Published in final edited form as:

Semin Nephrol. 2012 May ; 32(3): 287–294. doi:10.1016/j.semnephrol.2012.04.008.

Retinoid and TGF- β families: Crosstalk in development, neoplasia, immunity and tissue repair

Qihe Xu¹ and Jeffrey Kopp²

¹Department of Renal Medicine, King's College London, London UK

²Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, MD, USA

Abstract

TGF- β isoforms are pro-fibrotic cytokines, par excellence, and have complex, multifunctional effects on many systems, depending on the biologic setting. Retinoids are vitamin A derivatives that also have diverse effects in development, physiology, and disease. The interactions between these classes of molecules are, not surprisingly, highly complex and are dependent upon the tissue, cellular, and molecular settings.

Introduction

TGF- β isoforms and retinoids regulate many biologic processes, and the interactions between these molecules have been studied for many years. Two decades ago, Roberts and Sporn reviewed interactions between these two superfamilies¹. This review will provide an update on particular aspects of the molecular crosstalk and their relevance in development, neoplasia, the immune system, tissue repair and the kidney. Our belief is that insights into interactive pathways in other settings may be worth exploring in nephrology research.

Retinoids are a family of vitamin A metabolites or analogs, including (i) natural provitamin A, vitamin A, and other retinoic acid precursors, which cannot bind retinoid nuclear receptors, but are characterized by their potential to be converted into retinoic acids; (ii) natural retinoic acids, including all-*trans*-retinoic acid (ATRA) and 13-*cis*-retinoic acid, which bind and activate retinoic acid receptors (RARs α , β and γ), and 9-*cis*-retinoic acid, which binds and activates both RARs and retinoid X receptors (RXRs α , β and γ); and (iii) synthetic retinoids, which bind one or more RAR or/and RXR isotypes and exert agonistic or antagonistic actions².

As the major functions of retinoids are RXR/RAR-dependent, conversion of vitamin A into retinoic acids is largely a process of vitamin A activation. This involves two oxidation steps, catalyzed by alcohol dehydrogenases (ADHs 1–4) and retinaldehyde dehydrogenases (RALDHs 1–3), respectively. While the first step is reversible, the RALDH-driven second step is not. Eventually, following catalysis by cytochrome P450 enzymes Cyp26A, B and C,

© 2012 Elsevier Inc. All rights reserved.

Corresponding author, Jeffrey Kopp, MD, 10 Center Drive, NIH, Bethesda, MD 20892, 301.594.403 jbkopp@nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

retinoic acids can be converted into metabolites with reduced capacity to activate the canonical RXR/RAR pathway².

It has been said that TGF- β is like a switch that turns some systems on and other systems off and sometimes turns the same switch on or off, depending on the context (Michael Sporn, personal communication). Thus TGF- β can have opposite effects depending on the physiologic (developmental state, age, organ system, cell type, species) or pathologic setting. With this in mind, it is perhaps not surprising that retinoid/TGF- β interactions are also complex.

Molecular basis of retinoid/TGF β crosstalk

TGF- β signaling via SMADs and other pathways and retinoid signaling via nuclear receptors intersect in complex ways that are frequently cell and context-dependent. First, there is *shared repression*. TGIF (TG-interacting factor) is a transcriptional corepressor of SMAD signaling, that inhibits access of co-activators to phosphorylated SMADs (pSMADs). TGIF is also a co-repressor for RXR- α , in part by recruiting the general co-repressor C-terminal binding protein (CtBP) and suppressing RXR- α mediated transcription (Bartholin, 2006). Thus, TGIF inhibits both TGF- β - and retinoid-driven gene transcription.

Second, retinoids may *suppress* TGF- β signaling. It was reported that ATRA suppresses the TGF- β superfamily member BMP4 by enhancing ubiquitin-mediated degradation of pSMAD1; future studies might address whether similar mechanisms are operative in TGF- β signaling³. With similar action but via a secreted mediator, 9-cis-retinoic acid suppresses TGF- β -mediated induction of several pro-fibrotic molecules, e.g., fibronectin and plasminogen activator inhibitor-1 (PAI-1), in cultured human mesangial cells and this effect is mediated by the stimulation of hepatocyte growth factor⁴. In isolated heart tissue and in cultured NIH-3T3 fibroblasts, ATRA increases TGF- β stimulated pSMAD2 and pSMAD3, but decreases nuclear accumulation of these transcription factors and decreases pSMAD-mediated transcriptional activity⁵.

Third, retinoids may *amplify* TGF- β signaling, via transcriptional and post-translational mechanisms. ATRA increases TGF- β transcript levels and TGF- β 1 protein production by PC12 cells, acting on the TGF- β 1 promoter⁶. In mesenchymal stem cells, ATRA induces SMAD RNA expression and protein nuclear localization⁷. In retinal pigment epithelial cells, ATRA increases expression of thrombospondin-1 and this in turn converts TGF- β 1 to its active form⁸. ATRA induces production of TGF- β 2 by pancreatic cancer cells in vitro, as discussed further below⁹.

Fourth, TGF- β may affect tissue levels of retinoid ligands and expression of nuclear receptors. For example, Alb/TGF- β 1 transgenic mice have reduced tissue levels of retinoids¹⁰; TGF- β 1 induces expression of RARs and RXRs in osteoblasts¹¹ and inhibits Cyp26b1, a metabolizing enzyme of ATRA, in T cells¹².

Embryonic and fetal development

Retinoids/RAR and TGF- β are involved in embryogenesis and organ development, with significant crosstalk between the two pathways^{13–17}. Retinoids and TGF- β also have crosstalk in embryonic stem cells. In embryonic stem cells, ATRA induces the expression of Foxa1, which acts as a pioneer transcription factor, binding and poising chromatin for intersection with the TGF- β -induced SMAD signaling, and cooperates with the latter in *de novo* activation of α -fetoprotein gene expression¹⁷. In C2C12 mouse myoblasts, both ATRA and 9 *cis*-retinoic acid are potent inhibitors of the anti-myogenic effect of TGF- β 1, likely through a SMAD-independent mechanism¹⁸.

Vitamin A is required for normal organogenesis, including the heart and other tissues. Vitamin A-deficient (VAD) quail embryos lack retinoic acids and are characterized by a grossly abnormal cardiovascular system that can be rescued by ATRA. In VAD embryos TGF- β 2 mRNA and protein expression, as well as TGF- β receptor II are greatly elevated. Administration of TGF- β 2-specific antisense oligonucleotides or an antibody specific for TGF- β 2 to VAD embryos normalizes posterior heart development and vascularization, while the administration of exogenous active TGF- β 2 protein to normal quail embryos mimics the excessive TGF- β 2 status of VAD embryos and induces a VAD cardiovascular phenotype. In VAD embryos pSMAD2/3 and pErk1 are not activated, while pErk2 and pCraf are elevated and pSMAD 1/5/8 are diminished. Thus, in the early avian embryo TGF- β 2 has a major role in the retinoic acid-regulated posterior heart morphogenesis for which it does not use SMAD2/3 pathways, but may use other signaling pathways¹⁹. Retinoic acid/RXR-RAR regulation of TGF- β 2 in developing heart is evolutionarily conserved as RAR α 1/RAR β -/-, RAR α 1/RXR α -/- and RXR α -/- mice also show increased TGF- β 2 expression and defects in the differentiation of the second heart field and heart outflow tract septation defects^{20,21}.

In the developing lung, it appears that endogenous ATRA acts as a major regulatory signal integrating Wnt and TGF- β pathways in the control of Fgf10 expression during induction of the mouse primordial lung, inhibiting TGF- β signaling²², while activating Wnt signaling through local repression of its antagonist, Dickkopf homolog 1 (Dkk1)²³. In addition, TGF- β 2 is required for the development of pancreatic and cerebral cortex; administration of excess ATRA before neurulation inhibits TGF- β 2 expression in pancreas and brain and disrupts morphogenesis of pancreas and cerebral cortex^{24,25}. TGF- β 3 is required for chondrocyte differentiation, which is suppressed by ATRA. It is now known that ATRA/RAR suppresses chondrogenesis through suppressing SMAD2 and SMAD3 phosphorylation, increasing Smad7 expression and TGIF^{26,27}.

Either excess or deficiency of retinoic acid during a critical stage of inner ear development can produce teratogenic effects. *In utero* exposure of the developing mouse inner ear to a high dose of ATRA results in severe malformations of the inner ear that are associated with diminished levels of endogenous TGF- β 1, TGF- β type II receptor and Smad2 in the inner ear, while suppression of RAR α expression by an antisense oligonucleotide leads to a reduction in endogenous TGF- β 1 and a marked suppression of chondrogenesis, which can be partially rescued by exogenous TGF- β 1. Thus, TGF- β 1 may play important roles in the physiologic and pathologic effects of RA on inner ear development²⁸.

Retinoid/TGF- β crosstalk may contribute to kidney development but a definitive role remains to be established. In the induction of avian pronephros (the first kidney to arise in development), the neural tube releases TGF- β family member activin, and competence of the intermediate mesoderm cells to respond and differentiate appears to be driven by retinoic acid-dependent expression of Hoxb4, a critical transcription factor²⁹. RXR/RAR-mediated canonical transcriptional activity is predominantly located in the ureteric bud lineage of the pre- and post-natal kidneys³⁰ and mice with specific deletion of TGF- β type II receptor from the ureteric bud lineage develop grossly normal kidneys do not support indispensable crosstalk between the two pathways in the ureteric bud³¹.

Neoplasia

Retinoids are approved for promyelocytic leukemia; acting as a differentiating agent, it has substantially improved patient outcomes. In HL-60 human promyelocytic leukemia cells, TGF- β 1 enhances ATRA-induced suppression of cell proliferation and inhibits ATRA-induced apoptosis³²; while ATRA directs differentiation to granulocytes in a RAR-

dependent manner, TGF- β SMAD2/3-dependently directs differentiation to monocytes; simultaneous treatment of these cells with TGF- β 1 and RA, which leads to almost equal numbers of granulocytes and monocytes, significantly reduced the level of phospho-Smad2/3 and its nuclear accumulation, compared with that in cells treated with TGF- β 1 alone³³. ATRA also reduces expression of microRNA-146A in an acute promyelocytic cell line; this microRNA targets SMAD4, and thus the effect is to increase TGF- β signaling³⁴. ATRA also promotes differentiation of Wilms tumor cells, normalizing the expression of multiple genes associated with the neoplastic phenotype³⁵.

Human concentrative nucleoside transporter-3 (hCNT3) is a sodium-coupled nucleoside transporter that exhibits high affinity and broad substrate selectivity, making it the most suitable candidate for mediating the uptake and cytotoxic action of most nucleoside-derived drugs. The drug of this class most commonly used in the treatment of chronic lymphocytic leukemia (CLL) is the pro-apoptotic nucleoside analog fludarabine (Flu), which enters CLL cells primarily through human equilibrative nucleoside transporters (hENTs). Although CLL cells lack hCNT3 activity, they do express this transporter protein, which is located mostly in the cytosol. Interestingly, RA increases hCNT3-related activity through a mechanism that involves trafficking of pre-existing hCNT3 proteins to the plasma membrane. This effect is mediated by the autocrine action of TGF- β 1, which is transcriptionally activated by ATRA in a p38-MAP kinase dependent manner³⁶.

ATRA suppresses the expression of TGF- β 1 and TGF- β -dependent growth of malignant pleural mesothelioma in a subcutaneous xenograft mouse model³⁷, while inducing active TGF- β 2 and suppressing Capan-2 and Hs766T human pancreatic cancer cells in a TGF- β -dependent manner⁹.

Immune system

The TGF- β family and the retinoid family molecules both function as immunomodulators^{38–41}. Although crosstalk between retinoids and TGF- β in immunity have long been suspected due to indirect evidence, such as their similar effects on cell growth and viral production, as well as RA induction of TGF- β and TGF- β receptor in HL-60 human promyelocytic leukemia cells¹, direct evidence on such interactions has not appeared until the recent years^{42,43}.

TGF- β is a master regulator of T cells and plays an indispensable role in immune tolerance³⁹. Thus autoimmune inflammation was triggered by T cell-specific over-expression of a dominant negative mutant of TGF- β type II receptor⁴⁴ and was observed in TGF- β 1 knockout mice^{45–47}. TGF- β 2 and TGF- β 3 knockout mice did not show such a phenotype^{48,49}, likely due to the predominant expression of TGF- β 1 in the T cell lineage. It is currently believed that TGF- β is required for the development of CD8⁺ T cells, natural regulatory T cell (nTreg), natural Th17 cells (nTh17) and natural killer T (NKT) cells from CD4⁺CD8⁺ immature T cells in the thymus^{39,50}. In the periphery, TGF- β is believed to suppress the functions of natural killer cells, CD8⁺ cytotoxic T lymphocytes, dendritic cells, macrophages and neutrophils⁵¹, while differently regulating inducible regulatory T cell (iTreg), Th1, Th2, and Th17 T helper cells, which are characterized by the expression of different transcription factors Foxp3, T-bet/STAT4, GATA3/STAT6 and ROR γ t/STAT3, respectively⁵². In brief, TGF- β is indispensable for the development of Foxp3⁺ iTreg cells⁵¹, suppresses Th1 development^{53,54} and indirectly promotes Th17 development^{53–55}. Although development of Th1 and Th2 cells are both suppressed by TGF- β *in vitro* and promoted by partial TGF- β signaling attenuation *in vivo*, Th1 development is exclusively promoted when TGF- β signaling elimination is more complete, such as in TGF- β type II receptor knockout mice³⁹. In TGF- β 1 and/or TGF- β 1 type II receptor knockout mice, due to loss of Treg cells,

polarization of the Th1/Th2 axis to Th1, un-checked autoimmunity and/or over-response to weak immunogens, serum IgM, IgG and IgE antibodies are increased, in contrast to a significant reduction in serum IgA^{56,57}. The latter is in keeping with the concept that TGF- β directly targets B cells to induce IgA production^{58,59}.

TGF- β regulation of iTreg, Th1 and Th17 development involve both Smad-dependent and -independent pathways. Although Smad2 and Smad3 were shown to play redundant roles in regulating iTreg and Th1 development⁶⁰, another study showed that selective deletion of Smad2 from the T lymphocyte lineage led to slightly increased nTreg numbers in thymus and other lymphoid tissues, impaired TGF- β conversion of naïve T cells into iTreg cells, reduced Th17 differentiation both *in vitro* and *in vivo* and, importantly, ameliorated a model of experimental autoimmune encephalomyelitis⁶¹. Based on the effects of chemical inhibition and/or gene deletion of MAP kinase isoforms, it appears that ERK (e.g., ERK1) mediates iTreg cell development, p38 mediates Th17 development and JNK (e.g., JNK2) modulates both iTreg and Th17 development⁶².

Animal and clinical studies of vitamin A deficiency (VAD) and vitamin A supplementation indicate that vitamin A is required to defend against various infections, because VAD compromises functions of antigen presenting cells (APCs) and neutrophils, reduces total T cell and NKT cell numbers, increases Th1 and Th17 cells, reduces Th2 and Treg cells, as well as diminishing antibody-mediated immunity^{41,63}. The thymus is known to express the synthetic enzymes and nuclear receptors necessary for a functional endogenous retinoid signaling, but the exact role for such an endogenous retinoid system in thymus remains poorly understood. Nevertheless, exogenous retinoids have been shown to act on thymocytes to suppress CD8⁺ development, enhance CD4⁺ development, increase total immature CD4⁺CD8⁺ cell number by preventing apoptosis, and increase egress of mature T cells from the thymus to augment total peripheral T cell numbers⁶³.

In peripheral tissues, ATRA plays an important role in sustaining the stability and functionality of nTregs in the presence of inflammatory cytokines such as IL-6⁶⁴ and is required for bone marrow cells to differentiate into dendritic cells, which continue to synthesize ATRA to maintain the acquired phenotype and functions, including releasing ATRA to direct the differentiation and control gut-homing of T and B cells in a paracrine fashion^{40,65}. It is not fully understood how ATRA synthesis is regulated in dendritic cells, but it appears that some pathogen-derived components, pro-inflammatory cytokines and Toll-like receptor (TLR) agonists up-regulate RALDH expression in dendritic cells⁴⁰. The constitutive expression of RALDH2 in dendritic cells is critically dependent on the constitutive activation of the Wnt- β -catenin signaling pathway⁶⁶ and pathogen infection can stimulate TLR2 on dendritic cells to promote RALDH2 expression and ATRA synthesis⁶⁷. ATRA can directly promote maturation and activation of B cells and also indirectly regulate B cells through modulating T cells, differentially regulating IgA, IgG1, IgG2a, IgG2b, IgG3 and IgM responses. Specifically, B1 cells represent a distinct subset of B cells that produce most of the natural serum IgM and much of the gut IgA and function as an important component of early immune responses to pathogens. The development of B1 cells is severely impaired in mice fed on a VAD diet and enhanced by exogenous ATRA treatment. Thus, the ATRA-dependent pathway is critical for regulating B1-mediated humoral responses⁶⁸. Importantly, ATRA regulates APCs and T cells in a cell type- and context-dependent manner⁶³. ATRA treatment of APCs from different origins might lead to release of cytokines that either favor Th1 or Th2 response⁶³. For example, although ATRA is known to directly target T cells, diverting TGF- β -induced Treg/Th17 balance toward Treg^{41,63}, in the presence of IL-15, ATRA induces dendritic cells to release pro-inflammatory cytokines IL-12 and IL-23, which together with ATRA, suppress Treg development and promote Th1 and Th17 conversion⁶⁹, indicating that ATRA regulation of

Th1, Th17 and Treg developments is condition-dependent⁴³. In addition, ATRA regulation of Th2 development is also condition-dependent, especially depending on the stage of T cell differentiation. Exposure of naïve T cells without initial activation to ATRA suppresses both Th1 and Th2 development, however, in naïve CD4 cells that have undergone initial activation *in vitro*, ATRA enhances Th2 development⁴³. Different retinoid nuclear receptors might play different roles in immunomodulation. Using selective retinoid agonists or antagonists, RXR- and RAR-, especially RAR α -, mediated mechanisms have been suggested in mediating ATRA regulation of the Th1/Th2 axis^{70–73}. RAR β and/or RAR α have been suggested to play an important role in expression of homing receptors in T cells⁷⁴. In contrast, data from RAR γ knockout mice indicate that RAR γ is required for CD8⁺ T cell response to *Listeria monocytogenes* infection and macrophage response to TLR stimulation, although it is dispensable for T and B lymphocyte development, humoral immune response and *in vitro* Th cell differentiation⁷⁵.

In 2007, Mucida D, et al, first identified ATRA as a key regulator of the TGF- β -dependent Treg/Th17 axis, inhibiting ROR γ t-dependent induction of Th17 cells and promoting Foxp3-dependent Treg differentiation⁷⁶. It has been shown that ATRA not only synergizes with TGF- β and IL-2 to induce Treg cells, but also make them more resistant to pro-inflammatory cytokines⁷⁷. ATRA and TGF- β cooperate to promote foxp3 expression, not only in naïve T cells⁷⁸, but also in differentiated CD4⁺ and CD8⁺ T cells^{79,80}, highlighting a role for retinoid-TGF- β crosstalk in regulating the plasticity of T cells. Interestingly, ATRA synergizes with peroxisome proliferator-activated receptor (PPAR) α and γ agonists to promote TGF- β conversion of human CD4⁺CD25[−] T cells into functional Treg cells⁸¹, suggesting that they might regulate Treg development via distinct mechanisms. In keeping with this observation, PPAR agonists promote Foxp3 expression by inhibiting DNA methyltransferases and thus inducing demethylation of the Foxp3 promoter⁸¹, while ATRA augmentation of TGF- β -induced Treg development involves the binding of RAR and RXR to a dominant site in the enhancer I of the Foxp3 gene and a subordinate site in the promoter⁸². The latter leads to increased histone acetylation in the region of the Smad3 binding site and increased binding of pSMAD3, which is in contrast to the action of IL-27, i.e., inhibition of Foxp3 expression through binding of pStat3 to a gene silencer in another conserved enhancer region (enhancer II) downstream from enhancer I, leading to loss of pSMAD3 binding to enhancer I. Thus, control of accessibility and binding of pSmad3 provides a common framework for positive and negative regulation of TGF- β -induced Foxp3 transcription⁸².

In T cells, besides the effects of ATRA on the actions of TGF- β , it appears that TGF- β also affects the ATRA pathway through inhibiting Cyp26b1, a metabolizing enzyme of ATRA, thus sustaining ATRA-dependent signaling¹². In follicular dendritic cells, where ATRA is abundant, however, ATRA activates RAR signaling and cooperates with TLRs to up-regulate secretion and activation of TGF- β ⁸³, which, together with ATRA, directly and synergistically targets B cells to induce IgA class switching in a Runx-dependent manner, although the detailed mechanism is still to be defined⁵⁹. ATRA and TGF- β 1 also have crosstalk upon regulating expression of gut-homing receptors on T cells, i.e., ATRA induces integrin α 4 β 7 and CCR9; TGF- β induces integrin α E β 7; the combination of TGF- β and ATRA results in further up-regulation of both integrins α 4 β 7 and α E β 7, but down-regulates the expression of CCR9⁴³.

Tissue repair: Cytoprotection and anti-fibrosis

Isotretinoin (13 cis-retinoic acid) is FDA-approved for nodular acne. Its favorable effects include reversing the pathogenic processes of follicular retention hyperkeratosis, sebaceous lipogenesis, inflammation, and bacterial colonization. It has been proposed that therapeutic

benefit depends upon the export of the nuclear factor FOXO1 from the nucleus, which leads to suppression of transcription of genes encoding the androgen receptor, proliferative factors, lipid biosynthesis, and inflammatory cytokines⁸⁴. This may serve as a paradigm for how retinoids may alter transcriptional networks in ways that alter cellular phenotype, restoring normal cellular function.

While model systems differ, the predominant theme is that retinoids suppress TGF- β production or signaling. Thus VAD is associated with increased TGF- β activity. VAD rat pups exhibit increased pulmonary alveolar basement membrane thickness by approximately two-fold, with increased fibrotic collagen; this was associated with increased production of TGF- β and reactive oxygen species⁸⁵. ATRA inhibits TGF- β stimulation of pro-fibrotic molecules in cultured mesangial cells, including fibronectin and PAI-1⁸⁶. Similarly, ATRA inhibits TGF- β -driven liver fibrosis in a rat common bile duct ligation model⁸⁷. TGF- β increases vascular endothelial growth factor (VEGF) production by cultured smooth muscle cells⁸⁸ and endometrial cells; in the latter cells, this effect requires ATRA, which initiates a process whereby VEGF mRNA transcripts are directed toward larger, poly-ribosomes that are more translationally active⁸⁹.

Under some circumstances, retinoids can enhance TGF- β activity. ATRA stimulates TGF- β production by neoplastic HL-60 cells (as noted above), stimulates TGF- β 2 in mouse keratinocytes *in vitro* and *in vivo*⁹⁰ and stimulates TGF- β production in cultured chondrocytes⁹¹ although it inhibits TGF- β production in cultured myocytes⁹¹.

In experimental kidney disease, ATRA has shown therapeutic effect in models with various degrees of inflammation and fibrosis, including Thy-1 rat glomerulonephritis (with down-regulation of TGF- β and TGF- β receptor II)⁹², the 5/6 nephrectomy rat model (with reduced TGF- β expression)⁹³ and the mouse unilateral ureteral ligation model⁹⁴. On the other hand, ATRA therapy ameliorates mouse MLR/lpr lupus model while increasing renal TGF- β expression and suppressing glomerular inflammation; the authors offered the interpretation that TGF- β was acting to suppress inflammation, although there was no demonstration that this was the critical pathway⁹⁵. However, while Alb/TGF- β 1 transgenic mice exhibit glomerulosclerosis and reduced renal tissue levels of ATRA, therapeutic administration of ATRA increased fibrosis and mortality, toxicity which may have been dose related¹⁰.

Conclusion

TGF- β and retinoid family members play major roles in development, neoplasia, immune response and immunologic disease, tissue repair, and fibrotic disease. As shown above, there is complex crosstalk between the TGF- β and retinoid signaling pathways. Various retinoids have been approved for therapeutic uses, including cancer and acne, with the common theme being promotion of cellular differentiation. Various retinoids with different affinities for particular RARs have been developed. As a class, retinoids hold considerable promise as therapeutic agents for human kidney disease, although no trials have been completed to date. There is compelling opportunity to harness retinoid activities, including interactions with TGF- β family members, to treat disease.

Acknowledgments

We thank Professor Randolph J. Noelle, King's College London, for his excellent comments on this manuscript. This work was supported in part by the NIDDK Intramural Research Program.

Grant Support: NIDDK Intramural Research Program and Kidney Research UK Innovation Grant

References

1. Roberts AB, Sporn MB. Mechanistic interrelationships between two superfamilies: the steroid/retinoid receptors and transforming growth factor-beta. *Cancer surveys*. 1992; 14:205–220. [PubMed: 1330304]
2. Xu Q, Lucio-Cazana J, Kitamura M, et al. Retinoids in nephrology: promises and pitfalls. *Kidney Int*. 2004; 66(6):2119–2131. [PubMed: 15569301]
3. Sheng N, Xie Z, Wang C, et al. Retinoic acid regulates bone morphogenic protein signal duration by promoting the degradation of phosphorylated Smad1. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107(44):18886–18891. [PubMed: 20956305]
4. Wen X, Li Y, Hu K, Dai C, Liu Y. Hepatocyte growth factor receptor signaling mediates the anti-fibrotic action of 9-cis-retinoic acid in glomerular mesangial cells. *Am J Pathol*. 2005; 167(4):947–957. [PubMed: 16192631]
5. Hoover LL, Burton EG, O'Neill ML, et al. Retinoids regulate TGFbeta signaling at the level of Smad2 phosphorylation and nuclear accumulation. *Biochimica et biophysica acta*. 2008; 1783(12):2279–2286. [PubMed: 18773928]
6. Cosgaya JM, Perona R, Aranda A. Retinoic acid induces secretion of transforming growth factors by PC12 pheochromocytoma cells. *Oncogene*. 1997; 14(5):579–587. [PubMed: 9053856]
7. Dingwall M, Marchildon F, Gunanayagam A, Louis CS, Wiper-Bergeron N. Retinoic acid-induced Smad3 expression is required for the induction of osteoblastogenesis of mesenchymal stem cells. *Differentiation; research in biological diversity*. 2011
8. Uchida H, Kuroki M, Shitama T, Hayashi H. Activation of TGF-beta1 through up-regulation of TSP-1 by retinoic acid in retinal pigment epithelial cells. *Curr Eye Res*. 2008; 33(2):199–203. [PubMed: 18293192]
9. Singh B, Murphy RF, Ding XZ, et al. On the role of transforming growth factor-beta in the growth inhibitory effects of retinoic acid in human pancreatic cancer cells. *Mol Cancer*. 2007; 6:82. [PubMed: 18157915]
10. Xu Q, Hendry BM, Maden M, et al. Kidneys of Alb/TGF-beta1 transgenic mice are deficient in retinoic acid and exogenous retinoic acid shows dose-dependent toxicity. *Nephron Exp Nephrol*. 2010; 114(4):e127–e132. [PubMed: 20110732]
11. Chen Y, Takeshita A, Ozaki K, Kitano S, Hanazawa S. Transcriptional regulation by transforming growth factor beta of the expression of retinoic acid and retinoid X receptor genes in osteoblastic cells is mediated through AP-1. *J Biol Chem*. 1996; 271(49):31602–31606. [PubMed: 8940178]
12. Takeuchi H, Yokota A, Ohoka Y, Iwata M. Cyp26b1 regulates retinoic acid-dependent signals in T cells and its expression is inhibited by transforming growth factor-beta. *PLoS One*. 2011; 6(1):e16089. [PubMed: 21249211]
13. Dolle P. Developmental expression of retinoic acid receptors (RARs). *Nucl Recept Signal*. 2009; 7:e006. [PubMed: 19471585]
14. Mark M, Ghyselinck NB, Chambon P. Function of retinoic acid receptors during embryonic development. *Nucl Recept Signal*. 2009; 7:e002. [PubMed: 19381305]
15. Moustakas A, Heldin CH. The regulation of TGFbeta signal transduction. *Development*. 2009; 136(22):3699–3714. [PubMed: 19855013]
16. Watabe T, Miyazono K. Roles of TGF-beta family signaling in stem cell renewal and differentiation. *Cell Res*. 2009; 19(1):103–115. [PubMed: 19114993]
17. Taube JH, Allton K, Duncan SA, Shen L, Barton MC. Foxa1 functions as a pioneer transcription factor at transposable elements to activate Afp during differentiation of embryonic stem cells. *J Biol Chem*. 2010; 285(21):16135–16144. [PubMed: 20348100]
18. Krueger C, Hoffmann FM. Identification of retinoic acid in a high content screen for agents that overcome the anti-myogenic effect of TGF-beta-1. *PLoS One*. 2010; 5(11):e15511. [PubMed: 21152098]
19. Ghatpande SK, Zhou HR, Cakstina I, et al. Transforming growth factor beta2 is negatively regulated by endogenous retinoic acid during early heart morphogenesis. *Dev Growth Differ*. 2010; 52(5):433–455. [PubMed: 20507358]

20. Kubalak SW, Hutson DR, Scott KK, Shannon RA. Elevated transforming growth factor beta2 enhances apoptosis and contributes to abnormal outflow tract and aortic sac development in retinoic X receptor alpha knockout embryos. *Development*. 2002; 129(3):733–746. [PubMed: 11830573]
21. Li P, Pashmforoush M, Sucov HM. Retinoic acid regulates differentiation of the secondary heart field and TGFbeta-mediated outflow tract septation. *Dev Cell*. 2010; 18(3):480–485. [PubMed: 20230754]
22. Chen F, Desai TJ, Qian J, et al. Inhibition of Tgf beta signaling by endogenous retinoic acid is essential for primary lung bud induction. *Development*. 2007; 134(16):2969–2979. [PubMed: 17634193]
23. Chen F, Cao Y, Qian J, et al. A retinoic acid-dependent network in the foregut controls formation of the mouse lung primordium. *J Clin Invest*. 2010; 120(6):2040–2048. [PubMed: 20484817]
24. Colakoglu N, Kukner A. Teratogenicity of retinoic acid and its effects on TGF-beta2 expression in the developing cerebral cortex of the rat. *J Mol Histol*. 2004; 35(8–9):823–827. [PubMed: 15609095]
25. Colakoglu N, Kukner A, Oner J, et al. Effects of high dose retinoic acid on TGF-beta2 expression during pancreatic organogenesis. *J Mol Histol*. 2005; 36(6–7):413–418. [PubMed: 16479313]
26. Yu Z, Xing Y. All-trans retinoic acid inhibited chondrogenesis of mouse embryonic palate mesenchymal cells by down-regulation of TGF-beta/Smad signaling. *Biochem Biophys Res Commun*. 2006; 340(3):929–934. [PubMed: 16410076]
27. Zhang H, Li N, Tang Y, et al. Negative functional interaction of retinoic acid and TGF-beta signaling mediated by TG-interacting factor during chondrogenesis. *Cell Physiol Biochem*. 2009; 23(1–3):157–164. [PubMed: 19255510]
28. Butts SC, Liu W, Li G, Frenz DA. Transforming growth factor-beta1 signaling participates in the physiological and pathological regulation of mouse inner ear development by all-trans retinoic acid. *Birth Defects Res A Clin Mol Teratol*. 2005; 73(4):218–228. [PubMed: 15799023]
29. Preger-Ben Noon E, Barak H, Guttman-Raviv N, Reshef R. Interplay between activin and Hox genes determines the formation of the kidney morphogenetic field. *Development*. 2009; 136(12):1995–2004. [PubMed: 19439491]
30. Wong YF, Kopp JB, Roberts C, et al. Endogenous retinoic acid activity in principal cells and intercalated cells of mouse collecting duct system. *PLoS One*. 2011; 6(2):e16770. [PubMed: 21326615]
31. Gewin L, Bulus N, Mernaugh G, et al. TGF-beta receptor deletion in the renal collecting system exacerbates fibrosis. *J Am Soc Nephrol*. 2010; 21(8):1334–1343. [PubMed: 20576806]
32. Soucek K, Pachernik J, Kubala L, et al. Transforming growth factor-beta1 inhibits all-trans retinoic acid-induced apoptosis. *Leuk Res*. 2006; 30(5):607–623. [PubMed: 16242776]
33. Cao Z, Flanders KC, Bertolotto D, et al. Levels of phospho-Smad2/3 are sensors of the interplay between effects of TGF-beta and retinoic acid on monocytic and granulocytic differentiation of HL-60 cells. *Blood*. 2003; 101(2):498–507. [PubMed: 12393416]
34. Zhong H, Wang HR, Yang S, et al. Targeting Smad4 links microRNA-146a to the TGF-beta pathway during retinoid acid induction in acute promyelocytic leukemia cell line. *International journal of hematology*. 2010; 92(1):129–135. [PubMed: 20577838]
35. Zirn B, Samans B, Spangenberg C, et al. All-trans retinoic acid treatment of Wilms tumor cells reverses expression of genes associated with high risk and relapse in vivo. *Oncogene*. 2005; 24(33):5246–5251. [PubMed: 15897880]
36. Fernandez-Calotti P, Pastor-Anglada M. All-trans-retinoic acid promotes trafficking of human concentrative nucleoside transporter-3 (hCNT3) to the plasma membrane by a TGF-beta1-mediated mechanism. *J Biol Chem*. 2010; 285(18):13589–13598. [PubMed: 20172853]
37. Tabata C, Tabata R, Hirayama N, et al. All-trans-retinoic acid inhibits tumour growth of malignant pleural mesothelioma in mice. *Eur Respir J*. 2009; 34(5):1159–1167. [PubMed: 19443527]
38. Palladino MA, Morris RE, Starnes HF, Levinson AD. The transforming growth factor-betas. A new family of immunoregulatory molecules. *Ann N Y Acad Sci*. 1990; 593:181–187. [PubMed: 2197960]

39. Li MO, Flavell RA. TGF-beta: a master of all T cell trades. *Cell*. 2008; 134(3):392–404. [PubMed: 18692464]
40. Pino-Lagos K, Guo Y, Noelle RJ. Retinoic acid: a key player in immunity. *Biofactors*. 2010; 36(6): 430–436. [PubMed: 20803520]
41. Duriancik DM, Lackey DE, Hoag KA. Vitamin A as a regulator of antigen presenting cells. *J Nutr*. 2010; 140(8):1395–1399. [PubMed: 20554902]
42. Mucida D, Cheroutre H. TGFbeta and retinoic acid intersect in immune-regulation. *Cell Adh Migr*. 2007; 1(3):142–144. [PubMed: 19262136]
43. Mucida D, Park Y, Cheroutre H. From the diet to the nucleus: vitamin A and TGF-beta join efforts at the mucosal interface of the intestine. *Semin Immunol*. 2009; 21(1):14–21. [PubMed: 18809338]
44. Gorelik L, Flavell RA. Abrogation of TGFbeta signaling in T cells leads to spontaneous T cell differentiation and autoimmune disease. *Immunity*. 2000; 12(2):171–181. [PubMed: 10714683]
45. Shull MM, Ormsby I, Kier AB, et al. Targeted disruption of the mouse transforming growth factor-beta 1 gene results in multifocal inflammatory disease. *Nature*. 1992; 359(6397):693–699. [PubMed: 1436033]
46. Kulkarni AB, Huh CG, Becker D, et al. Transforming growth factor beta 1 null mutation in mice causes excessive inflammatory response and early death. *Proc Natl Acad Sci U S A*. 1993; 90(2): 770–774. [PubMed: 8421714]
47. Diebold RJ, Eis MJ, Yin M, et al. Early-onset multifocal inflammation in the transforming growth factor beta 1-null mouse is lymphocyte mediated. *Proc Natl Acad Sci U S A*. 1995; 92(26):12215–12219. [PubMed: 8618872]
48. Sanford LP, Ormsby I, Gittenberger-de Groot AC, et al. TGFbeta2 knockout mice have multiple developmental defects that are non-overlapping with other TGFbeta knockout phenotypes. *Development*. 1997; 124(13):2659–2670. [PubMed: 9217007]
49. Kaartinen V, Voncken JW, Shuler C, et al. Abnormal lung development and cleft palate in mice lacking TGF-beta 3 indicates defects of epithelial-mesenchymal interaction. *Nat Genet*. 1995; 11(4):415–421. [PubMed: 7493022]
50. Marks BR, Nowyhed HN, Choi JY, et al. Thymic self-reactivity selects natural interleukin 17-producing T cells that can regulate peripheral inflammation. *Nat Immunol*. 2009; 10(10):1125–1132. [PubMed: 19734905]
51. Flavell RA, Sanjabi S, Wrzesinski SH, Licona-Limon P. The polarization of im cells in the tumour environment by TGFbeta. *Nat Rev Immunol*. 2010; 10(8):554–567. [PubMed: 20616810]
52. Ooi JD, Kitching AR, Holdsworth SR. Review: T helper 17 cells: their role in glomerulonephritis. *Nephrology (Carlton)*. 2010; 15(5):513–521. [PubMed: 20649870]
53. Das J, Ren G, Zhang L, et al. Transforming growth factor beta is dispensable for the molecular orchestration of Th17 cell differentiation. *J Exp Med*. 2009; 206(11):2407–2416. [PubMed: 19808254]
54. Santarlasci V, Maggi L, Capone M, et al. TGF-beta indirectly favors the development of human Th17 cells by inhibiting Th1 cells. *Eur J Immunol*. 2009; 39(1):207–215. [PubMed: 19130583]
55. Maeda H, Shiraishi A. TGF-beta contributes to the shift toward Th2-type responses through direct and IL-10-mediated pathways in tumor-bearing mice. *J Immunol*. 1996; 156(1):73–78. [PubMed: 8598496]
56. van Ginkel FW, Wahl SM, Kearney JF, et al. Partial IgA-deficiency with increased Th2-type cytokines in TGF-beta 1 knockout mice. *J Immunol*. 1999; 163(4):1951–1957. [PubMed: 10438931]
57. Cazac BB, Roes J. TGF-beta receptor controls B cell responsiveness and induction of IgA in vivo. *Immunity*. 2000; 13(4):443–451. [PubMed: 11070163]
58. van Vlasselaer P, Punnonen J, de Vries JE. Transforming growth factor-beta directs IgA switching in human B cells. *J Immunol*. 1992; 148(7):2062–2067. [PubMed: 1347548]
59. Watanabe K, Sugai M, Nambu Y, et al. Requirement for Runx proteins in IgA class switching acting downstream of TGF-beta 1 and retinoic acid signaling. *J Immunol*. 2010; 184(6):2785–2792. [PubMed: 20142360]

60. Takimoto T, Wakabayashi Y, Sekiya T, et al. Smad2 and Smad3 are redundantly essential for the TGF-beta-mediated regulation of regulatory T plasticity and Th1 development. *J Immunol.* 2010; 185(2):842–855. [PubMed: 20548029]
61. Martinez GJ, Zhang Z, Reynolds JM, et al. Smad2 positively regulates the generation of Th17 cells. *J Biol Chem.* 2010; 285(38):29039–29043. [PubMed: 20667820]
62. Lu L, Wang J, Zhang F, et al. Role of SMAD and non-SMAD signals in the development of Th17 and regulatory T cells. *J Immunol.* 2010; 184(8):4295–4306. [PubMed: 20304828]
63. Pino-Lagos K, Benson MJ, Noelle RJ. Retinoic acid in the immune system. *Ann N Y Acad Sci.* 2008; 1143:170–187. [PubMed: 19076350]
64. Zhou X, Kong N, Wang J, et al. Cutting edge: all-trans retinoic acid sustains the stability and function of natural regulatory T cells in an inflammatory milieu. *J Immunol.* 2010; 185(5):2675–2679. [PubMed: 20679534]
65. Feng T, Cong Y, Qin H, Benveniste EN, Elson CO. Generation of mucosal dendritic cells from bone marrow reveals a critical role of retinoic acid. *J Immunol.* 2010; 185(10):5915–5925. [PubMed: 20944006]
66. Manicassamy S, Reizis B, Ravindran R, et al. Activation of beta-catenin in dendritic cells regulates immunity versus tolerance in the intestine. *Science.* 2010; 329(5993):849–853. [PubMed: 20705860]
67. Manicassamy S, Ravindran R, Deng J, et al. Toll-like receptor 2-dependent induction of vitamin A-metabolizing enzymes in dendritic cells promotes T regulatory responses and inhibits autoimmunity. *Nat Med.* 2009; 15(4):401–409. [PubMed: 19252500]
68. Maruya M, Suzuki K, Fujimoto H, et al. Vitamin A-dependent transcriptional activation of the nuclear factor of activated T cells c1 (NFATc1) is critical for the development and survival of B1 cells. *Proc Natl Acad Sci U S A.* 2011; 108(2):722–727. [PubMed: 21187378]
69. DePaolo RW, Abadie V, Tang F, et al. Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. *Nature.* 2011; 471(7337):220–224. [PubMed: 21307853]
70. Stephensen CB, Rasooly R, Jiang X, et al. Vitamin A enhances in vitro Th2 development via retinoid X receptor pathway. *J Immunol.* 2002; 168(9):4495–4503. [PubMed: 11970994]
71. Iwata M, Eshima Y, Kagechika H. Retinoic acids exert direct effects on T cells to suppress Th1 development and enhance Th2 development via retinoic acid receptors. *Int Immunol.* 2003; 15(8):1017–1025. [PubMed: 12882839]
72. Dawson HD, Collins G, Pyle R, Key M, Taub DD. The Retinoic Acid Receptor-alpha mediates human T-cell activation and Th2 cytokine and chemokine production. *BMC Immunol.* 2008; 9:16. [PubMed: 18416830]
73. Hall JA, Cannons JL, Grainger JR, et al. Essential role for retinoic acid in the promotion of CD4(+) T cell effector responses via retinoic acid receptor alpha. *Immunity.* 2011; 34(3):435–447. [PubMed: 21419664]
74. Iwata M, Hirakiyama A, Eshima Y, et al. Retinoic acid imprints gut-homing specificity on T cells. *Immunity.* 2004; 21(4):527–538. [PubMed: 15485630]
75. Dzhagalov I, Chambon P, He YW. Regulation of CD8+ T lymphocyte effector function and macrophage inflammatory cytokine production by retinoic acid receptor gamma. *J Immunol.* 2007; 178(4):2113–2121. [PubMed: 17277115]
76. Mucida D, Park Y, Kim G, et al. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. *Science.* 2007; 317(5835):256–260. [PubMed: 17569825]
77. Lu L, Zhou X, Wang J, Zheng SG, Horwitz DA. Characterization of protective human CD4CD25 FOXP3 regulatory T cells generated with IL-2, TGF-beta and retinoic acid. *PLoS One.* 2010; 5(12):e15150. [PubMed: 21179414]
78. Mucida D, Pino-Lagos K, Kim G, et al. Retinoic acid can directly promote TGF-beta-mediated Foxp3(+) Treg cell conversion of naive T cells. *Immunity.* 2009; 30(4):471–472. author reply 472–473. [PubMed: 19371709]
79. Kim BS, Kim IK, Park YJ, et al. Conversion of Th2 memory cells into Foxp3+ regulatory T cells suppressing Th2-mediated allergic asthma. *Proc Natl Acad Sci U S A.* 2010; 107(19):8742–8747. [PubMed: 20421479]

80. Kishi M, Yasuda H, Abe Y, et al. Regulatory CD8+ T cells induced by exposure to alltrans retinoic acid and TGF-beta suppress autoimmune diabetes. *Biochem Biophys Res Commun.* 2010; 394(1): 228–232. [PubMed: 20206130]
81. Lei J, Hasegawa H, Matsumoto T, Yasukawa M. Peroxisome proliferator-activated receptor alpha and gamma agonists together with TGF-beta convert human CD4+CD25- T cells into functional Foxp3+ regulatory T cells. *J Immunol.* 2010; 185(12):7186–7198. [PubMed: 21057085]
82. Xu L, Kitani A, Stuelten C, et al. Positive and negative transcriptional regulation of the Foxp3 gene is mediated by access and binding of the Smad3 protein to enhancer I. *Immunity.* 2010; 33(3): 313–325. [PubMed: 20870174]
83. Suzuki K, Maruya M, Kawamoto S, et al. The sensing of environmental stimuli by follicular dendritic cells promotes immunoglobulin A generation in the gut. *Immunity.* 2010; 33(1):71–83. [PubMed: 20643338]
84. Melnik BC. Is nuclear deficiency of FoxO1 due to increased growth factor/PI3K/Akt-signalling in acne vulgaris reversed by isotretinoin treatment? *The British journal of dermatology.* 2010; 162(6):1398–1400. [PubMed: 20394627]
85. Esteban-Pretel G, Marin MP, Renau-Piqueras J, Barber T, Timoneda J. Vitamin A deficiency alters rat lung alveolar basement membrane: reversibility by retinoic acid. *The Journal of nutritional biochemistry.* 2010; 21(3):227–236. [PubMed: 19269151]
86. Liu X, Lu L, Tao BB, Zhu YC. All-trans retinoic acid inhibits the increases in fibronectin and PAI-1 induced by TGF-beta1 and Ang II in rat mesangial cells. *Acta Pharmacol Sin.* 2008; 29(9): 1035–1041. [PubMed: 18718172]
87. Wang H, Dan Z, Jiang H. Effect of all-trans retinoic acid on liver fibrosis induced by common bile duct ligation in rats. *Journal of Huazhong University of Science and Technology Medical sciences = Hua zhong ke ji da xue xue bao Yi xue Ying De wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban.* 2008; 28(5):553–557. [PubMed: 18846337]
88. Tanabe K, Tokuda H, Takai S, et al. Modulation by the steroid/thyroid hormone superfamily of TGF-beta-stimulated VEGF release from vascular smooth muscle cells. *J Cell Biochem.* 2006; 99(1):187–195. [PubMed: 16598785]
89. Sidell N, Feng Y, Hao L, et al. Retinoic acid is a cofactor for translational regulation of vascular endothelial growth factor in human endometrial stromal cells. *Molecular endocrinology.* 2010; 24(1):148–160. [PubMed: 19910455]
90. Glick AB, Flanders KC, Danielpour D, Yuspa SH, Sporn MB. Retinoic acid induces transforming growth factor-beta 2 in cultured keratinocytes and mouse epidermis. *Cell Regul.* 1989; 1(1):87–97. [PubMed: 2519621]
91. Jakowlew SB, Cubert J, Danielpour D, Sporn MB, Roberts AB. Differential regulation of the expression of transforming growth factor-beta mRNAs by growth factors and retinoic acid in chicken embryo chondrocytes, myocytes, and fibroblasts. *J Cell Physiol.* 1992; 150(2):377–385. [PubMed: 1734039]
92. Morath C, Dechow C, Lehrke I, et al. Effects of retinoids on the TGF-beta system and extracellular matrix in experimental glomerulonephritis. *Journal of the American Society of Nephrology : JASN.* 2001; 12(11):2300–2309. [PubMed: 11675406]
93. Morath C, Ratzlaff K, Dechow C, et al. Chronic low-dose isotretinoin treatment limits renal damage in subtotally nephrectomized rats. *Journal of molecular medicine.* 2009; 87(1):53–64. [PubMed: 18795249]
94. Kishimoto K, Kinoshita K, Hino S, et al. Therapeutic Effect of Retinoic Acid on Unilateral Ureteral Obstruction Model. *Nephron Experimental nephrology.* 2011; 118(3):e69–e78. [PubMed: 21228601]
95. Perez de Lema G, Lucio-Cazana FJ, Molina A, et al. Retinoic acid treatment protects MRL/lpr lupus mice from the development of glomerular disease. *Kidney international.* 2004; 66(3):1018–1028. [PubMed: 15327395]

Table 1

Mechanisms of crosstalk between retinoid and TGF- β families.

Effect	Examples
Shared repression	TGIF, a transcriptional co-repressor acting on SMADs and RXR α
Retinoids suppress TGF-β signaling	<ul style="list-style-type: none"> Ubiquitin-mediated SMAD4 degradation Induce HGF production, antagonizing TGF-β activities Decrease nuclear accumulation of SMADs
Retinoids increase TGF-β activity	<ul style="list-style-type: none"> Increase transcription of TGFB1 and TGFB2 genes. Increase SMAD transcription and nuclear localization
TGF-β affects retinoid pathway	<ul style="list-style-type: none"> Induce RAR and RXR expression Suppresses Cyp26b1 expression Reducing tissue concentrations of ATRA

Legend. Retinoids affect TGF- β signaling either positively or negatively in a cell type- and context-dependent manner. TGF- β also regulates the retinoid signaling pathway at multiple levels. More details and references, see text.

Table 2Effects of retinoids and TGF- β on the immune system

	Central functions, including direct and indirect	Peripheral functions
TGF-β (some effects are isform dependent, with TGF- β 1 playing a central role)	<i>Required:</i> development of CD8 ⁺ T cells, natural regulatory T cell (nTreg), natural Th17 cells (nTh17) and natural killer T (NKT) cells from CD4 ⁺ CD8 ⁺ immature T cells	<i>Essential:</i> development of inducible regulatory T cell (iTreg) <i>Suppressive:</i> development of Th1, Th2, NKT, CD8 ⁺ cytotoxic T cells, dendritic cells, macrophages, and neutrophils <i>Promoting:</i> development of Th17 cells
Retinoids	<i>Physiologic retinoids:</i> unknown <i>Exogenous retinoids:</i> suppress CD8 ⁺ development, enhance CD4 ⁺ development, increase total immature CD4 ⁺ CD8 ⁺ cell number, and increase egress of mature T cells from the thymus to augment total peripheral T cell numbers	<i>Physiologic retinoids:</i> decrease Th1 and Th7, increase Th2 and Treg; required for development of B1 cells, functions of neutrophils, antigen presenting cells (APC), humoral immune responses, as well as for maintaining total and NKT numbers <i>Exogenous retinoids:</i> augment total peripheral T cell numbers, promote development of B1 cells and maturation and activation of B cells; condition-dependently regulate Treg, Th1, Th2 and Th17 development
Retinoids modulating TGF-β production or effect	<ul style="list-style-type: none"> • Synergizes with TGF-β to promote nTreg differentiation • Cooperates with Toll receptors to stimulate TGF-β production 	<ul style="list-style-type: none"> • Synergizes with TGF-β to promote Treg resistance to inflammatory cytokines • Induces integrin α4β7 expression on T cells, while TGF-β induces αEβ7 expression on T cells, and the combination promotes gut homing

Legend. Shown are selected effects of TGF- β and retinoids on the immune system, as well as modulatory effects of retinoids on the actions of TGF- β on the immune system.