditions are determined by Eq. (8).

3. Analysis of a simplified model

We next study in detail a simplified version of our mathematical model that provides significant insight into individual and collective T cell behavior while keeping technicalities at a minimum. More precisely, we assume that only two receptor types (referred to as proliferation and death receptors) are present, and discuss separately the behavior of T cells resulting from the asymmetric division that naïve cells were postulated to undergo upon activation.

3.1. Apoptosis-sensitive T cells. The onset of clonal contraction

We will assume that in apoptosis-sensitive T cells, proliferation receptors are expressed upon TCR signaling, and simultaneously down-regulate their own expression and induce the production of

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death receptors (see Fig. 3). Eqs. (3) and (4) then become

$$\begin{cases} \dot{c}(t) = -\mu_{pc} p(t) \\ \dot{a}(t) = -\mu_{da} d(t) \\ \dot{p}(t) = \lambda_{Tp} r_T(t) - \lambda_{pp} p(t) \\ \dot{d}(t) = \lambda_{pd} p(t) \end{cases} \quad \begin{cases} c(0) = c_0 \\ a(0) = a_0 \\ p(0) = p_0 \\ d(0) = d_0 \end{cases} \tag{9}$$

where $p(t)$ and $d(t)$ denote the number of proliferation and death receptors at time t respectively and μ_{pc}, μ_{da}, λ_{Tp}, λ_{pp} and λ_{pd} are positive structural T cell parameters.

We now claim that so simple a model as (9) is, it suffices to account for the observed cell fate decisions of apoptosis-sensitive T cells during an immune response. In particular, it predicts seemingly paradoxical behaviors such as division of T cells that perceive no antigenic stimulation and apoptosis of T cells that have encountered antigens. To this end, we denote by t_0 the time at which a particular apoptosis-sensitive T cell receives its last antigenic signal. We thus assume that $r_T(t) = 0$ for $t > t_0$ and $r_T(t) > 0$ for $0 \le t \le t_0$. We rescale time by changing $(t - t_0)$ into $\lambda_{pp}(t - t_0)$ and continue to denote the new time by t for notational convenience. Eqs. (9) can then be written in non-dimensional form as follows:

$$\begin{cases} \dot{c}(t) = -p(t) \\ \dot{a}(t) = -d(t) \\ \dot{p}(t) = -p(t) \\ \dot{d}(t) = \tilde{\lambda}_{pd} p(t) \end{cases} \quad \begin{cases} c(0) = 1 \\ a(0) = 1 \\ p(0) = \tilde{p}_0 \\ d(0) = \tilde{d}_0 \end{cases} \tag{10}$$

with

$$\tilde{p}_0 = \frac{p(t_0)\,\mu_{pc}}{c(t_0)\,\lambda_{pp}}, \quad \tilde{d}_0 = \frac{d(t_0)\,\mu_{da}}{a(t_0)\,\lambda_{pp}} \quad \text{and} \quad \tilde{\lambda}_{pd} = \frac{c(t_0)\,\lambda_{pd}\,\mu_{da}}{a(t_0)\,\lambda_{pp}\,\mu_{pc}}.$$

For any fixed value of the parameter $\tilde{\lambda}_{pd}$, the evolution of the *decision* phase, and consequently the lymphocyte fate, is determined by the initial conditions $\tilde{p}_0$ and $\tilde{d}_0$. Integrating the previous equations we obtain an explicit expression for the quantity of cell cycle inhibitor:

$$c(t) = 1 + \tilde{p}_0 (e^{-t} - 1). \tag{11}$$

Analogously, for apoptosis inhibitor we have

$$a(t) = 1 - \tilde{d}_0 t + \tilde{\lambda}_{pd} \tilde{p}_0 (1 - e^{-t} - t). \tag{12}$$

From Eq. (11) we can calculate the time needed for cell cycle inhibitor to vanish (denoted by t_c):

$$t_c = \begin{cases} \ln\left(\dfrac{\tilde{p}_0}{\tilde{p}_0 - 1}\right) & \text{if } \tilde{p}_0 > 1 \\ \infty & \text{if } \tilde{p}_0 \le 1 \end{cases} \tag{13}$$

We notice that the T cell will only divide if appropriate initial conditions (summarized by $\tilde{p}_0 > 1$) are satisfied. On the other hand, if any of the parameters $\tilde{p}_0$ or $\tilde{d}_0$ is positive, $a(t)$ is monotonically decreasing, and will vanish at some $t = t_a < \infty$. Since antigenic contact results in the expression of proliferation receptors and these in turn promote the production of death receptors, both parameters are positive in activated T cells, which implies that the lymphocyte will eventually divide if the time it takes for the apoptosis inhibitor to vanish is greater than t_c and will die otherwise.

The sign of $a(t_c)$ determines therefore cell fate choice: if $a(t_c) > 0$ the T cell exits G1 phase and divides while, conversely, if $a(t_c) \le 0$ it starts the apoptosis program and eventually dies. Introducing this condition in Eq. (12), we conclude that, for any value of $\tilde{\lambda}_{pd}$, the T cell will divide if and only if

$$\tilde{d}_0 \le \frac{1}{t_c}(1 + \tilde{\lambda}_{pd}) - \tilde{\lambda}_{pd} \tilde{p}_0. \tag{14}$$

The number of inhibitory molecules and membrane receptors at $t = t_0$, and hence the value of both $\tilde{p}_0$ and $\tilde{d}_0$, depends on the number of accumulated antigenic signals since the birth of the T cell (that is, for $0 \le t \le t_0$). Activated T cells can therefore die if the amount of antigenic stimulation does not suffice to verify condition (14). Conversely, any T cell whose membrane receptors at t_0 verify condition (14) will eventually divide in the absence of any subsequent antigenic stimulation (Fig. 6A).

We recall that we are assuming that, in case of cell division, membrane receptors in the surface of the T cell will be distributed among the daughter cells as stated in Eq. (8). Hence, the number of membrane receptors in daughter T cells at the moment of their birth, which in turn decides their fate in case they receive no further antigenic stimulation, is determined by the past antigenic experience of their progenitor cell. As a matter of fact, daughter T cells whose membrane receptors at birth verify condition (14) are committed to divide even if antigen is no longer available. Since no TCR signals take place in the absence of pathogen cells (Kaech and Ahmed, 2001), Eq. (9) models the expected situation of

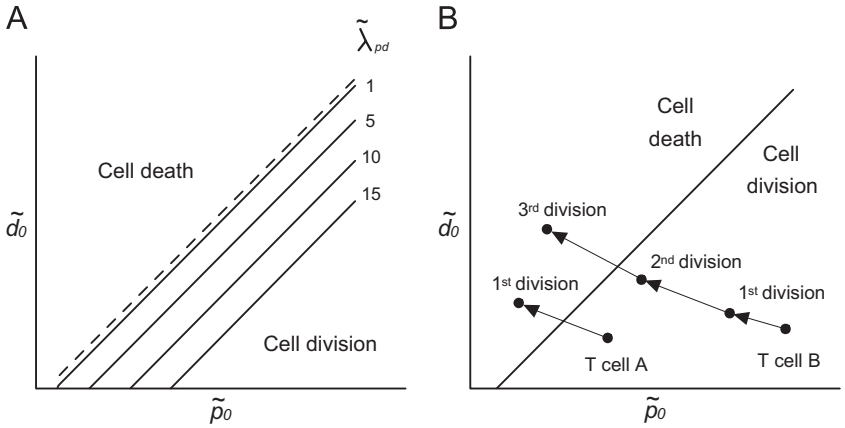

Fig. 6. Onset of clonal contraction. (A) Cell death and cell division for apoptosis-sensitive T cells. (B) Division and death alternatives for different values of parameter $\tilde{\lambda}_{pd}$. Condition (14) states that for any such parameter value, division or death depends on the number of proliferation and death receptors expressed in the membrane when antigenic signaling comes to an end. Cell division in the absence of antigenic stimulation is shown for two hypothetical lymphocytes when condition (14) is satisfied. For each cell the number of expressed cell and death receptors differs due to previous antigenic stimulation. It is assumed that membrane receptors are equally distributed among daughter cells. Since the number of proliferation receptors decreases in the absence of antigen, T cells generated after successive rounds of cell division are closer to the cell death zone, and eventually the progeny of lymphocytes A and B will die. However the number of divisions before entering that death region will be greater for lymphocyte B than for lymphocyte A.

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every effector T cell after the infectious agent has been eliminated. Thus, proliferation of apoptosis-sensitive T cell after pathogen clearance can be readily explained as a consequence of accumulated antigenic signals in its progenitor cells.

In the absence of antigen, negative auto-regulation of proliferation signals and their distribution among daughter cells after cell division imply that lymphocytes are closer to the cell death region displayed in Fig. 6A after each round of cell division. After a variable number of divisions, the progeny of a T cell will eventually violate condition (14), and T cells will stop dividing and will die (see Fig. 6B). The macroscopic manifestation of this fact is the onset of clonal contraction.

3.2. Apoptosis-resistant T cells. The origin of the immune memory

The number of memory cells after clonal contraction is higher than the number of initially available naïve T cells before the infection (Murali-Krishna et al., 1998; Peixoto et al., 2007), implying that apoptosis-resistant lymphocytes proliferate as a consequence of antigenic stimulation during an immune response. Sustained expression of survival receptors maintains the levels of apoptosis inhibitor at sufficiently high levels so as to avoid cell death (Tuma and Pamer, 2002). Accordingly, we will focus on the dynamics of cell cycle inhibitor only, assuming $d(t)=0$ for simplicity. To do that, we will assume that the contact with antigenic molecules induces the expression of proliferation receptors (see Fig. 3), which in turn promotes the elimination of cell cycle inhibitor, eventually leading to cell division. Under this assumption, Eqs. (3) and (4) can be written as

$$\begin{cases} \dot{c}(t) = -\mu_{pc} p(t) \\ \dot{p}(t) = \lambda_{Tp} r_T(t) - \lambda_{pp} p(t) \\ c(0) = c_0 \\ p(0) = p_0 \end{cases} \tag{15}$$

where μ_{pc}, λ_{Tp} and λ_{pp} are positive parameters. We remark that Eqs. (15) can be viewed as a particular case of Eq. (5), taking $\lambda_{pd}=0$ and $d_0=0$.

To show how the apoptosis-resistant T cells eventually stop dividing and produce a memory population (see Fig. 6), let t_0 denote the time at which the last antigenic contact takes places for a particular apoptosis-resistant lymphocyte, that is, suppose $r_T(t)=0$ for $t>t_0$ and $r_T(t)>0$ for $0\le t\le t_0$. Following an analogous reasoning to that in the previous section, we obtain that the time needed for the cell cycle to disappear is given by

$$t_c = \begin{cases} \dfrac{1}{\lambda_{pp}} \ln\left(\dfrac{\tilde{p}_0}{\tilde{p}_0 - 1}\right) & \text{if } \tilde{p}_0 > 1 \\ \infty & \text{if } \tilde{p}_0 \le 1 \end{cases} \tag{16}$$

where $\tilde{p}_0 = (p(t_0)/c(0))(\mu_{pc}/\lambda_{pp}) e^{\lambda_{pp} t_0}$.

Depending on the number of proliferation receptors and the amount of cell cycle inhibitor at $t=t_0$, the apoptosis-resistant T cell can continue to divide, even in the absence of further antigenic stimulation. However, since proliferation receptors in the cell membrane decrease after each round of cell division, apoptosis-resistant lymphocytes will eventually violate the condition $\tilde{p}_0>1$, and consequently, they will not divide any further (Fig. 7).

Hence, while the eventual existence of memory T cells is already determined after the activation and asymmetric division of naïve lymphocytes, the final number of memory T cells depends on the precise evolution of the infection.

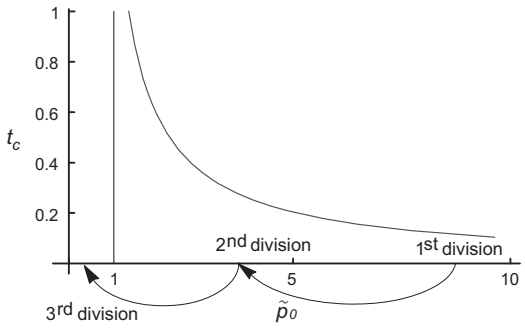

Fig. 7. Dependence of the time needed for the cell cycle inhibitor to disappear in apoptosis-resistant T cell. The negative auto-regulation of proliferation receptors, together with their successive allocation between daughter cells, implies that each new generation of apoptosis-resistant T cells is closer to the condition $\tilde{p}_0<1$ that precludes further divisions.

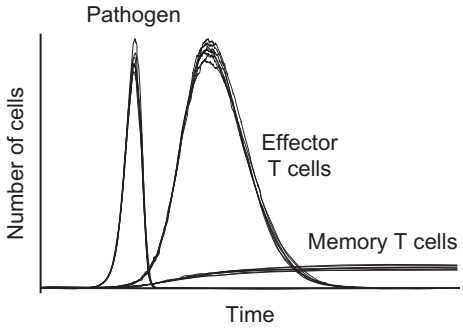

Fig. 8. The population model reproduces key qualitative features of the T cell immune response. Displayed are numerical simulations of that model with the following parameters: $\tilde{t}_{cycle}=0.15$, $\tilde{t}_{apo}=0.20$, $\tilde{\alpha}=10$, and $\tilde{\beta}=0.015$. For effector T cells, we assume $\tilde{\lambda}_{pd}=0.5$, and $\gamma\tilde{\lambda}_{Tp}=6\times10^{-5}$, and for memory T cells, $\tilde{\lambda}_{pd}=0$, and $\gamma\tilde{\lambda}_{Tp}=10^{-5}$. The initial number of specific T cells, n_0 is assumed to be 100. Initially, these cells express no proliferation or death receptors, that is, $\tilde{r}^x_{p0}=\tilde{r}^x_{d0}=0$, for $x=1,\ldots,n_0$. The ratios of distribution of proliferation and death receptors between daughter cells, δ^x_p and δ^x_d take, for every dividing T cell x, a random value between 0.4 and 0.6. Finally, the available antigen molecules are distributed randomly among coexisting effector and memory T cells.

3.3. Individual T cell behavior results in a coherent collective pattern in the course of immune response

In Fig. 8 we show a series of numerical simulations of the population model for a particular choice of the values of the non-dimensional parameters, obtained after rescaling time (by changing t into $\lambda_{pp}t$) in Eqs. (5) and (9).

Due to asymmetric division of naïve T cells, effector and memory T cells are in fact separate populations (apoptosis-susceptible and apoptosis-resistant respectively) that can proliferate as a consequence of antigen encounters. However, differences in the fine-tuning of the feedback mechanism suffices to explain why effector T cells eventually die leading to the onset of clonal contraction, while a population of memory cells remains.

3.4. T cell collective dynamics emerging from the previous algorithm adapts to different pathogen dynamics

Experimental studies reveal that T cell responses display persistent qualitative dynamics, even if quantitative details, regarding for instance the moment at which the peak of the expansion is reached or its magnitude, can vary among infection episodes (Murali-Krishna et al., 1998; Peixoto et al., 2007) (see Fig. 9A). In Fig. 9B numerical simulations of the model considered in this section are shown where all parameters are as in Fig. 8, except the pathogen-specific ones, which are allowed to change.

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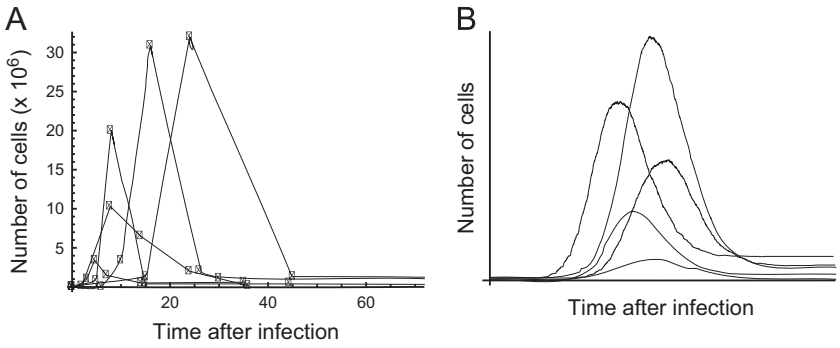

Fig. 9. (A) Experimental data (see Busch et al., 1998; Murali-Krishna et al., 1998; Peixoto et al., 2007) show that the precise quantitative details of the T cell immune response can differ among infection episodes (B) Experimental patterns reproduced in (A) are mimicked by simulating our model for different sets of pathogen-specific parameters when structural parameters are kept constant and as in Fig. 7.

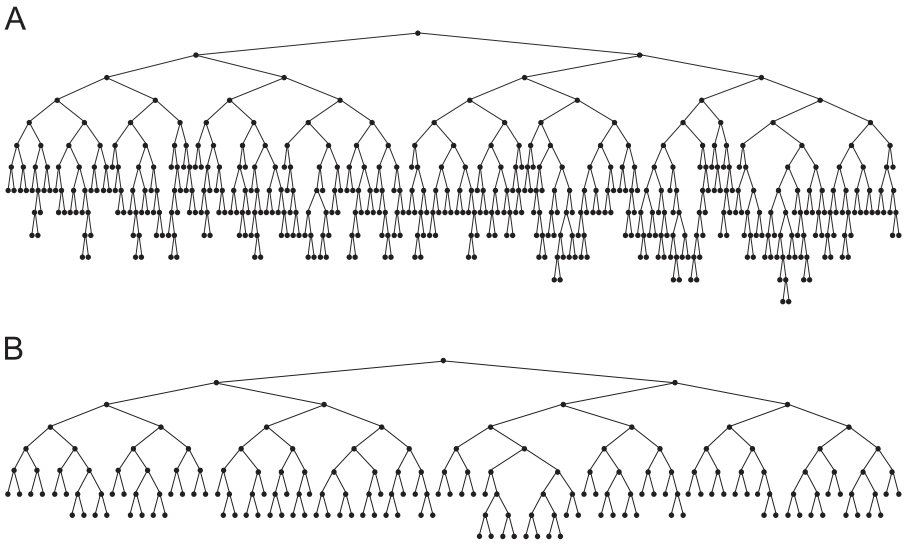

Fig. 10. Progeny of an effector T lymphocyte in the course of two different immune responses, obtained by using the same structural parameters and different pathogen-specific parameters in numerical simulations of the population model. In particular, they have been obtained by following the progeny of one of the initial naïve T cells in the simulations corresponding to the maximum and the minimum expansion shown in Fig. 8.

Note that the cases considered display a similar qualitative behavior, with quantitative differences (for instance, the peak T cell number during clonal expansion) resulting from differences in pathogen dynamics being considered. In particular, the ratio between such peak number and the final amount of memory cells is consistent with that observed in experimental studies (Peixoto et al., 2007; Busch et al., 1998).

3.5. The number of cell divisions after naïve T cell activation is an emergent output of the fate decision algorithm

The pattern of cell divisions in effector T cells can be highly variable depending on the dynamic parameters of the pathogenic agent acting in each case. Fig. 10 represents the progeny of an effector cell during immune responses against two different pathogens (parameters correspond to the maximum and the minimum expansion in Fig. 9). Given that the initial number of naïve T cells is the same in both scenarios, the differences in the peak number of T cells during clonal expansion shown in Fig. 9 result only from effector T cells going through a different number of cell divisions.

We remark that the number of cell divisions is not explicitly encoded in the algorithm, but emerges instead from the independent performance of such algorithm in individual T cells depending on their encounter with antigens.

4. Discussion

Mathematical models have been extensively used to analyze different aspects of the T cell immune response (Alarcón and Page, 2006, 2007; Bellomo et al., 2004; Bocharov et al., 2011; Day et al., 2009; Matzavinos et al., 2004; Joshi et al., 2009; Kirschner and Linderman, 2009; Molina-Paris and Lythe, 2011). In particular, models of T cell dynamics have deserved considerable interest (Antia et al., 2005; Joshi et al., 2009). When studying them, an important difficulty has to be addressed. Namely, the more comprehensive a model is, the larger the number of parameters involved. Unfortunately, little is known about the precise value of such parameters in many cases, so that their values are *ad hoc* selected, so that particular aspects of immune response could be recovered in the corresponding simulations. While this procedure undoubtedly provides useful insights in many situations, considerable caution is needed when assessing the conclusions thus derived. Indeed, it is well known that different models may give rise to similar dynamics, although the corresponding biochemical assumptions may be quite different in each case (cf. Kim et al., 2010; Antia et al., 2003).

Bearing these facts in mind, an attempt has been made in this work to formulate a model as simple as possible to address some specific issues in immune response. Namely, we focus on the way in which T cell population patterns emerge from individual cell

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decisions. To that end, we have proposed a decision algorithm, which relies in a small number of precise assumptions, based on current biological evidence, and we have formulated them as a mathematical model. A consequence of the model simplicity is that the number of parameters involved is comparatively small, mostly of structural character, and hopefully accessible to experimental evaluation.

Our basic proposal of individual fate choice is in sharp contrast with the hypothesis of a rigidly predetermined naïve T cell developmental program. According to such a scenario, the antigenic stimulation of naïve T cells during early stages of immune response mainly determines the fate of the whole progeny. Under this assumption, activated T cells generated during clonal expansion would have very limited control, if any, about their eventual choice between division and apoptosis, independent of their record of encounters with antigens. However, according to the picture proposed here, the antigenic experience of a T cell can actually be transmitted to its daughter cells. This would be done just by sharing the amount of receptors present at its membrane at the time of cell division. This inherited experience is integrated in daughter cells with their own individual antigenic experience, which allows for neighboring T cells to choose alternative fates even if they share a common ancestor. Indeed, the observed heterogeneity in cell fate, and in cell lifespan, in T cell populations (Hawkins et al., 2007) can thus be explained without resorting to intrinsic stochastic cell cycle or apoptosis mechanisms (Duffy and Hodgkin, 2012; Subramanian et al., 2008). Instead, it can emerge from a common deterministic algorithm, independently executed in T cells subject to heterogeneous or stochastic antigenic inputs.

The T cell response is antigen-specific and not pathogen-specific. The precise antigen recognized by a particular clone of T cells can be present in a wide variety of pathogen agents that can be highly heterogeneous in aspects such as growth rate or immune response escape mechanisms. For this reason, the performance of an individual cell fate algorithm as that proposed here should be independent of the events that mediate pathogen recognition by innate immune cells and T cell activation, since these events can greatly vary depending on the nature of the infection. At the same time, collective T cell behavior emerging from the intrinsic program must be highly flexible in order to provide an adequate response to such a variety of potential pathogens. However, such decision algorithm in itself needs not be flexible. On the contrary, it would be expected to be hardwired in T cells and should not be modified depending on the nature of the infectious agent or the progression of the infection. Accordingly, our model is characterized by a set of structural parameters, whose values are assumed to be similar for all clonal T cells and that represent explicit biological features that remain unchanged in the course of immune response. We have shown that a fixed set of such parameters can generate a flexible collective behavior, resulting in a robust response that adapts to a variety of infectious agents. Such adaptation results from a variable number of cell divisions, that depends on antigen encounters, and need not be fixed *a priori* as proposed, for instance, in Badovinac et al. (2002) and Kaech and Ahmed (2001).

We conclude by observing that the proposed algorithm of T cell fate and lifespan decision is not a closed model. Instead, it provides an open framework to integrate new knowledge about T cell biology. To illustrate this point, we will shortly discuss as an example that a set of proteins, other than Rb and Bcl-2, known to inhibit cell cycle and apoptosis in T cells (Massague, 2004), can be included as new elements of this algorithm. Given its central role in T cell fate determination, the previously described mechanism is expected to show robustness features with respect to failures in some of its elements. For instance, a mutation affecting a death receptor might impair the apoptosis pathway, and thus bias fate choice by restraining the possibility of cell death. In this case, the accumulation of proliferation signals might eventually lead to the division of a T cells that otherwise would have been marked for death. This, however, does not happen since T cells with defects in death receptors show a blockade not only of apoptosis, but also of cell cycle progression (Osborn et al., 2007; Hashimoto et al., 2011). Reciprocally, mutations in proliferation receptors have been shown to block both cell cycle and the apoptosis program (Huleatt et al., 2003).

We postulate that these facts can be explained as the consequence of a checkpoint mechanism preventing errors in the outcome of the algorithm of T cell fate determination due to impaired expression in proliferation or death receptors. In order for active Rb and Bcl-2 to determine T cell fate and lifespan as stated above, it suffices that the time it takes for cytokine receptors to remove alternative cell cycle and cell death inhibitors (denoted by C and D respectively) be shorter than that required by proliferation and death signals to complete the deactivation of Rb or Bcl-2. Once that D and C are deactivated, the T cell can progress into the cell cycle or initiate the apoptosis program as soon as Rb or Bcl-2 fall below their critical threshold (Fig. 11A). Assume that proliferation signals deactivate both Rb and death inhibitor D, while death signals remove both Bcl-2 and cell cycle inhibitor C proteins. In this scenario, a mutation causing impaired expression of death receptors would lead to a defect in apoptosis as expected,

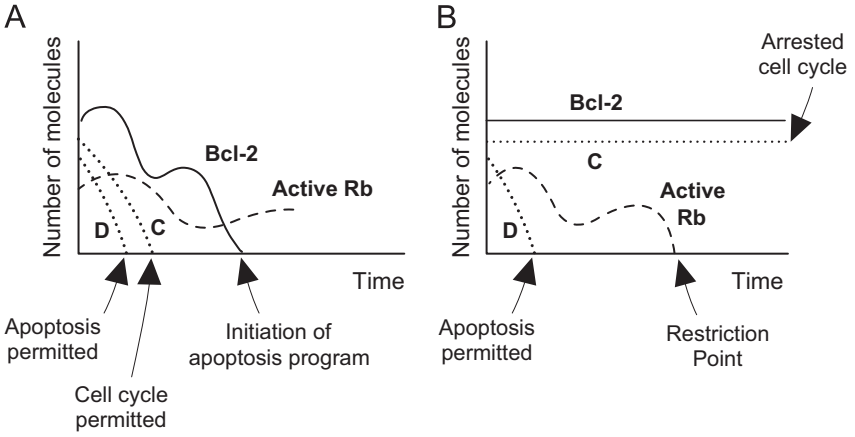

Fig. 11. Checkpoint mechanisms of the T cell fate algorithm. An example is provided where cell cycle and apoptosis inhibitors different from Rb and Bcl-2 would provide robustness with respect to impaired expression in proliferation and death receptors. (A) In a normal T cell, additional cycle and death inhibitors (termed C and D) are deactivated by functional death and proliferation receptors in a fast time scale, so that both cell cycle and apoptosis are permitted. (B) Lack of functionality in death receptors prevents Bcl-2 and the cell cycle inhibitor C to vanish, which results in both apoptosis and cell cycle to be arrested.

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due to the presence of Bcl-2 molecules. However, in the absence of death receptors, cycle inhibitor C would remain active preventing the progression into the cell cycle (Fig. 11B). Thus, the T cell would neither undergo apoptosis nor divide. A similar argument can be implemented to deal with apoptosis inhibitors different from Bcl-2.

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References

Alarcón, T., Page, K.M., 2006. Stochastic models of receptor oligomerization by bivalent ligand. J. R. Soc. Interface 3, 545–559.
Alarcón, T., Page, K.M., 2007. Mathematical models of the VEGF receptor and its role in cancer therapy. J. R. Soc. Interface 4, 283–304.
Antia, R., Bergstrom, C.T., Pilyugin, S.S., Kaech, S.M., Ahmed, R., 2003. Models of CD8+responses: 1. What is the antigen-independent proliferation program. J. Theor. Biol. 221 (4), 585–598.
Antia, R., Ganusov, V.V., Ahmed, R., 2005. The role of models in understanding CD8 (+) T-cell memory. Nat. Rev. Immunol. 5 (2), 101–111.
Arnold, R., Brenner, D., Becker, M., Frey, C.R., Krammer, P.H., 2006. How T lymphocytes switch between life and death. Eur. J. Immunol. 36, 1654–1658.
Badovinac, V.P., Porter, B.B., Harty, J.T., 2002. Programmed contraction of CD8(+) T cells after infection. Nat. Immunol. 3, 619–626.
Becskei, A., 2009. Linearization through distortion: a new facet of negative feedback in signalling. Mol. Syst. Biol. 5, 255.
Bellomo, N., Bellouquid, A., Delitala, M., 2004. Mathematical topics on the modelling of complex multicellullar systems and tumor immune competition. Math. Model. Methods Appl. Sci. 14 (11), 1683–1733.
Bocharov, G., Quiel, J., Luzyanina, T., Alkon, H., Chiglintsev, E., Chereshnev, V., Meier-Schellersheim, M., Paul, W.E., Grossman, Z., 2011. Feedback regulation of proliferation vs. differentiation rates explains the dependence of CD4 T cell expansion on precursor number. Proc. Natl. Acad. Sci. USA 108 (8), 3318–3323.
Brenner, D., Krammer, P.H., Arnold, R., 2008. Concepts of activated T cell death. Crit. Rev. Oncol. Hematol. 66, 52–64.
Buchholz, Veit R., et al., 2013. Disparate individual fates compose robust CD8+ T cell immunity. Science 340 (6132), 630–635.
Busch, D.H., Pilip, I.M., Vijh, S., Pamer, E.G., 1998. Coordinate regulation of complex T cell populations responding to bacterial infection. Immunity 8 (3), 353–362.
Chang, J.T., et al., 2007. Asymmetric T lymphocyte division in the initiation of adaptive immune responses. Science 315, 1687–1691.
Dai, Z., Arakelov, A., Wagener, M., Konieczny, B.T., Lakkis, F.G., 1999. The role of the common cytokine receptor gamma-chain in regulating IL-2-dependent, activation-induced CD8+ T cell death. J. Immunol. 163, 3131–3137.
Day, J., Friedman, A., Schlesinger, L.S., 2009. Modeling the immune rheostat of macrophages in the lung in response to infection. Proc. Natl. Acad. Sci. USA 106 (27), 11246–11251.
De Boer, R.J., Perelson, A.S., 2013. Quantifying T lymphocyte turnover. J. Theor. Biol. http://dx.doi.org/10.1016/j.jtbi.2012.12.025.
Duffy, K.R., Hodgkin, P.D., 2012. Intracellular competition for fates in the immune system. Trends Cell Biol. 22 (9), 457–464, http://dx.doi.org/10.1016/j.tcb.2012.05.004 (S0962-8924(12)00091-8).
Evan, G.I., Brown, L., Whyte, M., Harrington, E., 1995. Apoptosis and the cell cycle. Curr. Opin. Cell Biol. 7 (6), 825–834.
Fletcher, J.I., Meusburger, S., Hawkins, C.J., Riglar, D.T., Lee, E.F., Fairlie, W.D., Huang, D.C., Adams, J.M., 2008. Apoptosis is triggered when prosurvival Bcl-2 proteins cannot restrain Bax. Proc. Natl. Acad. Sci. USA 105 (47), 18081–18087, http://dx.doi.org/10.1073/pnas.0808691105.
Fluur, C., et al., 2007. Potential role for IL-7 in Fas-mediated T cell apoptosis during HIV infection. J. Immunol. 178, 5340–5350.
Gerlach, C., et al., 2010. One naïve T cell, multiple fates in CD8(+) T cell differentiation. J. Exp. Med. 207, 1235–1246.
Grayson, J.M., Harrington, L.E., Lanier, J.G., Wherry, E.J., Ahmed, R., 2002. Differential sensitivity of naïve and memory CD8(+) T cells to apoptosis in vivo. J. Immunol. 169, 3760–3770.
Hammerbeck, C.D., Mescher, M.F., 2008. Antigen controls IL-7R alpha expression levels on CD8 T cells during full activation or tolerance induction. J. Immunol. 180, 2107–2116.
Harrington, L.E., Janowski, K.M., Oliver, J.R., Zajac, A.J., Weaver, C.T., 2008. Memory CD4 T cells emerge from effector T-cell progenitors. Nature 452, 356–360.
Hashimoto, T., Kikkawa, U., Kamada, S., 2011. Contribution of caspase(s) to the cell cycle regulation at mitotic phase. PLoS One 6, e18449.
Hawkins, E.D., Turner, M.L., Dowling, M.R., van Gend, C., Hodgkin, P.D., 2007. A model of immune regulation as a consequence of randomized lymphocyte division and death times. Proc. Natl. Acad. Sci. USA 104 (12), 5032–5037, http://dx.doi.org/10.1073/Pnas.0700026104.
Huleatt, J.W., Cresswell, J., Bottomly, K., Crispe, I.N., 2003. P27(kip1) regulates the cell cycle arrest and survival of activated T lymphocytes in response to interleukin-2 withdrawal. Immunology 108, 493–501.
Joshi, B., Wang, X., Banerjee, S., Tian, H., Matzavinos, A., Chaplain, M.A.J., 2009. On immunotherapies and cancer vaccination protocols: a mathematical modelling approach. J. Theor. Biol. 259, 820–827.
Kaech, S.M., Ahmed, R., 2001. Memory CD8(+) T cell differentiation: initial antigen encounter triggers a developmental program in naïve cells. Nat. Immunol. 2, 415–422.
Kim, P.S., Lee, P.P., Levy, D., 2010. Emergent group dynamics governed by regulatory cells produce a robust primary T cell response. Bull. Math. Biol. 72 (3), 611–644.
Kirschner, D.E., Linderman, J.J., 2009. Mathematical and computational approaches can complement experimental studies of host–pathogen interactions. Cell. Microbiol. 11 (4), 531–539.
Knudsen, E.S., Knudsen, K.E., 2006. Retinoblastoma tumor suppressor: where cancer meets the cell cycle. Exp. Biol. Med. 231, 1271–1281.
Kogan, Y., Forys, U., Shukron, O., Kronik, N., Agur, Z., 2010. Cellular immunotherapy for high grade gliomas: mathematical analysis deriving efficacious infusion rates based on patient requirements. SIAM J. Appl. Math. 70 (6), 1953–1976.
Lezzi, G., Karjalainen, K., Lanzavecchia, A., 1998. The duration of antigenic stimulation determines the fate of naïve and effector T cells. Immunity 8, 89–95.
Massague, J., 2004. G1 cell-cycle control and cancer. Nature 432, 298–306.
Matzavinos, A., Chaplain, M.A.J., Kuznetsov, V., 2004. Mathematical modelling of the spatio-temporal response to cytotoxic T-lymphocytes to a solid tumor. IMA J. Math. Med. Biol. 21, 1–24.
Mercado, R., Vijh, S., Kerksiek, K., Pilip, I.M., Pamer, E.G., 2000. Early programming of T cell populations responding to bacterial infection. J. Immunol. 165, 6833–6839.
Miao, H.Y., Jin, X., Perelson, A.S., Wu, H.L., 2012. Evaluation of multitype mathematical models for CFSE-labeling experiment data. Bull. Math. Biol. 74 (2), 300–326, http://dx.doi.org/10.1007/S11538-011-9668-Y.
Migliaccio, M., Alves, P.M., Romero, P., Rufer, N., 2006. Distinct mechanisms control human naïve and antigen-experienced CD8+ T lymphocyte proliferation. J. Immunol. 176, 2173–2182.
Molina-Paris, C., Lythe, G. (Eds.), 2011. Mathematical Models and Immune Cell Biology. Springer, New York, Dordrecht Heidelberg, London.
Murali-Krishna, K., Altman, J.D., Suresh, M., Sourdive, D.J.D., Zajac, A.J., Miller, J.D., Slansky, J., Ahmed, R., 1998. Counting antigen-specific CD8 T cells: a reevaluation of bystander activation during viral infection. Immunity 8 (2), 177–187.
Nevozhay, D., Adams, R.M., Murphy, K.F., Josic, K., Balazsi, G., 2009. Negative autoregulation linearizes the dose-response and suppresses the heterogeneity of gene expression. Proc. Natl. Acad. Sci. USA 106, 5123–5128.
Osborne, L.C., Abraham, N., 2010. Regulation of memory T cells by gamma c cytokines. Cytokine 50, 105–113.
Osborn, S.L., Sohn, S.J., Winoto, A., 2007. Constitutive phosphorylation mutation in Fas-associated death domain (FADD) results in early cell cycle defects. J. Biol. Chem. 282, 22786–22792.
Peixoto, A., Evaristo, C., Munitic, I., Monteiro, M., Charbit, A., Rocha, B., Veiga-Fernandes, H., 2007. CD8 single-cell gene coexpression reveals three different effector types present at distinct phases of the immune response. J. Exp. Med. 204 (5), 1193–1205, http://dx.doi.org/10.1084/Jem.20062349.
Phillips, R., Kondev, J., Theriot, J., 2009. Physical Biology of the Cell. Garland Science, New York.
Plas, D.R., Rathmell, J.C., Thompson, C.B., 2002. Homeostatic control of lymphocyte survival: potential origins and implications. Nat. Immunol. 3, 515–521.
Quelle, F.W., 2007. Cytokine signaling to the cell cycle. Immunol. Res. 39, 173–184.
Regoes, R.R., Yates, A., Antia, R., 2007. Mathematical models of cytotoxic T lymphocyte killing. Immunol. Cell Biol. 85, 274–279.
Rehm, M., Huber, H.J., Dussmann, H., Prehn, J.H.M., 2006. Systems analysis of effector caspase activation and its control by X-linked inhibitor of apoptosis protein. EMBO J. 25, 4338–4349.
Rocha, B., Tanchot, C., 2006. The Tower of Babel of CD8(+) T-cell memory: known facts, deserted roads, muddy waters, and possible dead ends. Immunol. Rev. 211, 182–196.
Scaffidi, C., Kirchhoff, S., Krammer, P.H., Peter, M.E., 1999. Apoptosis signaling in lymphocytes. Curr. Opin. Immunol. 11, 277–285.
Schluns, K.S., Lefrancois, L., 2003. Cytokine control of memory T-cell development and survival. Nat. Rev. Immunol. 3, 269–279.
Singer, A., et al., 2004. Suppression of IL7R alpha transcription by IL-7 and other prosurvival cytokines: a novel mechanism for maximizing IL-7-dependent T cell survival. Immunity 21, 289–302.
Smith, K.A., 2005. Determining to divide: how do cells decide?. J. Biol. Phys. 31, 261–272.
Smith, K.A., 2010. The Quantal Theory of Immunity: The Molecular Basis of Autoimmunity and Leukemia. World Scientific Publishing Co Pte. Ltd., Singapore
Smith, K.A., Cantrell, D.A., 1985. Interleukin 2 regulates its own receptors. Proc. Natl. Acad. Sci. USA 82, 864–868.
Song, J.X., Salek-Ardakani, S., So, T., Croft, M., 2007. The kinases aurora B and mTOR regulate the G1-S cell cycle progression of T lymphocytes. Nat. Immunol. 8, 64–73.
Sprent, J., Surh, C.D., 2002. T cell memory. Annu. Rev. Immunol. 20, 551–579.
Stahl, M., et al., 2002. The forkhead transcription factor FoxO regulates transcription of p27(Kip1) and bim in response to IL-2. J. Immunol. 168, 5024–5031.

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Strasser, A., Puthalakath, H., O'Reilly, L.A., Bouillet, P., 2008. What do we know about the mechanisms of elimination of autoreactive T and B cells and what challenges remain. Immunol. Cell Biol. 86, 57–66.
Strasser, A., Jost, P.J., Nagata, S., 2009. The many roles of FAS receptor signaling in the immune system. Immunity 30, 180–192.
Subramanian, V.G., Duffy, K.R., Turner, M.L., Hodgkin, P.D., 2008. Determining the expected variability of immune responses using the cyton model. J. Math. Biol. 56 (6), 861–892, http://dx.doi.org/10.1007/S00285-007-0142-2.
Sun, J.C., Lehar, S.M., Bevan, M.J., 2006. Augmented IL-7 signaling during viral infection drives greater expansion of effector T cells but does not enhance memory. J. Immunol. 177, 4458–4463.
Swainson, L., Verhoeyen, E., Cosset, F.L., Taylor, N., 2006. IL-7R alpha gene expression is inversely correlated with cell cycle progression in IL-7-stimulated T lymphocytes. J. Immunol. 176, 6702–6708.
Tripathi, P., Mitchell, T.C., Finkelman, F., Hildeman, D.A., 2007. Cutting edge: limiting amounts of IL-7 do not control contraction of CD4(+) T cell responses. J. Immunol. 178, 4027–4031.
Tuma, R.A., Pamer, E.G., 2002. Homeostasis of naïve, effector and memory CD8 T cells. Curr. Opin. Immunol. 14, 348–353.
van Stipdonk, M.J.B., et al., 2003. Dynamic programming of CD8(+) T lymphocyte responses. Nat. Immunol. 4, 361–365.
Wardle, E.N., 2009. Guide to Signal Pathways in Immune Cells. Springer Verlag, New York
Weinberg, R.A., 1995. The retinoblastoma protein and cell-cycle control. Cell 81, 323–330.
Wherry, E.J., et al., 2007. Molecular signature of CD8+ T cell exhaustion during chronic viral infection. Immunity 27, 670–684.
Williams, M.A., Bevan, M.J., 2007. Effector and memory CTL differentiation. Annu. Rev. Immunol. 25, 171–292.
Xue, H.H., et al., 2002. IL-2 negatively regulates IL-7 receptor alpha chain expression in activated T lymphocytes. Proc. Natl. Acad. Sci. USA 99, 13759–13764.
Yoon, H., Kim, T.S., Braciale, T.J., 2010. The cell cycle time of CD8+ T cells responding in vivo is controlled by the type of antigenic stimulus. PLoS One 5, e15423.
Yu, R.C., et al., 2008. Negative feedback that improves information transmission in yeast signalling. Nature 456, 755–761.

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