

Controlling Tolerance and Protective Immunity from the Outside In

Hilde Cheroutre, Daniel Mucida, Yunji Park, Ildelfonso Vicente-Suarez and Femke van Wijk
(The La Jolla Institute for Allergy and Immunology, La Jolla, CA)

The intestinal mucosa forms the largest body surface exposed to exogenous antigens, both innocuous and pathogenic antigens. Consistent with chronic antigen exposure, the gut mucosa also lodges a large collection of activated lymphocytes that under physiological conditions remain in an immune quiescent state. This so-called “gut physiological inflammation” is controlled by distinct regulatory mechanisms, including different types of regulatory DCs and T cells. An important molecule in this context is TGF- β , abundantly produced in the gut and crucial for both systemic and mucosal immune-regulation. Among multiple roles, TGF- β has the capacity to block Th1 and Th2 differentiation and to convert naïve CD4 cells into Foxp3-expressing induced Treg cells. Paradoxically, TGF- β also displays pro-inflammatory roles and in the presence of pro-inflammatory cytokines such as IL-6, IL-21, IL-1 β and TNF, TGF- β promotes the conversion of naïve T cells into effector Th17 cells¹⁻³. This contrasting deviation puts TGF- β as a principal controller of immune responses and underscores a central role of this cytokine in orchestrating the pro- and anti-inflammatory nature of adaptive immunity. Nowhere else is a critical regulation of this balance between productive and suppressive immunity, of more significance that at the mucosal surface of the gut where efficient immune protection against pathogens has to coincide with maintenance of the mucosal barrier integrity and self-tolerance as well as tolerance towards the vast load of harmless non-self antigens derived from food and beneficial commensal bacteria. We recently identified a metabolite of the nutrient vitamin A, retinoic acid (RA), as a key regulator of TGF- β -dependent differentiation, capable of inhibiting the IL-6-driven induction of pro-inflammatory Th17 cells⁴ and on the other hand we and others also found that RA greatly promotes the peripheral differentiation of anti-inflammatory Foxp3⁺ induced Tregs^{4,5}. This RA-induced regulatory mechanism allows for environmental factors to control endogenous immune responses from the outside in. RA-induced immune tolerance however, is not irreversible and in the presence of innate danger signals RA effects on T cells condense but synergize with innate responses in DCs to promote and enhance protective immunity.

References

1. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. *Immunity*. 2006 Feb;24(2):179-89.
2. Transforming growth factor-beta induces development of the T(H)17 lineage. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR, Weaver CT. *Nature*. 2006 May 11;441(7090):231-4.
3. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK. *Nature*. 2006 May 11;441(7090):235-8.
4. **Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, Cheroutre H. *Science*. 2007 Jul 13;317(5835):256-60.**
5. **From the diet to the nucleus: Vitamin A and TGF-beta join efforts at the mucosal interface of the intestine. Mucida D, Park Y, Cheroutre H. *Semin Immunol*. 2009 Feb;21(1):14-21. Epub 2008 Sep 21.**