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An analysis of *early-stage* IL-2 capture times in populations of T cells diffusively interacting in a confined environment

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HIGHLIGHTS

- A methodology is presented for calculating the effects of diffusive interactions in large populations of Th and Treg cells. The premise of this work is the behavior of a confined representative subpopulation reflects that of the entire population.
- This methodology is used to examine the effects of *early-stage* competition among the cells for IL-2 secreted by the Th.
- Typical Tregs are good IL-2 scavengers but their effect on autocrine capture is shorter-ranged than previously reported.
- Correlations are provided for estimating IL-2 autocrine and paracrine capture over a wide range of conditions.

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ABSTRACT

This numerical analysis examines *early-stage* Interlukin-2 (IL-2) capture in large populations of secreting T helper (Th) and absorbing T regulatory (Treg) cells in an attempt to provide rational guidelines for when diffusive interactions can affect the Th autocrine cycle, as reflected in capture times. Autocrine and paracrine capture is calculated over a wide range of conditions: the mix of cells in a population; cell size and spacing; antigen activated IL-2 secretion and Th receptor expression rates; receptor dissociation constant; and number of resting Treg receptors. Correlations for quickly estimating IL-2 capture over these conditions are provided. This study suggests that a typical Treg can scavenge a significant amount of IL-2 without affecting autocrine capture by the Th. As a result, Treg influence on autocrine capture is shorter-ranged than previously reported. It is conjectured that high *early-stage* paracrine relative to autocrine capture leads to faster receptor enhancement for a Treg than a Th. The resulting enhancement time gap is considerably longer and, thus, diffusive suppression more likely, for a weakly- as opposed to strongly-activated Th. The methodology can be extended to *later-stage* capture to confirm this conjecture and to diffusive interactions in other cell-type populations.

1. Introduction

Cells within a large population can communicate by exchanging various chemical factors (i.e., cytokines and chemochines) with neighboring cells via diffusion through the surrounding medium. To analytically study of this exchange requires a detailed knowledge of the factor concentration within the population, consisting perhaps of millions of cells/ml. The concentration, in turn, depends on the rates of secretion and capture of the chemical factors. Of interest here is the transfer of the cytokine Interleukin-2 (IL-2) in populations of T helper (Th) and T regulatory (Treg) cells. IL-2, secreted by antigen-activated Th cells, is a growth factor that among other actions stimulates cell proliferation and division (Wang and Smith, 1987; Forsten and Lauffenburger, 1992, 1994; Lauffenburger and Linderman, 1993; Nelson and Willerford, 1998; Myszka et al., 1996; Fallon and Lauffenburger, 2000; Rickert et al., 2005, 2004; Feinerman et al., 2008, 2010; Malek, 2008; Busse et al., 2010; Pillet et al., 2010; Francois et al., 2013; Kolitz and Lauffenburger, 2012; Garcia-Martinez and Leon, 2012; Cotari et al., 2013; Tkach et al., 2014). Secreted IL-2 (Fig. 1A) that is self-captured (autocrine capture) by the Th instead of by neighboring cells (paracrine capture) can lead to dysfunction in the autoimmune system and unregulated tumor cell growth (Forsten and Lauffenburger, 1992). A Th begins to secrete IL-2 and express low-affinity (α) receptors only after antigen activation, with secretion (S) and α-expression (E) rates depending on the degree of activation (Feinerman et al., 2010). Tregs, on the other hand, compete with the Ths for available IL-2. Tregs do not secrete but constitutively have about 10K α-receptors (Feinerman et al., 2010; Garcia-Martinez and Leon, 2012) and are presumed to regulate by disrupting the autocrine cycle of the Th through theft of IL-2 (Busse et al., 2010) and, thus, preventing proliferation of activated Th cells and/or curbing immune

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Nomenclature

a_h	Number of IL-2 molecules captured by the Th
a_r	Number of IL-2 molecules captured by the Treg by the time a Th has captured a_h molecules
$a''\|_h$	Number of captured IL-2 molecules per unit area at a point on the surface of the Th
$a''\|_r$	Number of captured IL-2 molecules per unit area at a point on the surface of the Th
$a_{r,weak}$	Number of IL-2 molecules captured by the Treg by the time a weakly-activated Th has captured a_h molecules
$a_{r,strong}$	Number of IL-2 molecules captured by the Treg by the time a strongly-activated Th has captured a_h molecules
b	A factor that measures the degree of non-equilibrium on the Th cell surfaces
CAP_h	Capture rate of the Th
CAP_h	Capture rate of the Treg
C	IL-2 concentration
C^*	Dimensionless IL-2 concentration ($=C/K_d$)
C_b^*	Dimensionless bulk concentration
C_h^*	Average dimensionless concentration on the Th
$C^*\|_i$	Dimensionless concentration at a point on the surface of a Th (i=h) or Treg (i=r)
C_r^*	Average dimensionless concentration on a Treg
C_w^*	Average dimensionless concentration on the outer wall
D	Diffusion coefficient
E	Low affinity Th receptor expression rate
f	Dimensional correction factor
k_e	Endocytosis rate constant (not used)
k_{on}	Association rate constant
k_{off}	Dissociation rate constant
K_d	Dissociation constant ($=k_{off}/k_{on}$)
$\mathcal{L}$	Dimensional center-to-center spacing of the cells
L	Dimensionless center-to-center spacing ($\mathcal{L}/\mathcal{R}_{cell}$)
N_h	Number of Ths in a subpopulation
N_i	Number of non-capturing cells in a subpopulation
N_r	Number of Tregs in a subpopulation
N_T	Total number of cells in a subpopulation
$\mathcal{R}_{cell}$	Cell radius
$\mathcal{R}_w$	Radius of the outer (non-porous) shell of the subpopulation
R_w	Dimensionless radius of the outer (non-porous) shell of the subpopulation ($=\mathcal{R}_w/\mathcal{R}_{cell}$)
t	Time (h)
t_{ah}	Time required for a Th to capture ah molecules based on an AM calculation
$t_{ah,eq}$	Estimated time for a Th to capture ah molecules based on the assumption of surface equilibrium
$t_{ah,eq,Tr=o}$	$t_{ah,eq}$ when the Tregs have no receptors
$t_{ah=1}$	Time required for a Th to capture its first molecule
T_h	Number of receptors on the surface of a Th
T_r^o	Number of receptors on the surface of a Treg
$\mathcal{V}_{cell}$	The volume of a cell ($4\pi\mathcal{R}_{cell}^3/3$)
$\mathcal{V}$	$\mathcal{V}_{cell}\, N_T(1-\phi)/\phi$
S	IL-2 secretion rate (#/h)
$''$	Refers to per unit area
$\|$	Refers to a local value

Greek

ϕ	Volume fraction of cells $=(4\pi/3L^3)$
τ	Dimensionless time ($=Dt/\mathcal{R}_{cell}^2$)

over-response after infection. Tregs suppress weakly-but not strongly-activated Ths (Feinerman et al., 2010). A weakly-activated Th has S and E values considerably lower than a strongly-activated Th (Feinerman et al., 2010). The question then becomes under what conditions is diffusive suppression possible? In this regard, some authors claim the cells have to be in close contact (Shevach, 2000) while Busse et al. (2010), using a 2D model, concluded Tregs are such efficient IL-2 *thieves* that they can compete with a Th for available IL-2 even at large cell spacings, thus, making suppression possible. The conclusion in Busse et al. (2010), however, is based on a criterion of autocrine/paracrine parity. As will be seen, Tregs can be long-ranged scavengers but are usually short-ranged IL-2 thieves. As a result, a Treg can capture a substantial amount of IL-2 without disrupting the autocrine cycle of the Th at least during *early-stage* interaction. *Early-stage* interaction is considered here to begin when the Th starts to secrete IL-2 and express low-affinity receptors and ends after autocrine capture of the first few IL-2 molecules before receptor endocytosis and the expression of high-affinity receptors.

Discerning large population behavior, a complex (insurmountable) task-beyond the scope of any one paper, has to begin locally. IL-2 is captured by binding with receptors on the cell surface. These receptors can be of low-(α), intermediate-($\beta\gamma$) and high-affinity($\alpha\beta\gamma$). The binding kinetics have been extensively studied (Wang and Smith, 1987; Forsten and Lauffenburger, 1992, 1994; Lauffenburger and Linderman, 1993; Nelson and Willerford, 1998; Myszka et al., 1996; Fallon and Lauffenburger, 2000; Rickert et al., 2005, 2004; Feinerman et al., 2008, 2010; Malek, 2008; Busse et al., 2010; Pillet et al., 2010; Francois et al., 2013; Kolitz and Lauffenburger, 2012; Garcia-Martinez and Leon, 2012). Capture apparently occurs in a multi-step process in which IL-2 first binds to a low-affinity receptor that then migrates to bind with an intermediate to form an occupied high-affinity-receptor (Forsten and Lauffenburger, 1994; Lauffenburger and Linderman, 1993; Rickert et al., 2005; Malek, 2008; Feinerman et al., 2010; Garcia-Martinez and Leon, 2012) that can signal through the cell membrane stimulating enhanced receptor expression. In addition to concentration, the rate of capture also depends on the number (and affinity) of receptors on a cell's surface. This number, however, changes with time due to receptor expression and endocytosis. An analysis of diffusive interactions, therefore, depends on a large number of physical, kinetic, and transport variables and properties. Further, cells are confined in a vial or organ. Any excess IL-2 that escapes initial capture tends to accumulate in the medium, temporally raising the local concentration and, thus, the capture rates. A detailed cell history requires adoption of a specific set of rate constants for IL-2 capture. In this regard, various values for the dissociation constant (K_d), the receptor expression and endocytosis rate constants and even the value of the diffusion coefficient (D) appear in the literature. For example, low-affinity K_d values range from 10 to 37 nM (Wang and Smith, 1987; Forsten and Lauffenburger, 1994; Nelson and Willerford, 1998; Myszka et al., 1996; Fallon and Lauffenburger, 2000; Rickert et al., 2004; Malek, 2008; Feinerman et al., 2010; Pillet et al., 2010; Cotari et al., 2013; Wang et al., 2005) while Busse et al., (2010) uses a D of $36K\mu^2/h$ that is an order of magnitude lower than other investigators ($360K\mu^2/h$) (Forsten and Lauffenburger, 1992; Forsten and Lauffenburger, 1994; Feinerman et al., 2010; Geankoplis, 1983; Annunziata et al., 2005). With so many independent and uncertain