



Foxp3+ regulatory T-cells and IL-2: the Moirai of T-cell fates?

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Regulatory T-cells (T_{reg}) have emerged as a crucial cellular checkpoint acting to prevent potentially harmful immune responses. Due to its highly diverse activities, regulating the immune system requires more than general suppression. Particularly, during the developing immune response to infection, T_{reg} need to balance the host reaction to achieve both an effective response against the invading pathogen as well as to prevent immunopathology from excessive or inappropriate activity. In this opinion article we discuss the dual roles of IL-2 as both a key inducer of T_{reg} activity and also a target of T_{reg} control during the acute phase of infection. We propose a model in which Foxp3+ regulatory T-cells dynamically “measure” IL-2 availability and restrict its access to effector T-cells, thereby controlling differentiation of these useful but potentially harmful cells.

CD4+ T-lymphocytes play a central role in orchestrating immune responses by modifying the functionality of other immune cells and guiding the qualitative features of a response to one optimal for resisting a particular microorganism. Besides augmenting both innate and adaptive immune responses, CD4+ T-cells limit excessive immune activation and immunopathology during infections. Among CD4+ T-cells, Foxp3+ regulatory T-cells (T_{reg}) are essential for the maintenance of peripheral tolerance (Kim et al., 2007; Lahl et al., 2007). These cells also modulate the responses to pathogens (Belkaid and Tarbell, 2009). A plethora of mechanisms for how T_{reg} exert their function have been suggested (Shevach, 2009; Josefowicz et al., 2012). However, there is still an ongoing debate as to which functions of T_{reg} are essential under which circumstances. Likely, T_{reg} function can be attuned to specific conditions and

distinct “rules” govern T_{reg} behavior in the steady-state versus inflammatory environments, secondary lymphoid (SLO) versus peripheral organs, developing versus ongoing immune responses, or acute versus chronic infections, for example. In this article we focus on the function of T_{reg} in the SLO during a developing acute infection and, although several cytokines are relevant, we concentrate on IL-2 as a central platform that enables effective immune control, as it (1) links activation of effector and regulatory responses, (2) establishes a feed-back loop for T-cell expansion, and (3) allows control over T-cell differentiation and fate decisions, preserving memory formation.

IL-2 IS A CENTRAL CYTOKINE FOR T-CELL ACTIVATION

IL-2, originally discovered as a mitogenic factor for T-cells, is bound as a quaternary complex with CD25 (IL2R α -chain), CD122 (IL2R β -chain), and CD132 (common γ -chain). The α/β -heterodimer facilitates IL-2 capture with high affinity and, further stabilized by the γ -chain, forms a very stable complex which is terminated via receptor internalization rather than ligand dissociation (Smith, 2006). Upon activation by TCR interactions and additional co-stimulation via CD80/CD86, conventional T-cells (T_{conv}) produce IL-2 and upregulate CD25 expression, which enhances IL-2 capture and consequently IL-2 signaling, further promoting CD25 expression, T-cell activation, and proliferation. This feed-forward loop can lead to activation-induced cell death, but highly activated, proliferating T-cells also undergo apoptosis when acutely deprived of IL-2 signals. Therefore, IL-2 is a master regulator of T-cell activation, proliferation, and death, excellently reviewed in Malek and Castro (2010), Boyman and Sprent (2012).

ACTIVATION OF T_{REG} THROUGH IL-2: ANTICIPATION AND SENSING OF EFFECTOR RESPONSES

In contrast to conventional T-cells (T_{conv}), T_{reg} constitutively express CD25 (Sakaguchi et al., 1995) and have STAT5 phosphorylation in the steady-state, arguing for continuous or high frequency intermittent IL-2 signaling in the absence of infection. Indeed, IL-2 signals seem to be pivotal for T_{reg} survival because animals that lack IL-2, CD25, or CD122 are largely devoid of peripheral T_{reg} and suffer from severe autoimmunity (Sadlack et al., 1993; Suzuki et al., 1995; Willerford et al., 1995; Fontenot et al., 2005). T_{reg} do not produce IL-2 themselves when stimulated through the TCR and therefore rely on paracrine IL-2 for their maintenance. T_{conv} produce IL-2 upon activation and then gradually upregulate CD25. Since T_{reg} constitutively express CD25, they can sense and signal via IL-2 as soon as it is produced, assuming that these T_{reg} are within suitable proximity to the cytokine secreting cells. Because IL-2 signaling further upregulates CD25, T_{reg} can even increase their ability to capture IL-2 as compared to T_{conv} which need to initiate CD25 expression post TCR-mediated activation (Feinerman et al., 2010). Indeed, it has been shown *in vivo* that T_{reg} are the first cells to respond to IL-2 upon antigenic challenge of T_{conv} (O’Gorman et al., 2009). As the amount of IL-2 produced by T-cells correlates with the extent of co-stimulation from DC *in vitro* (Shahinian et al., 1993) and *in vivo* (Kastenmuller et al., 2011), it might reflect the magnitude of pathogen burden and the extent of innate stimulation. Therefore, T_{reg} “sense” the initiation of an adaptive immune response in a qualitative and potentially quantitative manner when responding to IL-2 signals derived from adaptive effectors.

T_{REG} CONTROL THE AVAILABILITY OF IL-2

Given the relative abundance of T_{reg} in SLO, where adaptive responses are initiated and IL-2 is being produced, it seems likely that the “sensing” of IL-2 by T_{reg} consumes a significant amount of the totally available IL-2. In this scenario, the mere presence of T_{reg} could reduce IL-2 availability and limit T_{eff} responses, without a need for active regulation (cytokine-sink model). Indeed, the presence of T_{reg} leads to substantial competition for IL-2, resulting in impaired proliferation of T_{eff} cells *in vitro*. Competition was further demonstrated *in vivo*, with a primary effect on the survival of T_{eff} and not on their proliferation (Pandiyana et al., 2007; Kastenmuller et al., 2011). T_{reg} also control IL-2 production (Thornton and Shevach, 1998), either by directly acting on T-cells (Bodor et al., 2007; Vaeth et al., 2011) or indirectly, through DC (Onishi et al., 2008). The latter concept is based on *in vitro* evidence of a positive correlation between IL-2 production by T_{eff}, the strength of ConA stimulation, and the amount of CD28 expression (Shahinian et al., 1993). T_{reg} express significant levels

of surface CTLA-4 on their surface and this molecule can directly block co-stimulatory molecules and CD28-CD80/86-interactions, or, via trans endocytosis, modulate the amount of CD80/86 that is displayed by DC (Wing et al., 2008; Qureshi et al., 2011). Importantly, the amount of CTLA-4 expressed on T_{reg} is again regulated by IL-2 signals. Consequently, T_{reg} control the level of co-stimulation through CD80/CD86 surface expression not only during steady-state (Schildknecht et al., 2010), but, importantly, also during highly inflammatory processes such as viral infection (Kastenmuller et al., 2011).

Therefore, DC appear to constitute a platform on which both stimulation and regulation of conventional T-cells is executed, with IL-2 being a central mediator that activates both T_{eff} and T_{reg}. Feed-back loops involving the constitutive high levels of CD25 on T_{reg} and the IL-2-promoted upregulation of CTLA-4 on these cells operate in concert to restrict IL-2 availability to activated T_{eff}, controlling their expansion, differentiation, and survival (Figure 1).

T_{REG} SELECTIVELY REGULATE EFFECTOR T-CELL RESPONSES BUT PRESERVE MEMORY DEVELOPMENT

Recently, the effects of IL-2 during acute infection have been further refined through analysis of the role of this cytokine in the various stages of CD8+ T-cell differentiation. After their initial activation and induction of CD25 expression, a subpopulation of CD8+ T-cells decrease CD25 levels and become unresponsive to further IL-2 signals, and, at the same time, upregulate the IL-7R α -chain and develop into long-lived memory cells. This is in contrast to T-cells that are exposed to IL-2 for a prolonged period and maintain CD25 expression, undergo enhanced expansion, but differentiate into short-lived effector cells (SLEC) that are prone to apoptosis and severe population contraction after the peak of the response (Kalia et al., 2010; Obar et al., 2010; Pipkin et al., 2010). The recent development of genetic models allowing the specific depletion of Foxp3⁺ T_{reg} (Kim et al., 2007; Lahl et al., 2007) without blocking IL-2/CD25 interactions (Murakami et al., 2002; Suvas et al., 2003; Toka et al., 2004; Heit et al., 2008) enabled asking whether T_{reg} differentially affect these CD8+ T-cell subpopulations. Indeed, manipulating the numbers of activated T_{reg} *in vivo* impacted CD25 expression on activated CD8+ T-cells, indicative of altered IL-2 availability. This resulted in specific changes in numbers of SLEC while leaving the memory CD8+ T-cell compartment largely unaltered (Kastenmuller et al., 2011; McNally et al., 2011). Interestingly, the “window of opportunity” for the regulation of CD8+ T-cell responses by T_{reg} overlapped with the time of CD25 expression on CD8+ T-cells: depletion of T_{reg} cells as late as d2–3 post infection enhanced antigen-specific T-cell numbers in a viral infection model, but depletion later than d5 (when CD8+ T-cells do not express CD25) failed to do so (Kastenmuller et al., 2011). In addition, enhanced expansion of SLEC in the absence of T_{reg} was abrogated through the neutralization of IL-2 (McNally et al., 2011). Therefore, by controlling the availability of IL-2, T_{reg} cells can act as rheostats that balance the differentiation and expansion of pathogen-specific CD8+ effector T-cells. Importantly, by selectively regulating SLEC over memory precursor T-cells, which rapidly seem to become independent of IL-2 signals (d2–3), T_{reg} can limit the extent of acute effector responses

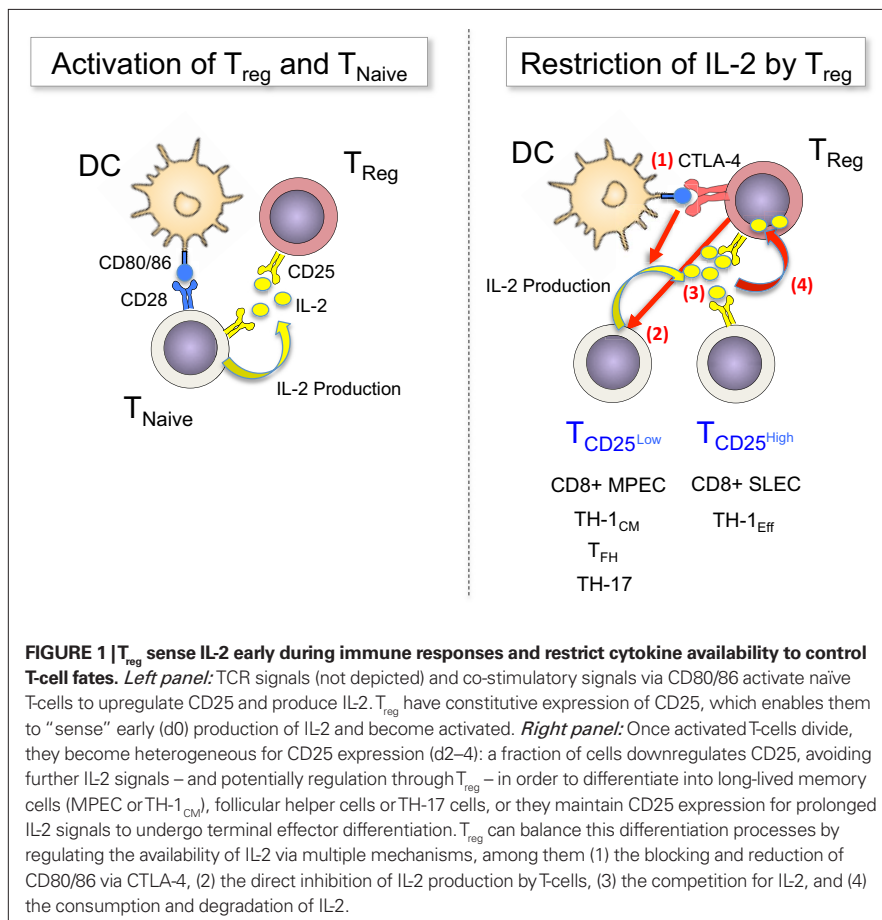


FIGURE 1 | T_{reg} sense IL-2 early during immune responses and restrict cytokine availability to control T-cell fates. *Left panel:* TCR signals (not depicted) and co-stimulatory signals via CD80/86 activate naïve T-cells to upregulate CD25 and produce IL-2. T_{reg} have constitutive expression of CD25, which enables them to “sense” early (d0) production of IL-2 and become activated. *Right panel:* Once activated T-cells divide, they become heterogeneous for CD25 expression (d2–4): a fraction of cells downregulates CD25, avoiding further IL-2 signals – and potentially regulation through T_{reg} – in order to differentiate into long-lived memory cells (MPEC or TH-1_{CM}), follicular helper cells or TH-17 cells, or they maintain CD25 expression for prolonged IL-2 signals to undergo terminal effector differentiation. T_{reg} can balance this differentiation processes by regulating the availability of IL-2 via multiple mechanisms, among them (1) the blocking and reduction of CD80/86 via CTLA-4, (2) the direct inhibition of IL-2 production by T-cells, (3) the competition for IL-2, and (4) the consumption and degradation of IL-2.

without blunting the development of long-lived memory (Kastenmuller et al., 2011). However, once memory is formed and the host is re-challenged with a pathogen, T_{reg} can again control the expansion of secondary effector cells adapted to the extent and requirements of the current infection.

T_{reg} MEDIATED RESTRICTION OF IL-2 AS A GENERAL MECHANISM TO REGULATE FATE DECISIONS IN T-CELLS

Beyond CD4⁺ T-cells, IL-2 likely serves as a central element that allows T_{reg} to regulate population size and differentiation of T-cells in general. A series of recent studies have established the role of IL-2 in CD4⁺ T-cell differentiation into T_{H1} , T_{H2} , T_{H17} , and T_{FH} cells (Liao et al., 2011; Boyman and Sprent, 2012). As with CD4⁺ T-cells discussed above, CD4⁺ T-cells segregate into CD25^{high} and CD25^{low} cells within the first days of a response to an acute infection, and prolonged IL-2 signals in CD25^{high} cells leads to terminal differentiation and Blimp1 and T-bet upregulation in CD4⁺ effector cells. In contrast, CD25^{low} cells gave rise to long-lived CXCR5^{high}CCR7^{high}T-bet^{low} precursors of central memory cells, as well as CXCR5^{high}Bcl6^{high} follicular T-helper cells (T_{FH} ; Choi et al., 2011; Pepper et al., 2011). In line with this, T_{reg} limit the expansion of antiviral CD4⁺ during acute infection, yet do not influence the generation of neutralizing antibodies (Kastenmuller et al., 2011).

Therefore, by limiting excessive IL-2, T_{reg} might not only blunt T_{eff} response but also ensure the generation of T_{FH} cells and consequently the development of appropriate humoral immunity early during acute infection, as IL-2 signals negatively regulate T_{FH} differentiation (Ballesteros-Tato et al., 2012; Johnston et al., 2012). By restricting IL-2 during acute infection, T_{reg} might additionally enhance mucosal immunity and regeneration (potentially preventing superinfection) through promotion of T_{H17} generation, because production of this class of effector cells is inhibited by IL-2 (Chen et al., 2011; Pandiyan et al., 2011).

SUMMARY AND PERSPECTIVE

In summary, we propose a model in which IL-2 availability is a central factor that controls the magnitude and shapes the character of adaptive immune responses. T_{reg} control access of other T-cells to this crucial cytokine by limiting its production

through interference with co-stimulatory molecule availability on DC, as well as by reducing its abundance through consumption. Importantly, this does not act to simply blunt the overall immune response but selectively impacts on T-cell fates that require larger amounts of IL-2. In contrast, other T-cell subpopulations, such as memory-precursors or T_{FH} , are not suppressed, allowing for the generation of cellular and humoral immunological memory to protect the host from future pathogen encounters (Figure 1). T_{reg} are therefore not merely immunosuppressive, they actively participate in guiding the differentiation and fate decisions of other T-cells by regulating the availability of IL-2 in SLO. In this regard, T_{reg} controlling IL-2 availability remind us of the three Moirai (the incarnation of destiny in greek mythology) who controlled the thread of life and thereby directed the fate of individuals.

In addition to this early regulation of effector responses through IL-2, T_{reg} can undergo functional specialization that parallels the differentiation of conventional CD4⁺ T-cells in terms of transcription factor usage and expression of chemokine receptors important for homing to peripheral sites (Chaudhry et al., 2009; Koch et al., 2009; Zheng et al., 2009; Chung et al., 2011; Linterman et al., 2011). This differentiation might facilitate T_{reg} control of fully differentiated effector cells in infected tissues, which is likely to involve mechanisms distinct from regulating or competing for IL-2 (Soper et al., 2007), such as the production of immunosuppressive cytokines (Rubtsov et al., 2008) or cytotoxic molecules (Cao et al., 2007; Loebbermann et al., 2012).

Based on the emerging picture of selective control of effector T-cell fates, we speculate that interfering with T_{reg} function will help to optimize short-term immunotherapeutic approaches, but might be less promising to increase the efficacy of prophylactic vaccines aiming at the induction of long-term memory through T- and B-cells.

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