

INSIGHTS

A new chapter in the CD8 T reg story

Harvey Cantor^{1,2} and Hye-Jung Kim^{1,2}

CD8⁺ T reg cells play an important role in the maintenance of self-tolerance and can inhibit the development of autoimmune disease. In this issue of JEM, Mishra et al. (<https://doi.org/10.1084/jem.20200030>) reveal that TGF- β signaling and an Eomes-dependent genetic program contribute to CD8 T reg cell differentiation and function.

The central task of the immune system is destruction of invading pathogens while sparing host tissues. Regulatory T (T reg) cells that belong to both major T cell subsets—CD4 and CD8—play essential but distinct protective roles by dampening potential autoimmune reactions against self tissues and maintaining immunological homeostasis. Although the division of the CD4 T cell subset into separate effector and regulatory lineages is well established, separation of the CD8 T cell subset into effector and regulatory arms is the subject of more recent and ongoing research. Experimental definition of the genetic and molecular elements of CD8 T reg cell differentiation and immunological function represents a major goal of contemporary immunology.

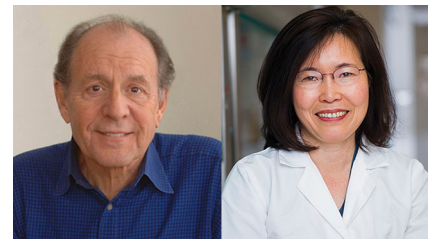
In this issue, Mishra et al. (2020) report that TGF- β signaling and Eomes-dependent genetic programming are essential to the development and maintenance of CD8 T reg cells. Mice deficient in both the TGF- β receptor 2 (*Tgfb β 2*) and the Eomes transcription factor (*Tgfb β 2*^{-/-}*Eomes*^{-/-}) develop a severe autoimmune phenotype characterized by spontaneous germinal center (GC) formation, increased numbers of T follicular helper cells (T_{FH} cells) and GC B cells, and autoantibody production. Although CD4⁺ T follicular regulatory cells (T_{FR} cells) can regulate the GC response, the autoimmune phenotype of *Tgfb β 2*^{-/-}*Eomes*^{-/-} mice does not reflect defective T_{FR} function. Instead, the core pathology of this disorder is a dramatic reduction in the numbers and function

of CD8 T reg cells, as judged by tracking of T cells that express the CD44, CD122, and Ly49 surface marker triad as well as the Helios transcription factor (TF; Kim et al., 2015; Kim et al., 2011; Saligrama et al., 2019). These findings are consistent with earlier observations that defective CD8 T reg cell function results in a lupus-like disorder characterized by uncontrolled T_{FH} expansion and autoantibody production (Kim et al., 2010).

Identity and location

Maintenance of the CD8 T reg cell specialized phenotype along with the ability to localize near or within the GC are essential prerequisites for efficient control of the GC response. However, the genetic basis for these properties of CD8 T reg cells has been uncertain. Mishra et al. (2020) show that deletion of *Tgfb β 2* in T cells (*Tgfb β 2*^{f/d}*Lck-cre*) results in failed expression of the Helios TF, which has been implicated in their regulatory identity and survival (Kim et al., 2015).

When is the TGF- β signal required for CD8 T reg cell differentiation? Mishra et al. (2020) have examined the effects of TGF- β signaling on CD8 T reg cell differentiation after deletion of *Tgfb β 2* expression in peripheral T cells. Previous studies of the effects of TGF- β signaling on thymic differentiation using *Tgfb β 2*^{f/d}CD4-Cre mice revealed a sharp reduction of CD44⁺CD122⁺Ly49⁺ CD8 single-positive thymocytes and evidence that the TGF- β signaling pathway may



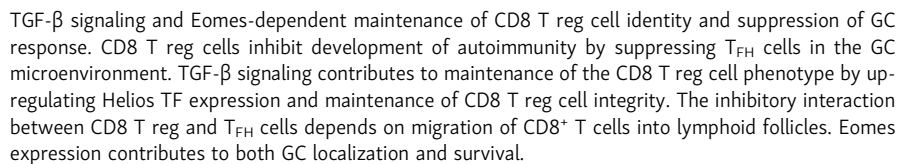
Insights from Harvey Cantor and Hye-Jung Kim.

regulate early stages of CD8 T reg cell selection and differentiation (McCarron and Marie, 2014). Possibly, TGF- β -dependent up-regulation of Helios during early maturation of CD8 T reg cells avoids deletion of these autoreactive cells in the thymus (Nakagawa et al., 2018). Mishra et al. (2020) also note that deficient TGF- β signaling impairs Helios expression by CD8 T reg cells but not CD4⁺ FoxP3⁺ T reg cells (T_{FR}), suggesting that distinct lineage-specific inducing signals may control Helios expression in the two regulatory cell types. Separate genetic programming of the two T reg cell subsets is consistent with the distinct and complementary roles they play in maintaining self-tolerance and regulating autoantibody responses. Analysis of bone marrow chimeras harboring selective deletions of Helios in either CD4 or CD8 T reg cells has pointed to a nonredundant and perhaps synergistic role of CD4 and CD8 T reg cells in restraining the development of dysregulated GC responses and autoimmune disease (Kim et al., 2015).

¹Department of Immunology, Harvard Medical School, Boston, MA; ²Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Boston, MA.

Harvey Cantor: Harvey_Cantor@dfci.harvard.edu.

© 2020 Cantor and Kim. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).



2 of 3

- Leavenworth, J.W., et al. 2013. *J. Clin. Invest.* <https://doi.org/10.1172/JCI66938>
- Liu, Z., et al. 2015. *Nature*. <https://doi.org/10.1038/nature16169>
- Mayer, C.T., et al. 2020. *Proc. Natl. Acad. Sci. USA*. <https://doi.org/10.1073/pnas.2015372117>
- McCarron, M.J., and J.C. Marie. 2014. *J. Clin. Invest.* <https://doi.org/10.1172/JCI76179>
- Miller, C.H., et al. 2020. *Nat. Immunol.* <https://doi.org/10.1038/s41590-020-0653-1>
- Mishra, S., et al. 2020. *J. Exp. Med.* <https://doi.org/10.1084/jem.20200030>
- Nakagawa, H., et al. 2018. *Adv. Immunol.* <https://doi.org/10.1016/bs.ai.2018.09.001>
- Saligrama, N., et al. 2019. *Nature*. <https://doi.org/10.1038/s41586-019-1467-x>
- Tarbell, K.V., et al. 2004. *J. Exp. Med.* <https://doi.org/10.1084/jem.20040180>