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Tfr cells trump autoimmune antibody responses to limit sedition

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Interleukin 2 inhibits follicular T helper cells and promotes Foxp3-expressing regulatory T cell generation. Ballesteros-Tato and colleagues shows that things are more complex for Tfr cell generation.

Germinal centers (GCs) form in secondary lymphoid tissues after infection or immunization, producing both memory B cells and antibody-secreting plasma cells that provide protection against subsequent infection[1]. GCs are absolutely dependent on T follicular helper (T_{FH}) cells for their formation and maintenance, and contain a population of $Foxp3^+$ follicular regulatory T (T_{FR}) cells whose biology has remained enigmatic since their discovery in 2011 (ref. 2). In this issue of *Nature Immunology*, Ballesteros-Tato and colleagues demonstrate an inhibitory role of interleukin 2 (IL-2) in T_{FR} cell differentiation, and show that preventing T_{FR} cell differentiation results in increased production of antibody-secreting plasma cells, including those with self-reactive specificity[3].

In contrast to T_{FH} cells, which provide help to GC B cells, T_{FR} cells have a suppressive function and are thought to limit the GC response. Despite their regulatory capacity, T_{FR} cells phenotypically resemble T_{FH} cells, expressing CXCR5, PD-1, and Bcl-6, the transcription factor that is essential for both T_{FH} and T_{FR} cell differentiation[4–6]. One common feature of both T_{FH} and T_{FR} cells that they do not express CD25, the α chain of the high-affinity interleukin 2 (IL-2) receptor[4,7,8]. In primed $CD4^+$ T cells signaling via CD25 inhibits *Bcl6* expression, thereby preventing T_{FH} cell differentiation[2]. However, it is not clear why T_{FR} cells do not express CD25; this is especially paradoxical as $Foxp3^+$ regulatory T (T_{reg}) cells require IL-2 signaling for their maintenance. Ballesteros-Tato and colleagues now show that abundance of IL-2 also suppresses T_{FR} cell differentiation (**Fig. 1**)[3]. In the context of influenza

infection this mechanism delays the differentiation of T_{FR} cells from $Foxp3^+$ precursors until IL-2 concentrations have declined. An inhibitory role of IL-2 on T_{FR} cell formation was recently also reported by another group[8]. IL-2 suppresses T_{FH} cell development by inducing STAT5 phosphorylation, a mechanism that is dependent on Blimp-1 expression[2]. Blimp-1 limits the size of the T_{FR} cell population in a cell-intrinsic way[4], and, interestingly, enhancing IL-2 availability in Blimp-1-deficient cells does not inhibit T_{FR} cell accumulation, suggesting that an IL-2–STAT5–Blimp-1 axis represses T_{FR} cell differentiation. However, not all Blimp-1-negative T_{reg} cells are T_{FR} cells, indicating that other signals events need to be delivered in parallel with IL-2 withdrawal before a T_{reg} cell is able to become a T_{FR} cell[3].

Intriguingly, influenza infection yields IL-2 concentrations sufficient to inhibit T_{FR}, but not T_{FH}, cell differentiation[3]. This difference in responses to IL-2 may be because T_{FR} cell precursors are more sensitive to IL-2 than T_{FH} precursors, due to higher CD25 expression. CD25 is expressed by the majority of T_{reg} cells and signaling via this receptor is essential for their survival and expansion under homeostatic conditions[9]. However, like T_{FR} cells, some T_{reg} cells do not express CD25; T_{reg} cells expressing T-bet, the transcriptional regulator of T_H1 cells, and T_{reg} cells with an effector/memory phenotype have also down-regulated CD25 expression[10,11]. Taken together, these studies may intimate a model in which "naïve" T_{reg} cells require IL-2 signaling for their maintenance, but that limiting IL-2 signaling is essential for T_{reg} cells to differentiate into effector subsets or memory T_{reg} cells.

The role that T_{FR} cells play in GC biology has been difficult to decipher, with multiple studies yielding conflicting results. Initially this was because there was no mouse model that specifically lacked T_{FR} cells. Because of this, all *in vivo* experiments were performed using mixed bone marrow chimeras or adoptive cell transfers, systems which have limitations. The generation of $Bcl6^{flox/flox}Foxp3^{cre}$ animals provides a mouse that specifically lacks T_{FR} cells[12]. Ballesteros-Tato and colleagues[3] use this model to demonstrate T_{FR} cells control the formation of antibody-secreting cells. This dysregulation in the absence of T_{FR} cells is not simply due to a change in magnitude of the response, as the antibody specificity is also altered: lack of T_{FR} cells does not alter anti-influenza antibody titer, but increases production of anti-nuclear autoimmune antibodies after influenza infection. Consistent with the role

of IL-2 in limiting T_{FR} cell formation, treating mice with recombinant IL-2 also results in autoantibody production[3].

The finding that T_{FR} cells limit the production of self-reactive antibody-secreting plasma cells is a key discovery in understanding the biology of these cells. Within the GC, B cells undergo somatic hypermutation of the genes encoding their B cell receptors. This mutation process is random and can result in the emergence of self-reactive clones. It is, therefore, essential that the selection of mutated GC B cells is stringent, ~~in order~~ to ensure these cells do not exit the GC as long-lived plasma cells or memory B cells. Selection within the GC is a process thought to be driven through positive feedback to B cells from follicular dendritic cells and T_{FH} cells, while self-reactive B cells perish through neglect[1]. The discovery that, in the absence of T_{FR} cells, B cells with a self-reactive B cell receptor can emerge from the GC suggests that these cells may have an active role in negative B cell selection. Alternatively, T_{FR} cells may act to limit the provision of positive signals from either T_{FH} cells or follicular dendritic cells. The mechanism by which T_{FR} cells control autoreactivity from the GC, and the main cell types on whom they act are pertinent questions in understanding not just the role for T_{FR} cells, but the biology of the GC.

Legend to Figure 1
When IL-2 binds the high affinity IL-2 receptor, composed of CD122, the common γ chain (γc) and CD25, STAT5 is phosphorylated leading to repression of Bcl6, and increase in Blimp1 expression. The lack of Bcl6 and increase in Blimp1 inhibits Tfr cell differentiation in $Foxp3^+$ precursors.

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