

The Dynamics of CD4+ T Cell Proliferation in Autopilot Model

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Abstract. Under the assumption of the autopilot model, after antigen stimulation exceeds a threshold, the proliferation and effector function of CD4+ T cells are self-sustained and do not need further antigen stimulation. However, CD4+ T cell proliferation is driven by their production of IL-2, which then binds to cells and triggers proliferation. Without regulation, this autocrine process forms a positive feedback loop that causes uncontrolled proliferation. This study mathematically modeled the regulatory mechanisms of the CD4+ T cell response after infection, focusing on the role of IL-2 self-regulation and Treg in this mechanism. We performed a phase-space analysis to study the long-term behavior of the proliferation process. Our results show that IL-2 self-regulation alone is not sufficient to fully inhibit CD4+ T cell response, and that the involvement of Treg cells is essential to regulate the immune response effectively. In particular, when the rate of CD4+ T cell proliferation is controlled by the rate of IL-2-mediated CD4+ T cell removal, Treg cells control CD4+ T cell proliferation by releasing immunosuppressive cytokines such as IL-10 and TGF- β , thus inhibiting the unregulated immune response.

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1 Introduction

CD4+ T cells are the principal coordinators of the adaptive immune system, governing both CD8+ T response and the antibody response. In a primary response, naive

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CD4+ T cells are activated when major histocompatibility complex class II molecules (MHC-II) on the surface of antigen presenting cells (APCs, such as dendritic cells) bind to T cell receptors (TCR) on CD4+ T cells. Full activation requires co-stimulatory molecules (such as CD28 and B7 family ligands) to produce a secondary signal that reduces invalid or self-responsiveness [23]. Upon activation, CD4+ T cells differentiate into different effector subpopulations (Th1, Th2, Th17, Treg) to influence the characteristics of the immune response [28]. This differentiation is driven by cytokines such as interleukin-6 (IL-6), interleukin-12 (IL-12), and transforming growth factor-beta (TGF- β).

Since the adaptive immune system can recognize an immense number of distinct antigens (in the order of 10^7 to 10^{14}) [19], only a tiny fraction of CD4+ T cells are activated. Thus, they must undergo a proliferation process to reach a sufficient level for effective function. This proliferation process significantly influences the magnitude and efficacy of the immune response, therefore determining the success or failure of viral clearance [10].

Interleukin-2 (IL-2) is a key driver for CD4+ T cell proliferation [2], and is primarily produced by CD4+ T cells [20]. This autocrine action of IL-2 in CD4+ T cells forms a positive feedback loop, which ensures the efficacy and duration of immune response through their rapid proliferation and functional maintenance [14, 18].

The duration of TCR stimulation must exceed a specific threshold for T cells to fully activate, start helper activities, and encourage cell proliferation. This threshold mechanism ensures effective recognition and robust response of the immune system to antigens, while preventing nonspecific activation by transient or weak stimuli [9, 12]. However, once the activation threshold is reached, T cells adopt a 'automatic driving' state, i.e. they maintain proliferation and effector activities without continued TCR stimulation after initial activation [13, 24]. This phenomenon is referred to as the 'autopilot model' [1, 3].

If appropriate negative controls are lacking, the autocrine action of IL-2 and CD4+ T cells in the autopilot model will result in uncontrolled proliferation, tissue damage and autoimmune diseases including multiple sclerosis [4, 15]. Thus, T cell proliferation must be regulated to prevent excessive immune activation and to mitigate immune-mediated tissue damage and inflammation. The adaptive immune system has multiple mechanisms for such regulation.

The main mechanism is provided by regulatory T (Treg) cells. Treg cells regulate the proliferation of activated CD4+ T cells via two cytokines: interleukin-10 (IL-10) and TGF- β . TGF- β promotes Treg differentiation while reducing the differentiation of helper phenotypes [5]. In addition, IL-10 inhibits antigen presentation of antigen-presenting cells. TGF- β and IL-10 also directly inhibit IL-2 production, whereby limiting CD4+ T cell proliferation. TGF- β does this via the Smad2/3 pathway which suppresses the activity of the transcription factor associated with the IL-2 gene promoter [25], while IL-10 directly suppresses critical transcription factors for IL-2 production (NF- κ B and NFAT) via the STAT3 pathway [11]. Furthermore, TGF- β upregulates cell cycle inhibitors such as p21 and p27, inducing apoptosis in CD4+ T cells [27].

In addition, multiple self-regulating mechanisms of IL-2 guarantee that a high concentration of IL-2 has a negative impact on CD4+ T cell proliferation. For example, IL-2