

TFR cells trump autoimmune antibody responses to limit sedition

Linterman, Michelle A; Toellner, Kai-Michael

DOI:

[10.1038/ni.3856](https://doi.org/10.1038/ni.3856)

[10.1038/ni.3856](https://doi.org/10.1038/ni.3856)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Linterman, MA & Toellner, K-M 2017, 'TFR cells trump autoimmune antibody responses to limit sedition', *Nature Immunology*, vol. 18, no. 11, pp. 1185-1186. <https://doi.org/10.1038/ni.3856>, <https://doi.org/10.1038/ni.3856>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Final publication: *Nature Immunology* 18, 1185–1186 (2017) doi:10.1038/ni.3856 Published online 18 October 2017

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Tfr cells trump autoimmune antibody responses to limit sedition

Michelle A. Linterman¹ & Kai-Michael Toellner²

1. Lymphocyte Signaling and Development, Babraham Institute, Cambridge, UK

2. Institute for Immunology and Immunotherapy, University of Birmingham Medical School, Birmingham, UK.

Correspondence to Michelle Linterman: michelle.linterman@babraham.ac.uk

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 infection¹. 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 specificity³.

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 differentiation⁴⁻⁶. 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 differentiation². 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 group⁸. IL-2 suppresses T_{FH} cell development by inducing STAT5 phosphorylation, a mechanism that is dependent on Blimp-1 expression². Blimp-1 limits the size of the T_{FR} cell population in a cell-intrinsic way⁴, 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} cell³.

Intriguingly, influenza infection yields IL-2 concentrations sufficient to inhibit T_{FR}, but not T_{FH}, cell differentiation³. 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 conditions⁹. 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} cells¹². Ballesteros-Tato and colleagues³ 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 production³.

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 neglect¹. 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.

References

1. Zhang, Y., Garcia-Ibanez, L. & Toellner, K.M. *Immunol. Rev.* **270**, 8–19 (2016). doi: 10.1111/imr.12396.
2. Vinuesa, C.G., Linterman, M.A., Yu, D. & MacLennan, IC. *Annu. Rev Immunol.* **34**, 335–368 (2016). doi: 10.1146/annurev-immunol-041015-055605.
3. Botta, D. *et al. Nat. Immunol.* **18**, XXX–XXX (2017).
4. Linterman, M.A. *et al. Nat. Med.* **17**, 975–982 (2011). doi: 10.1038/nm.2425.
5. Chung, Y. *et al. Nat. Med.* **17**, 983–988 (2011). doi: 10.1038/nm.2426
6. Wollenberg, I. *et al. J. Immunol.* **187**, 4553–4560 (2011). doi: 10.4049/jimmunol.1101328.

7. Wing, J.B. *et al. Proc. Natl. Acad. Sci. USA* **114**, E6400-E6409 (2017). doi: 10.1073/pnas.1705551114.
8. Ritvo, P.G. *et al. Sci. Immunol.* (8 September 2017) **2**(15). pii: eaan0368.
9. Pierson, W. *et al. Nat. Immunol.* **14**, 959–965 (2013). doi: 10.1038/ni.2649.
10. Koch, M.A. *et al. Nat. Immunol.* **10**, 595–602 (2009). doi: 10.1038/ni.1731.
11. Huehn, J. *et al. J. Exp. Med.* **199**, 303–313 (2004).
12. Wu, H. *et al. Eur. J. Immunol.* **46**, 1152–1161 (2016). doi: 10.1002/eji.201546094.