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Regulating the diverse outcomes of interferon's interference

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Abstract

Regulatory T cells are crucial for preventing autoimmunity, but how their function is restrained to allow optimal effector T cells responses in appropriate contexts is unclear. In a recent paper in the *Journal of Experimental Medicine*, Campbell and colleagues demonstrate that virus-induced type I interferon acts directly on Treg cells to allow for functional antiviral T cell responses.

Perhaps no single cell type exemplifies the double-edged sword concept of immunity better than regulatory T (Treg) cells. They are absolutely required to maintain normal immune homeostasis, but their function must also be transiently suppressed to enable the necessary burst of effector T cell responses against pathogenic microorganisms. Thus, FoxP3⁺ Treg cell number, function, and location must be exquisitely controlled. Recent studies have examined the roles of Treg cells during infection, and shown that they can restrain the magnitude, effector function, and migration of antiviral T cells depending on the type of pathogen and tissue affected [1]. Although these functions limit T cell responses to pathogens, they are also thought to help limit immunopathology associated with cytolytic and inflammatory effectors deployed during the immune response to a pathogen. Thus, Treg cells must be transiently restrained during acute infections to allow for an efficient effector T cell response, and then regain function to promote resolution following pathogen clearance. A new study by Srivastava *et al.* provides insight into the mechanisms underlying this transient suppression of Treg cell function. The authors show that type I interferons (IFN- $\alpha\beta$), a family of proinflammatory cytokines induced to high levels during many viral infections, directly inhibit Treg cell proliferation and function during acute infection by lymphocytic choriomeningitis virus (LCMV) [2].

For the past 50+ years, scientists have identified inductive signals, mapped signaling cascades, defined the necessary transcription factors, and charted the regulatory feedback loops that control the production of IFN- $\alpha\beta$ during infection. Originally named for its ability to interfere with viral replication, IFN- $\alpha\beta$ is now recognized as one of the most pleiotropic family of cytokines in the immune system. The 14 members of the mammalian IFN- $\alpha\beta$ family bind to a single dimeric IFN- α receptor (IFNAR) and activate signaling through the JAK/STAT and the IRF (interferon regulatory factor) pathways that culminate in the transcription of interferon-stimulated genes (ISG). Different ISG transcriptional signatures

may be induced due to cell type specific and temporally or environmentally regulated expression of STATs and IRFs, as well as in response to specific viruses. Thus, the IFN response is tailored to the cell type and infectious context, allowing for a diverse array of physiological outcomes. In the case of antiviral effector T cells, the timing of IFN- $\alpha\beta$ signals profoundly influences how the cells respond. For example, direct IFN- $\alpha\beta$ signals are required upon activation for the survival of antiviral T cells. In its absence T cell proliferation is blunted more than 100x [3], and the antiviral T cells become susceptible to NK cell mediated elimination [4,5]. However, IFN- $\alpha\beta$ signals prior to TCR signaling results in blunted proliferation of T cells that are activated later in the response [6]. One layer of regulation that controls these divergent outcomes is the differential utilization of STAT1 and STAT4 in naïve and activated T cells. Higher levels of STAT1 in naïve T cells results in a STAT1-dependent ISG signature that inhibits proliferation, whereas reduced levels of STAT1 and higher STAT4 expression in activated T cells switches IFN- $\alpha\beta$ signaling to a STAT4-dependent program that promotes proliferation and survival [7].

In addition to modulating T cell proliferation, IFN- $\alpha\beta$ induces the apoptosis of CD44^{hi} memory CD4⁺ and CD8⁺ T cells, via mechanisms that are partially dependent on the proapoptotic molecule Bim [8]. This attrition of memory T cells occurs even in the presence of antigen, suggesting that antigen-specific memory T cells in a recall response are not protected from IFN- $\alpha\beta$ -mediated apoptosis. Accordingly, vaccine-boosting vectors that induce minimal IFN- $\alpha\beta$, such as vesicular stomatitis virus (VSV), promote the survival and maintenance of memory T cells [9]. However, mathematical modeling studies suggest that the loss of pre-existing memory T cells is actually beneficial as it may allow for a broad repertoire of 1° T cells (those responding for the first time) that could otherwise be dominated by memory or cross-reactive 2° effector T cells [10]. Consequently, instead of narrowing the collection of memory T cells present after boosting or reinfection, IFN- $\alpha\beta$ works to maintain an extensive T cell repertoire, which is critical for protection against highly mutable viruses such as influenza.

Srivastava *et al.* show that, like memory T cells, the number of CD44^{hi} Treg cells was also reduced during the acute phase of LCMV infection [2]. This drop in Treg cell number correlated with decreased proliferation and was dependent on direct IFN- $\alpha\beta$ signals because IFNAR^{-/-} Treg cell numbers remained stable *in vitro* and during infection *in vivo*. Moreover, direct IFN- $\alpha\beta$ signals suppressed CD28-dependent ICOS expression on Treg cells, which promotes the proliferation of Treg cells. Thus, IFN- $\alpha\beta$ inhibited the proliferation of Treg cells during infection by restricting costimulatory signals delivered by CD28 and ICOS. Furthermore, when Treg-depleted mice were reconstituted with IFNAR^{-/-} Treg cells, fewer LCMV-specific CD8⁺ and CD4⁺ T cells expressed IFN- γ and the CD8⁺ T cells exhibited diminished cytolytic function, which correlated with prolonged viremia *in vivo*. Thus, direct IFN- $\alpha\beta$ signals suppressed the proliferation and maintenance of CD44^{hi} Treg cells during LCMV, which allowed for optimal antiviral T cell responses and viral control. STAT1 is phosphorylated in Treg cells at early time points after infection, suggesting that, as in the case of naïve T cells, STAT1-mediated IFN- $\alpha\beta$ signaling may curb Treg cell proliferation. Whether Treg cells are also susceptible to Bim-mediated apoptosis remains to be addressed.

Taken together, IFN- $\alpha\beta$ produced in response to viral infection allows for a broad CD8 T cell response by eliminating pre-existing memory T cells, a vigorous T cell response by serving as a costimulatory signal acting through STAT4 during activation, and a functional effector T cell response by suppressing Treg cells (Figure 1). IFN- $\alpha\beta$ and Treg cells also modulate CD4 Th1 and Tfh cell fates as well as CD8 terminal effector and memory precursor differentiation, yet the detailed mechanisms as to how, when and where these signals influence effector T cell differentiation is not clear. Finally, although IFN- $\alpha\beta$ promotes optimal antiviral T cell responses, it is a highly inflammatory cytokine that can exacerbate immune pathology during chronic infections and autoimmunity. Therefore, unraveling the diverse actions of IFN- $\alpha\beta$ on distinct cell populations during different disease states will allow for the identification of targeted immune-therapeutics to modulate type I interferon pathways.

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Figure 1.

Effects of $\text{IFN-}\alpha\beta$ on effector CTL responses. $\text{IFN-}\alpha\beta$ induces the apoptosis of memory T cells, which promotes a broad CTL response. Additionally, $\text{IFN-}\alpha\beta$ stimulates the proliferation and survival of activated T cells, which permits a vigorous CTL response. Finally, $\text{IFN-}\alpha\beta$ restricts the maintenance of Treg cells, which suppress T cell effector functions such as cytolysis and $\text{IFN-}\gamma$ production, thereby allowing for a functional CTL response.