[Cell Adhesion & Migration 1:3, 142-144; July/August/September 2007]; ©2007 Landes Bioscience

Commentary & View

TGFβ and Retinoic Acid Intersect in Immune-Regulation

Daniel Mucida

Hilde Cheroutre*

La Jolla Institute for Allergy and Immunology; La Jolla, California USA

*Correspondence to: Hilde Cheroutre; La Jolla Institute for Allergy and Immunology; 9420 Athena Circle; La Jolla, California 92037 USA; Email: hilde@liai.org

Original manuscript submitted: 08/16/07
Manuscript accepted: 09/20/07

Previously published online as a *Cell Adhesion & Migration* E-publication: http://www.landesbioscience.com/journals/celladhesion/article/5062

KEY WORDS

TGFβ, retinoic acid, Foxp3, TH17, IL-6, mucosal immune regulation, oral tolerance, transcription factors

ABSTRACT

Transforming growth factor (TGFβ) prevents T_H1 and T_H2 differentiation and converts naïve CD4 cells into Foxp3-expressing T regulatory (Treg) cell.[1,2] In sharp contrast, in the presence of pro-inflammatory cytokines, including IL-6, TGFβ not only inhibits Foxp3 expression but also promotes the differentiation of pro-inflammatory IL17-producing CD4 effector T (T_H17) cells.[3-5]

This reciprocal TGFβ-dependent differentiation imposes a critical dilemma between pro- and anti-inflammatory immunity and suggests that a sensitive regulatory mechanism must exist to control TGFβ-driven T_H17 effector and Treg differentiation. A vitamin A metabolite, retinoic acid (RA), was recently identified as a key modulator of TGFβ-driven-immune deviation capable of suppressing T_H17 differentiation while promoting Foxp3$^+$Treg generation.[6-10]

RA and TGFβ are both abundantly produced in the gut and TGFβ is crucial for both systemic and mucosal immune-regulation.[11,12] Although the so-called thymus-derived naturally occurring Treg cells (nTreg) are important for the control of a variety of auto-immune processes, it has been shown using monoclonal TCR transgenic mice devoid of nTreg that peripheral neoconverted Foxp3$^+$ Treg cells are efficient and sufficient for oral tolerance induction.[2] Furthermore, Mucida et al. also showed that blocking of TGFβ during feeding of the antigen (OVA) inhibited both; the establishment of oral tolerance and the peripheral conversion of OVA-induced Treg cells.[2] The abundant production of TGFβ and RA in the mucosa and the ability of RA to promote TGFβ-dependent Treg differentiation may thus be directly related to the increased frequency of Foxp3-expressing Treg cells in the lamina propria in normal mice.[6-10,13]

TGFβ and RA each are known to play significant roles in a variety of developmental processes, including the differentiation of lymphocyte lineages. Whereas TGFβ mediates the direct inhibition of T_H1 and T_H2 cytokine polarization concomitant with the generation of Tregs.[14] RA, in contrast, is a potent stimulator of T_H2 differentiation but a profound inhibitor of IFNγ synthesis.[15] In addition to their separate actions, the functions of TGFβ and RA are also known to merge in a variety of biological processes, including embryogenesis, organ development and carcinogenesis.[16] For example, TG-interacting factor (TGIF) is a transcriptional repressor common to the TGFβ and retinoic acid signaling pathways.[17] Moreover, mice with deficiency in the enzyme required for RA production, retinaldehyde dehydrogenase-2 (Raldh2), die before birth with several developmental defects and reduced TGFβ1.[18-20] On the other hand, RA can also inhibit TGFβ mediated effects, such as lung fibrosis.[21]

The finding that RA plays a central role in directing the immunological function of TGFβ expands the consequences of their interrelationship to the adaptive immune system.[6-10,13,22] Recent evidence shows that the signaling through RA-receptors may play an important role in the control of inflammation in the gut.[6-10,13] Exogenous RA was shown to inhibit induction of T_H17 cells in vivo using an infection model whereas injection of RAR antagonists resulted in decrease of Foxp3$^+$Treg cells in the lamina propria.[6] Iwata and co-workers have previously shown that RA production by mucosal DCs is crucial for the homing of T cells to the intestinal lamina propria,[23] and Mora et al. extended this finding to B cells migration to the gut and IgA class switching.[24] Whether the production of RA by mucosal DCs is crucial for the development of oral tolerance and for the conversion of naïve T cells into Foxp3$^+$Treg in the gut, as well as for the mucosal in situ control of T_H17 cells, is not yet known.

Our study and those of others show that RA signaling through RAR receptors in the T cell blocks the inhibitory effects of inflammatory cytokines, such as IL-6, on the TGFβ mediated Foxp3 induction. Similarly to the RA and TGFβ pathways interaction, several studies have shown that RA may synergize or antagonize with IL-6 signaling or production.[21,24] Moreover, RA has been shown to improve clinical symptoms and reduce the levels of inflammatory cytokines, including IL-6, TNFα and IFNγ in a model of arthritis,[25] an autoimmune disease shown to correlate with increased production of IL-17.[26] Finally, it was shown that RA directly inhibits retinoic acid orphan receptor γ T (RORγt) that is involved in T_H17 differentiation and which requires IL-6 for its expression.[27] It is not known, however, whether RA antagonistic effects on IL-6 signaling extend to the recently described IL-21 pathway of T_H17 differentiation.[28-30]

Transcription factors STAT5 and STAT3 have been shown to be important for the transcription of Foxp3 and IL-17 respectively.[22,27,31] The enhanced expression of Foxp3 in the presence of RA suggests a potential relationship between STAT5 and RARs in a similar fashion as the cooperation between STAT3 and RORγt. It is therefore perhaps not a coincidence that RORγt shows strong homology with the RARs and also appears to function in the context of transcriptional activators and repressors.[32] STAT5 and RARs have also been shown to physically interact in vivo to promote RAR-mediated transcription.[33] In addition, it was shown that the STAT5 consensus binding site overlaps with a RAR-response element which leads to promoting coordinated transcription activity rather than competition for the same site.[33] The cooperation between STAT5 and RARs resulted in STAT5-enhanced responsiveness of the RARs to RA induced transcription of target genes.[33] It was further demonstrated that RAR and STAT5 can bind the same repressor of transcription, SMRT, which can be released by RA.[34] RA mediated effects may thus reflect the intense communication between the STAT and RAR families of transcription factors, which has not been explored for the differentiation of T lymphocytes. It is also possible that RA might synergize with Smads that act downstream of TGFβ receptor signaling, and/or with the transcription factor Runx3, which is involved in the induction of CD103 expression and which physically interacts with Smads to cooperate in TGFβ mediated signaling.[35]

The immune regulatory mechanism we have delineated has particular relevance for the mucosal immune system. The intestinal mucosa forms the largest surface that is exposed to microbes, innocuous and pathogenic, and diet proteins; and also houses the largest proportion of lymphocytes that in physiological conditions have an immune quiescent state.[36] Therefore, an improper balance between inflammatory and suppressive immunity can jeopardize mucosal homeostasis. The abundant production of RA by the intestinal epithelium and dendritic cells, and the dominance of RA over IL-6 in balancing the effects of TGFβ, may account for the predominance of $Foxp3^+$ T cells in the intestine, allowing tolerance to prevail in the face of the extensive microbial load.

References

1. Wahl SM, Wen J, Moutsopoulos N. TGF-beta: A mobile purveyor of immune privilege. Immunol Rev 2006; 213:213-27.
2. Mucida D, Kutchukhidze N, Erazo A, Russo M, Lafaille JJ, Curotto de Lafaille MA. Oral tolerance in the absence of naturally occurring Tregs. J Clin Invest 2005; 115:1923-33.
3. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR, Weaver CT. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature 2006; 441:231-4.
4. Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity 2006; 24:179-89.
5. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006; 441:235-8.
6. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, Cheroutre H. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science 2007; 317:256-60.
7. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, Hall J, Sun CM, Belkaid Y, Powrie F. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. J Exp Med 2007; 204:1757-64.
8. Benson MJ, Pino-Lagos K, Rosemblatt M, Noelle RJ. All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. J Exp Med 2007; 204:1765-74.
9. Sun CM, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR, Belkaid Y. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. J Exp Med 2007; 204:1775-85.
10. Kang SG, Lim HW, Andrisani OM, Broxmeyer HE, Kim CH. Vitamin A metabolites induce gut-homing FoxP3+ regulatory T cells. J Immunol 2007; 179:3724-33.
11. Monteleone G, Pallone F, MacDonald TT. Smad7 in TGF-beta-mediated negative regulation of gut inflammation. Trends Immunol 2004; 25:513-7.
12. Shull MM, Ormsby I, Kier AB, Pawlowski S, Diebold RJ, Yin M, Allen R, Sidman C, Proetzel G, Calvin D, et al. Targeted disruption of the mouse transforming growth factor-beta 1 gene results in multifocal inflammatory disease. Nature 1992; 359:693-9.
13. Schambach F, Schupp M, Lazar MA, Reiner SL. Activation of retinoic acid receptor-alpha favours regulatory T cell induction at the expense of IL-17-secreting T helper cell differentiation. Eur J Immunol 2007; 37:2396-9.
14. Li MO, Wan YY, Sanjabi S, Robertson AK, Flavell RA. Transforming growth factor-beta regulation of immune responses. Annu Rev Immunol 2006; 24:99-146.
15. Cantorna MT, Nashold FE, Hayes CE. In vitamin A deficiency multiple mechanisms establish a regulatory T helper cell imbalance with excess Th1 and insufficient Th2 function. J Immunol 1994; 152:1515-22.
16. Roberts AB, Sporn MB. Mechanistic interrelationships between two superfamilies: The steroid/retinoid receptors and transforming growth factor-beta. Cancer Surv 1992; 14:205-20.
17. Bartholin L, Powers SE, Melhuish TA, Lasse S, Weinstein M, Wotton D. TGIF inhibits retinoid signaling. Mol Cell Biol 2006; 26:990-1001.
18. Vermot J, Gallego Llamas J, Fraulob V, Niederreither K, Chambon P, Dolle P. Retinoic acid controls the bilateral symmetry of somite formation in the mouse embryo. Science 2005; 308:563-6.
19. Niederreither K, Subbarayan V, Dolle P, Chambon P. Embryonic retinoic acid synthesis is essential for early mouse post-implantation development. Nat Genet 1999; 21:444-8.
20. Bohnsack BL, Lai L, Dolle P, Hirschi KK. Signaling hierarchy downstream of retinoic acid that independently regulates vascular remodeling and endothelial cell proliferation. Genes Dev 2004; 18:1345-58.
21. Tabata C, Kubo H, Tabata R, Wada M, Sakuma K, Ichikawa M, Fujita S, Mio T, Mishima M. All-trans retinoic acid modulates radiation-induced proliferation of lung fibroblasts via IL-6/IL-6R system. Am J Physiol Lung Cell Mol Physiol 2006; 290:L597-606.
22. Yang XO, Panopoulos AD, Nurieva R, Chang SH, Wang D, Watowich SS, Dong C. STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. J Biol Chem 2007; 282:9358-63.
23. Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. Retinoic acid imprints gut-homing specificity on T cells. Immunity 2004; 21:527-38.
24. Mora JR, Iwata M, Eksteen B, Song SY, Junt T, Senman B, Otipoby KL, Yokota A, Takeuchi H, Ricciardi-Castagnoli P, Rajewsky K, Adams DH, von Andrian UH. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science 2006; 314:1157-60.
25. Nozaki Y, Yamagata T, Sugiyama M, Ikoma S, Kinoshita K, Funauchi M. Anti-inflammatory effect of all-trans-retinoic acid in inflammatory arthritis. Clin Immunol 2006; 119:272-9.
26. Hirota K, Hashimoto M, Yoshitomi H, Tanaka S, Nomura T, Yamaguchi T, Iwakura Y, Sakaguchi N, Sakaguchi S. T cell self-reactivity forms a cytokine milieu for spontaneous development of IL-17+ Th cells that cause autoimmune arthritis. J Exp Med 2007; 204:41-7.
27. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17(+) T helper cells. Cell 2006; 126:1121-33.

28. Korn T, Bettelli E, Gao W, Awasthi A, Jager A, Strom TB, Oukka M, Kuchroo VK. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature 2007; 448:484-7.
29. Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, Schluns K, Tian Q, Watowich SS, Jetten AM, Dong C. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature 2007; 448:480-3.
30. Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T, Levy DE, Leonard WJ, Littman DR. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat Immunol 2007; 8:967-74.
31. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, Blank RB, Meylan F, Siegel R, Hennighausen L, Shevach EM, O'Shea JJ. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity 2007; 26:371-81.
32. Winoto A, Littman DR. Nuclear hormone receptors in T lymphocytes. Cell 2002; 109:57-66.
33. Si J, Collins SJ. IL-3-induced enhancement of retinoic acid receptor activity is mediated through Stat5, which physically associates with retinoic acid receptors in an IL-3-dependent manner. Blood 2002; 100:4401-9.
34. Nakajima H, Brindle PK, Handa M, Ihle JN. Functional interaction of STAT5 and nuclear receptor co-repressor SMRT: Implications in negative regulation of STAT5-dependent transcription. Embo J 2001; 20:6836-44.
35. Woolf E, Brenner O, Goldenberg D, Levanon D, Groner Y. Runx3 regulates dendritic epidermal T cell development. Dev Biol 2006; 303:703-14.
36. Cheroutre H. Starting at the beginning: New perspectives on the biology of mucosal T cells. Annu Rev Immunol 2004; 22:217-46.