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Regulation of the Immune Response by TGF-β: From Conception to Autoimmunity and Infection

Shomyseh Sanjabi,[1,2,4] Soyoung A. Oh,[3,4] and Ming O. Li[3]

[1]Institute of Virology and Immunology, Gladstone Institutes, San Francisco, California 94158

[2]Department of Microbiology and Immunology, University of California, San Francisco, California 94143

[3]Immunology Program, Memorial Sloan Kettering Cancer Center, New York, New York 10065

Correspondence: shomyseh.sanjabi@gladstone.ucsf.edu; lim@mskcc.org

Transforming growth factor β (TGF-β) is a pleiotropic cytokine involved in both suppressive and inflammatory immune responses. After 30 years of intense study, we have only begun to elucidate how TGF-β alters immunity under various conditions. Under steady-state conditions, TGF-β regulates thymic T-cell selection and maintains homeostasis of the naïve T-cell pool. TGF-β inhibits cytotoxic T lymphocyte (CTL), Th1-, and Th2-cell differentiation while promoting peripheral (p)Treg-, Th17-, Th9-, and Tfh-cell generation, and T-cell tissue residence in response to immune challenges. Similarly, TGF-β controls the proliferation, survival, activation, and differentiation of B cells, as well as the development and functions of innate cells, including natural killer (NK) cells, macrophages, dendritic cells, and granulocytes. Collectively, TGF-β plays a pivotal role in maintaining peripheral tolerance against self- and innocuous antigens, such as food, commensal bacteria, and fetal alloantigens, and in controlling immune responses to pathogens.

In mammals, the innate and adaptive arms of the immune system orchestrate host–defense and inflammatory responses. For example, leukocytes of the myeloid cell lineage use germline-encoded receptors to detect conserved molecular patterns associated with pathogens, which allows them to alert and activate the rest of the immune system, including adaptive immunity. Alternatively, lymphocytes of the adaptive immune system express antigen-specific receptors that distinguish small differences in macromolecules and establish long-term immunity by forming immunological memory. The coupling of these innate and adaptive recognition pathways, and their precise modes of communication provide a robust mechanism that stimulates immunity and protects the host against pathogens. Nevertheless, the immune system tolerates antigens originating from self-, commensal organisms, and the allogeneic fetus. By maintaining this balance between immunity and tolerance, the immune system can promote the physiological well-being of an individual.

A pivotal and pleiotropic regulator of immune responses is transforming growth factor β (TGF-β), which was first reported to control

[4]These authors contributed equally to this work.

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immune cell function three decades ago (Kehrl et al. 1986b). TGF-β controls the magnitude and type of immune responses against microbes, and has fundamentally important roles in maintaining immune tolerance and homeostasis against self- and benign antigens at steady-state (Li et al. 2006b; Oh and Li 2013; Travis and Sheppard 2014). In this review, we discuss how TGF-β regulates the differentiation and function of different classes of leukocytes, and how it modulates immune activities, from conception to autoimmunity and infection.

TGF-β IN THE IMMUNE SYSTEM

T Cells

Thymic Development

T cells arise from bone marrow–derived precursors that traffic to the thymus, where their developmental process is completed. In the thymus, T-cell precursors are exposed to a variety of extrinsic signals, for example, peptides presented by major histocompatibility complexes (MHCs), costimulation, and cytokines, which stimulate molecular changes that cause differentiation into distinct T-cell lineages. The differentiation of conventional $CD4^+$ and $CD8^+$ αβ T cells requires T-cell receptor (TCR) engagement that follows the Goldilocks principle, in which both too little and too much TCR signaling are detrimental to the successful development of mature T cells. T-cell precursors require appropriate TCR signaling to trigger their survival and maturation, a process termed positive selection. "Too little" signaling results in death of the developing T cells. Yet "too much" TCR signaling, which reflects strong reactivity to self-peptide:MHC complexes, can also cause death of the developing T cell. This process of negative selection, a key aspect of central tolerance, eliminates autoreactive T cells from the T-cell repertoire. However, this process is not complete, and some autoreactive T cells mature in the thymus and exit to the periphery, where they must be kept in check to prevent the development of autoimmunity. The immunosuppressive functions of TGF-β have long been appreciated, and TGF-β signaling is one mechanism by which such "escaped" autoreactive T cells can be controlled in the periphery, a process called peripheral tolerance. Although TGF-β is well known for its tolerance-inducing activities in the periphery, its contributions to T-cell biology clearly extend beyond its role as an immunosuppressive cytokine. Indeed, TGF-β also has important functions in the development of several T-cell lineages.

In the thymus, the differentiation of conventional $CD8^+$ T cells requires both TCR engagement and signaling through the common γ-chain family cytokine interleukin 7 (IL-7) (Park et al. 2010). Consequently, maintaining expression of the IL-7 receptor on $CD8^+$ T-cell precursors is critical given the role of IL-7 signaling in the specification of the $CD8^+$ T-cell fate. TGF-β regulates the expression of the IL-7 receptor α-chain (IL-7Rα) in developing $CD8^+$ T cells (Ouyang et al. 2013), thus supporting IL-7 signaling, and therefore $CD8^+$ T-cell lineage commitment. Mechanistically, TGF-β signaling promotes IL-7Rα expression on $CD8^+$ thymocytes by suppressing the expression of the transcriptional repressor Gfi-1, a known inhibitor of *Il7ra* expression in $CD8^+$ T cells (Park et al. 2004). This cross talk between TGF-β and IL-7 signaling pathways is an essential aspect of conventional $CD8^+$ T-cell development (Fig. 1A).

TGF-β also regulates the development of multiple subsets of regulatory and innate-like T cells. Thymus-derived $CD4^+CD25^+Foxp3^+$ regulatory T (tTreg) cells, invariant natural killer T (iNKT) cells, and $CD8\alpha\alpha^+TCR\alpha\beta^+$ intraepithelial lymphocytes (IELs) share a common thread: their development requires high-affinity interactions with MHC-presenting self-ligands, which are referred to as agonist ligands (Stritesky et al. 2012). Because TGF-β promotes the survival of precursor populations for each of these lineages (discussed in more detail below), it functions as a unifying molecule to promote the differentiation of T-cell populations that require strong agonist ligands for their development (Fig. 1A).

Treg cells are essential for the maintenance of immune tolerance (Josefowicz et al. 2012).

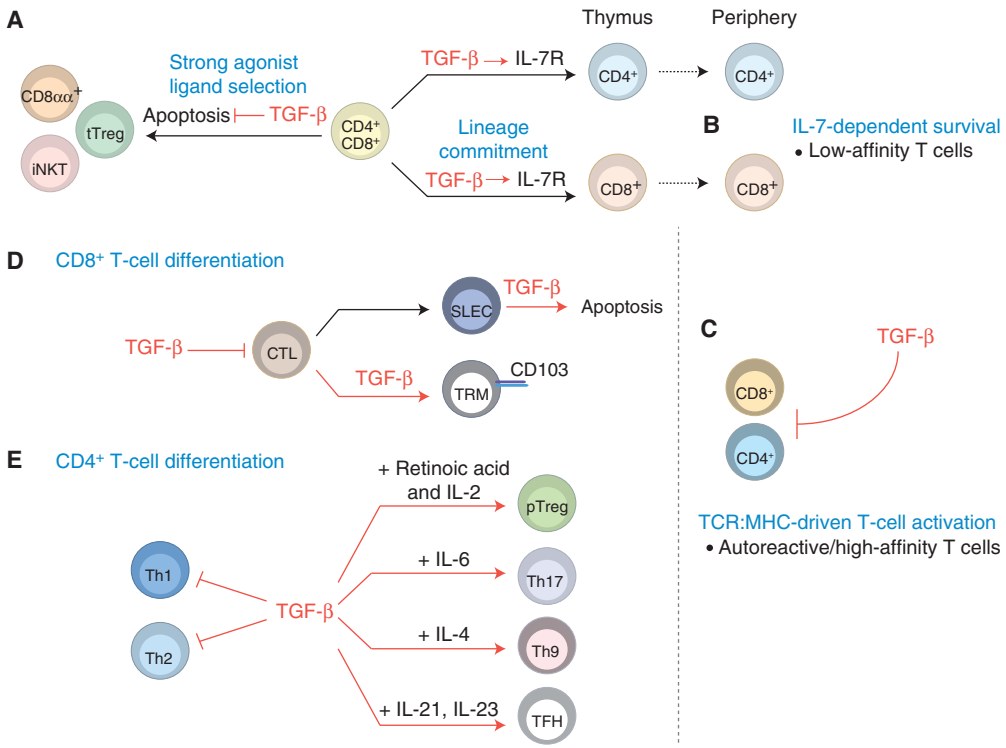

Figure 1. Regulation of T cells by transforming growth factor β (TGF-β). (*A*) TGF-β promotes the thymic development of multiple T-cell lineages. TGF-β supports the survival of thymus-derived Treg (tTreg), invariant natural killer T (iNKT), and CD8αα$^+$ T-cell precursors, and thus promotes the development of T-cell populations that are induced by strong agonist ligands. TGF-β also supports the development of conventional CD8$^+$ T cells by promoting thymocyte expression of interleukin (IL)-7Rα. (*B*) TGF-β regulates peripheral T-cell homeostasis by promoting IL-7-dependent survival of low-affinity T cells, through its control of thymocyte IL-7Rα expression, and by (*C*) inhibiting T-cell receptor (TCR)-driven activation of autoreactive or high-affinity T cells. (*D*) In early stages of CD8$^+$ T-cell differentiation, TGF-β inhibits cytotoxic T lymphocyte (CTL) development. However, TGF-β also promotes the apoptosis of short-lived effector cells (SLECs) and the differentiation of CD103-expressing tissue resident memory (TRM) cells. (*E*) Whereas TGF-β inhibits T helper 1 (Th1)- and Th2-cell differentiation, TGF-β (in concert with other factors) promotes the development of peripheral Treg (pTreg), Th17, Th9, and T follicular helper (Tfh) cells.

Although Treg cells can be generated in the periphery by the conversion of conventional naïve CD4$^+$ T cells, the thymus gives rise to the majority of Treg cells, which are referred to as thymus-derived Treg (tTreg) cells (Shevach and Thornton 2014). The development of tTreg cells is driven by a combination of stringent TCR interactions, costimulation, and cytokine signals. The TGF-β signaling pathway plays a role in the early development of tTreg cells, and 3- to 5-day old mice lacking the TGF-β type I receptor (TβRI) show a dramatic reduction in the frequency of Foxp3$^+$ thymocytes (Liu et al. 2008). Although a conserved DNA sequence for Smad3 binding is present in *Foxp3* gene regulatory sequences (Tone et al. 2008), TGF-β signaling is dispensable for the induction of Foxp3 expression in tTreg cells (Zheng et al. 2010; Schlenner et al. 2012), showing that TGF-β does not promote tTreg-cell development by directly regulating Foxp3 expression. Instead, TGF-β signaling promotes tTreg-cell development by antagonizing thymic-negative selection, and therefore

promoting the survival of tTreg-cell precursors (Ouyang et al. 2010).

iNKT cells recognize lipids presented by the MHC class I–like molecule CD1d, and possess qualities that are reminiscent of both the innate and adaptive immune responses. This subset of lipid-sensing T cells has been shown to play both beneficial and pathogenic roles in a variety of inflammatory and disease conditions (Brennan et al. 2013). Strong agonist ligand interactions are also thought to promote iNKT-cell development (Stritesky et al. 2012), and, as observed with tTreg cells, TGF-β signaling appears to play a critical role in promoting the survival of iNKT-cell precursors. T-cell-specific deletion of the TGF-β type II receptor (TβRII) leads to a reduction of both thymic and peripheral iNKT cells (Li et al. 2006a; Marie et al. 2006; Doisne et al. 2009), which results, in part, from increased apoptosis of immature precursor cells in the absence of TGF-β signaling (Doisne et al. 2009).

CD8αα$^+$TCRαβ$^+$ IELs are innate-like T cells that play important roles in intestinal homeostasis (Cheroutre et al. 2011). The development of these innate-like T cells is thought to occur both in and outside the thymus, and also appears to be driven by high-affinity TCR interactions with their selection ligands (Pobezinsky et al. 2012). In the absence of TGF-β signaling, the CD8αα$^+$TCRαβ$^+$ IEL population is decreased, which is partially driven by a reduction in numbers of thymic precursors of these innate-like T cells (Konkel et al. 2011).

Collectively, the studies of tTreg cells, iNKT cells, and CD8αα$^+$TCRαβ$^+$ IEL development highlight the importance of TGF-β signaling in mediating the survival of a precursor population in the ontogeny of multiple T-cell lineages.

Peripheral Homeostasis

An effective immune system must maintain a diverse pool of naïve T cells within the confines of a relatively constant number of peripheral T cells. TGF-β critically contributes to the maintenance of an effective naïve T-cell population by regulating T-cell proliferation, homeostasis, and repertoire diversity.

TGF-β was first shown to immunoregulate and reduce proliferation of human T cells through studies in cell culture (Kehrl et al. 1986b). During priming, TGF-β inhibits T-cell proliferation by inhibiting transcription of the *Il2* gene and suppressing IL-2 production (Brabletz et al. 1993; Tzachanis et al. 2001). At the molecular level, Smad3 mediates this suppression, as both Smad3-deficient CD4$^+$ and CD8$^+$ T cells are not sensitive to IL-2 inhibition mediated by TGF-β (McKarns et al. 2004; McKarns and Schwartz 2005). TGF-β also inhibits the expression of several cell-cycle regulators in primary T cells and T-cell lines (Ruegemer et al. 1990; Genestier et al. 1999; Nelson et al. 2003; Wolfraim et al. 2004). However, whether TGF-β inhibits T-cell priming under inflammatory conditions in vivo and the exact mechanism by which this regulation may occur are unclear.

Befitting the pleiotropic nature of TGF-β, its ability to regulate T-cell proliferation depends on the status of T-cell differentiation and the cumulative signaling pathways involved in cell activation. For example, TGF-β can inhibit the proliferation of naïve but not activated T cells, an effect associated with decreased TβRII expression on activated T cells (Cottrez and Groux 2001; Sanjabi et al. 2009). Additionally, in naïve T cells, CD28 engagement sends a costimulatory signal that abrogates TGF-β inhibition of proliferation (Sung et al. 2003), ensuring that TGF-β does not inhibit the ability of activated antigen-presenting cells (APCs) to prime naïve T cells.

T-cell proliferation must be properly regulated to maintain homeostasis under steady-state conditions and during immune challenges. The absence of TGF-β signaling alters homeostasis of both CD4$^+$ and CD8$^+$ T cells. For example, loss of TGF-β signaling in mice, in which CD4$^+$ T cells are engineered to express a single TCR, results in a dramatic reduction of the peripheral T-cell population (Li et al. 2006a; Ouyang et al. 2013). TGF-β supports the homeostasis of peripheral CD4$^+$ T cells by promoting IL-7Rα expression in the thymus during T-cell development, which allows naïve peripheral CD4$^+$ T cells to sense IL-7 for their

survival (Ouyang et al. 2013). Interestingly, this regulation is particularly important for the survival of low-affinity $CD4^+$ T cells (Fig. 1B). This phenomenon was shown in studies using transgenic expression of the AND TCR that possesses a higher affinity for its positive selection ligand in the MHC H-2^k background than that in the H-2^b background (Smith et al. 2001; Ouyang et al. 2013). In both genetic backgrounds, regardless of high or low affinity for the positive selection ligand, TβRII-deficient AND T cells express lower levels of IL-7Rα than their wild-type counterparts. However, comparison of the transgenic T cells between the two genetic backgrounds showed that TβRII-deficient AND T cells in the high-affinity background (i.e., H-2^k) express greater levels of IL-7Rα than even wild-type AND T cells in the low-affinity background (i.e., H-2^b), showing that TGF-β signaling and TCR signal strength both contribute to IL-7Rα expression. Thus, the absence of TGF-β signaling causes a more profound defect in IL-7Rα expression and correspondingly results in poor peripheral homeostasis in T cells bearing low-affinity TCRs. Notably, *Tgfb1*$^{-/-}$ mice show altered diversity of $CD4^+$ TCRs in the periphery, but not in the thymus (Robinson and Gorham 2007), which likely reflects repertoire changes caused by the preferential loss of low-affinity $CD4^+$ T cells.

TGF-β signaling is also important for the regulation of peripheral $CD8^+$ T cells. Defects in TGF-β signaling result in altered homeostasis and aberrant activation of $CD8^+$ T cells (Lucas et al. 2000; Johnson and Jameson 2012; Zhang and Bevan 2012). However, mice expressing certain transgenic TCRs do not show changes in $CD8^+$ T-cell homeostasis on loss of TGF-β signaling (Lucas et al. 2006). These differences may be explained by differences in the affinity of each of these transgenic TCRs for self-peptide MHC complexes. As such, T cells expressing high-affinity TCRs undergo greater homeostatic proliferation than T cells expressing low-affinity TCRs (Kieper et al. 2004). Indeed, homeostatic proliferation of $CD8^+$ T cells with defective TGF-β signaling depends on TCR and MHC class I (Fig. 1C) (Johnson and Jameson 2012). At its extreme, loss of control of $CD8^+$ T-cell homeostasis by TGF-β can lead to cell transformation, as expression of a dominant-negative form of TβRII (dnTβRII) in T cells causes mice to develop lymphoma (Lucas et al. 2004). Interestingly, expression of dnTβRII, but not deletion of TβRII, causes a $CD8^+$ T-cell lymphoproliferative disorder (Ishigame et al. 2013a). These findings suggest that either the dnTβRII exerts a dominant function independent of its inhibiting TGF-β signaling, or that T-cell homeostasis is regulated by TGF-β signaling in a dose-dependent manner (Ishigame et al. 2013a).

$CD8^+$ T cells undergo massive clonal expansion after becoming activated in response to pathogens, followed by apoptosis-mediated contraction on pathogen clearance. TGF-β plasma levels increase in response to acute *Listeria monocytogenes* (LM) infection. Mice expressing OTI TCR transgenic T cells, specific for MHC I–restricted ovalbumin SIINFEKL peptide, were crossed to dnTβRII animals and further crossed to RAG1$^{-/-}$ animals to eliminate V(D)J recombination of endogenous TCR locus. Naïve T cells from corresponding OTI-dnTβRII-RAG1$^{-/-}$ and OTI-RAG1$^{-/-}$ animals were adoptively cotransferred into wild-type animals that were then infected with a recombinant LM-expressing chicken ovalbumin (LM-OVA). Using this system, it was shown that TGF-β plays a major role in maintaining T-cell homeostasis during $CD8^+$ T-cell clonal expansion by promoting apoptosis of short-lived effector $CD8^+$ T cells that are enriched among the cells expressing the killer-cell lectin-like receptor subfamily G member 1 (KLRG1) (Fig. 1D) (Sanjabi et al. 2009). Similarly, adding TGF-β to cultures of human T cells at 72 h postactivation induces T-cell death (Sillett et al. 2001; Hernandez-Garay and Mendez-Samperio 2003). However, using a model in which TβRII expression is specifically inactivated in $CD8^+$ T cells, it was shown that higher proliferation rather than less apoptosis was responsible for expansion of *Tgfbr2*$^{-/-}$ $CD8^+$ T cells after pathogenic challenge (Hu et al. 2015). Although both dnTβRII-expressing and *Tgfbr2*$^{-/-}$ mouse models show an increase in the ratio of $KLRG1^+$ short-lived effector T

cells compared with KLRG1$^-$ memory precursor T cells, the exact mechanism of this increase during effector CD8$^+$ T-cell expansion remains unclear.

Differentiation

TGF-β broadly inhibits T-cell activation by interfering with TCR signaling (Chen et al. 2003a). It also specifically suppresses cytotoxic T lymphocytes (CTL) and T helper 1 (Th1) and T helper 2 (Th2) lymphocyte subset differentiation by inhibiting the expression of lineage-defining transcription factors such as T-bet and GATA-3, respectively (Fig. 1D,E) (Gorelik et al. 2000, 2002; Heath et al. 2000). TGF-β was also shown to suppress Th1 differentiation by inhibiting the expression of Stat4 (Lin et al. 2005), a transcription factor whose expression is activated in response to IL-12 signaling. TGF-β regulates T-bet and Stat4 expression to control Th1-cell differentiation in culture at distinct stages. Indeed, repressing *Stat4* activation inhibits interferon γ (IFN-γ) production during the priming phase, whereas loss of T-bet expression impairs IFN-γ production during the recall response, that is, the restimulation of T cells after initial priming (Lin et al. 2005). Mechanistically, Smad2 and Smad3 transcription factors may have a redundant role in TGF-β-mediated inhibition of Th1-cell differentiation (Takimoto et al. 2010; Gu et al. 2012). The Smad pathway also contributes to the inhibition of Th2-cell differentiation by TGF-β, by inducing the expression of Sox4, a transcription factor that can bind to GATA-3 (Kuwahara et al. 2012). Retroviral expression of wild-type Sox4, but not Sox4 mutants lacking the ability to interact with GATA-3, inhibits Th2 cytokine production in CD4$^+$ T cells (Kuwahara et al. 2012).

In contrast to its role in inhibiting Th1 and Th2-cell differentiation, TGF-β promotes the development of peripheral regulatory T (pTreg), Th17, Th9, and Tfh (follicular helper T) cells (Fig. 1E). Suboptimal stimulation of T cells, for example, using an altered peptide ligand (Windhagen et al. 1995), low-dose antigen (Gunnlaugsdottir et al. 2005; Kohyama et al. 2005), or absence of complement signaling (Strainic et al. 2012), stimulates TGF-β production and converts CD4$^+$ T cells into Treg cells. Indeed, TGF-β promotes regulatory activity in naïve CD4$^+$ T cells (Yamagiwa et al. 2001) by inducing Foxp3 expression (Chen et al. 2003b; Selvaraj and Geiger 2007) and pTreg-cell differentiation. Foxp3 then provides a positive feedback loop in TGF-β signaling by down-regulating TGF-β-induced expression of the inhibitory Smad7 (Fantini et al. 2004).

TGF-β plays both direct and indirect roles in Foxp3 expression. The *Foxp3* gene contains an enhancer element that allows for direct binding of Smad3 and nuclear factor of activated T (NFAT) cells (Tone et al. 2008) to a conserved DNA sequence (Xu et al. 2010; Zheng et al. 2010). TGF-β also promotes locus activation by opposing the recruitment of a DNA methyltranferase to the *Foxp3* locus (Josefowicz et al. 2009). As an indirect mechanism, TGF-β induces expression of the adaptor Nedd4 family interacting protein 1 (Ndfip1), which promotes JunB degradation through the E3 ubiquitin ligase Itch, and suppresses IL-4 production to support pTreg-cell differentiation (Beal et al. 2011). However, the presence of inflammatory cytokines and strong costimulatory signals potently inhibits *Foxp3* induction by TGF-β (Wei et al. 2007; Molinero et al. 2011; Battaglia et al. 2013). These findings show that pTreg-cell differentiation is modulated by the microenvironment, with highly inflammatory conditions favoring effector over Treg-cell generation.

TGF-β also regulates Th17-cell differentiation (Bettelli et al. 2006; Veldhoen et al. 2006a; Li et al. 2007; Manel et al. 2008; Yang et al. 2008; Gutcher et al. 2011). Th17 cells express the lineage-specific transcription factor RAR (retinoic acid receptor)-related orphan receptor C (RORC) in humans (and RORγt in mice) and produce many cytokines, including IL-17A, IL-17F, IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Ivanov et al. 2006; Korn et al. 2009). RORγt expression is induced by IL-21 or IL-23, and TGF-β together with IL-6 amplifies RORγt-dependent Th17-cell differentiation (Zhou et al. 2007). Although RORγt expression is activated independently of Smad2 and Smad3 (Takimoto et al. 2010),

Smad2 has been shown to directly associate with RORγt to enhance Th17-cell differentiation (Martinez et al. 2010). In addition, TGF-β promotes Th17-cell differentiation by inhibiting the expression of the transcription factors Stat4 and GATA-3 (Das et al. 2009), Eomesodermin (Eomes) (Ichiyama et al. 2011), and growth factor independent 1 (Gfi-1) (Zhu et al. 2009), thus preventing Th1- and Th2-cell differentiation. TGF-β also represses the expression of Blimp-1, a transcription factor that limits Th17-cell differentiation (Salehi et al. 2012). Thus, TGF-β promotes the differentiation of Th17 cells both directly and indirectly by inhibiting T-cell differentiation into other cell lineages.

Th17 cells can be both immunoregulatory and pathogenic (Sharma et al. 2013). Generation of regulatory Th17 cells is promoted by the combination of TGF-β and IL-6 (Esplugues et al. 2011; Chalmin et al. 2012; Zhao et al. 2012). Pathogenic Th17 cells, however, require further stimulation with IL-23 (McGeachy et al. 2007; Chikuma et al. 2012; Lee et al. 2012). Pathogenic Th17 cells can also be induced in cell culture without TGF-β, in the presence of IL-6, IL-1β, and IL-23 (Ghoreschi et al. 2010; Lee et al. 2012). At low concentrations, TGF-β synergizes with IL-6 and IL-21 to promote IL-23 receptor expression and Th17-cell differentiation, whereas high TGF-β concentrations repress IL-23 receptor expression and promote Treg-cell differentiation (Zhou et al. 2008). In Th17 cells, TGF-β also differentially regulates IL-22 and IL-17 expression. In the absence of TGF-β, IL-6 induces IL-22 (Basu et al. 2012); however, in the presence of TGF-β, expression of cMaf, a repressor of *Il22* gene expression, is induced (Rutz et al. 2011). Such opposing effects of TGF-β on Th17-associated cytokines may contribute to the regulatory or pathogenic functions of these cells. Intriguingly, Th17 cells transdifferentiate into regulatory T cells in a TGF-β- and aryl hydrocarbon receptor (AhR)-dependent manner at the resolution of inflammation (Gagliani et al. 2015), thus further showing the role of TGF-β in the plasticity and switch between immunity and tolerance.

TGF-β cooperates with the Notch pathway and IL-4 to induce IL-9^+IL-10^+ Th9 cells. These cells have effector rather than regulatory function, despite their ability to produce abundant levels of IL-10 (Dardalhon et al. 2008; Elyaman et al. 2012). They also play a critical and nonredundant role in host-protective type 2 immunity against gastrointestinal infection with parasitic worms (Licona-Limón et al. 2013). The ability of TGF-β and IL-4 to promote Th9-cell differentiation is enhanced by OX40 costimulation, which activates TRAF6 (the ubiquitin ligase tumor necrosis factor [TNF] receptor-associated factor 6) and, in turn, the noncanonical nuclear factor (NF)-κB pathway (Xiao et al. 2012). Additionally, Smad2 and Smad3 cooperate with IL-4-induced interferon regulatory factor 4 (IRF4) at the *Il9* locus, where they displace binding of enhancer of zeste homolog 2 (EZH2), causing derepression of chromatin modification in the locus (Tamiya et al. 2013; Wang et al. 2013). The exact contribution of TGF-β signaling to the various biological functions of Th9 cells remains to be further explored.

Tfh cells are an important component of humoral immunity as they help B cells generate antigen-specific antibody responses, and their differentiation depends on the transcription repressor Bcl6 (Crotty 2011). Together with IL-12 and IL-23, TGF-β is an important cofactor for the early differentiation of human Tfh cells in cell culture (Schmitt et al. 2014). Interestingly, TGF-β signaling in mouse $CD4^+$ T cells was also shown to be required for Tfh-cell development, although by using a different mechanism than what was shown in human cells. In response to influenza infection, TGF-β suppressed the expression of the high-affinity IL-2 receptor on virus-specific $CD4^+$ T cells, and dampened IL-2-induced Stat5 signaling and mammalian target of rapamycin (mTOR) activation in Tfh precursor cells (Marshall et al. 2015).

TGF-β plays an active role in the development and maintenance of IELs that reside in the epithelial layer of the mucosal lining and have immediate effector functions. As already discussed, TGF-β signaling is required for the thy-

mic development of CD8αα$^+$TCRαβ$^+$ IELs, and also maintains CD8α expression on peripheral T cells (Konkel et al. 2011). Once in the epithelium, IELs are maintained by the interaction between the cell-surface proteins CD103 (αEβ7) and epithelial (E)-cadherin (Cepek et al. 1993; Schon et al. 1999). CD103 shares the β7 subunit with α4β7, an integrin required for lymphocyte migration to the gut. TGF-β induces the expression of αE and enhances the constitutive expression of β7, leading to increased CD103 expression at the surface of IELs (Suzuki et al. 2002; Kang et al. 2011).

One subset of IELs, tissue-resident memory T cells (TRMs), are noncirculating memory cells that are maintained in the mucosal tissue, near the site of the first antigen encounter (Cauley and Lefrancois 2013; Schenkel and Masopust 2014). Most TRMs express CD69 and CD103 (Casey et al. 2012; Mackay et al. 2013; Skon et al. 2013). Environmental cytokines, including TGF-β, IL-33, and TNF, induce repression of Krüppel-like factor 2 (KLF2) expression and its target gene *S1pr1*. Thus, repressing sphingosine-1-phosphate receptor 1 (S1P1) and enhancing CD69 and CD103 expression allows the maintenance of TRMs in the tissue (Mackay et al. 2013; Skon et al. 2013). TGF-β is a potent inducer of CD103 expression by CD8$^+$ T cells (Fig. 1D) (El-Asady et al. 2005; Casey et al. 2012). Inactivation of TβRII expression in CD8$^+$ T cells results in a defect in the retention of intestinal TRMs in the IELs, most likely a result of the lack of CD103 expression (Zhang and Bevan 2013). In an oral model of LM infection, TGF-β signaling in CD8$^+$ T cells was required for the rapid generation of memory precursor cells that give rise to TRMs in the gut (Sheridan et al. 2014). In another oral infection study with *Yersinia pseudotuberculosis*, TGF-β signaling was required for the generation of the CD103$^+$ TRMs, but dispensable for the generation of CD103$^-$ TRMs that reside in the lamina propria and cluster with CD4$^+$ T and CX3CR1$^+$ myeloid cells (Bergsbaken and Bevan 2015). Additionally, the development of TRMs in the skin depends on TGF-β-mediated repression of T-bet and loss of Eomes expression, while forced expression of these transcription factors reduces TβRII and CD103 expression. A residual amount of T-bet is required for expression of IL-15R and IFN-γ, thus promoting TRM survival and effector function, respectively (Mackay et al. 2015). A deeper understanding of how TRMs are developed and maintained long term in various tissues will shed more light on the exact contribution of TGF-β signaling to the development and function of these memory cells.

Tolerance

Mice with impaired or total loss of TGF-β signaling in T cells develop severe autoimmunity, which shows the importance of TGF-β in controlling T-cell tolerance (Gorelik and Flavell 2000; Li et al. 2006a; Marie et al. 2006). The breach of tolerance that occurs without TGF-β signaling is not solely caused by altered activity of Treg cells (Li et al. 2006a; Marie et al. 2006), suggesting that a major mechanism by which TGF-β maintains tolerance is by directly regulating autoreactive T cells. This direct regulation is evident in a transgenic diabetes mouse model in which loss of TGF-β signaling in activated diabetogenic CD4$^+$ T cells, but not Treg cells, induces disease (Ishigame et al. 2013b). In addition, in the intestine, TGF-β signaling limits tissue damage by diverting pathogenic CD4$^+$ T cells to a nonpathogenic phenotype (Reis et al. 2013). Moreover, the control of autoreactive T cells by Treg cells in vivo may also occur through TGF-β signaling. Activated human and murine Treg cells express the glycoprotein A repetitions predominant (GARP) protein, which associates with the latent form of TGF-β, resulting in cell-surface expression of TGF-β on Treg cells (Stockis et al. 2009; Tran et al. 2009; Wang et al. 2009; Edwards et al. 2013). Indeed, active TGF-β can be generated from the membrane-bound complex of GARP and latent TGF-β (Wang et al. 2012). The activation of latent complexes of TGF-β has been reviewed (Robertson and Rifkin 2016).

Interestingly, recent studies indicate that loss of TGF-β signaling in mature T cells is not sufficient to induce autoimmunity. In stark contrast to mice in which *Tgfbr2* inactivation

occurs during the double-positive thymocyte stage of T-cell maturation (Li et al. 2006a; Marie et al. 2006), *Tgfbr2* deletion at later stages, using the distal Lck-Cre or a tamoxifen-induced Cre in mature $CD4^+$ T cells, does not induce development of overt autoimmunity (Zhang and Bevan 2012; Sledzinska et al. 2013). However, in both models, autoimmunity can be induced in *Rag*-deficient animals, suggesting that an added insult of extreme lymphopenia in combination with the absence of TGF-β signaling is required for the loss of tolerance. Notably, TGF-β signaling in double-positive thymocytes induces IL-7Rα expression, which serves a particularly important role in promoting the homeostatic survival of low-affinity TCR $CD4^+$ T cells (Ouyang et al. 2013). Thus, in the CD4-Cre model of *Tgfbr2* deletion, the absence of TGF-β signaling in developing T cells may create a lymphopenic environment, with preferential loss of low-affinity T cells, which favors activation of higher affinity autoreactive T cells. In addition, TGF-β-supported survival of low-affinity $CD4^+$ T cells may play an essential role in the maintenance of a novel regulatory population of $CD4^+$ T cells, termed "deletor" T cells, which contributes to the control of T-cell repertoire diversity and homeostasis. These deletor T cells limit the expansion of T-cell clones in a TCR-specific manner by outcompeting other T cells for subthreshold TCR ligands (e.g., positive selection ligands) that likely promote survival signals without causing overt T-cell activation (Singh et al. 2012).

B Cells

Proliferation and Survival

Early studies showed that TGF-β inhibits proliferation of mature human and immature murine B cells (Kehrl et al. 1986a; Petit-Koskas et al. 1988; Warner et al. 1992). Mechanistically, TGF-β induces growth arrest of B cells, which has been associated with decreased expression of the cell-cycle regulator cyclin A and inactivation of the cell-cycle-dependent kinase Cdk2 (Bouchard et al. 1997). TGF-β also regulates B-cell survival, as TGF-β signaling induces apoptosis in the murine B-cell line WEHI (Warner et al. 1992). Furthermore, TGF-β can promote B-cell death by inducing expression of the transcriptional E protein antagonist Id3 to stimulate apoptosis in B-cell progenitors (Kee et al. 2001).

Studies in mice with B-cell-specific loss of TGF-β signaling verified the cell-culture observations that TGF-β regulates B-cell proliferation and survival. Splenic B cells deficient in TβRII expression show increased BrdU incorporation when compared with wild-type B cells, confirming an important role for TGF-β in controlling B-cell proliferation in vivo (Cazac and Roes 2000). Mice with B-cell-specific deficiency in TGF-β signaling also show an expanded population of innate-like B cells, termed B1 cells (Cazac and Roes 2000). Interestingly, TβRII-deficient B1 cells are not characterized by increased BrdU incorporation, suggesting that their accumulation may be caused by enhanced survival in the absence of TGF-β signaling.

Activation and Differentiation

TGF-β regulates B-cell activation by inhibiting immunoglobulin synthesis and class switching to the majority of IgG isotypes (Kehrl et al. 1986a, 1991). Although mice with a B-cell-specific deficiency in TGF-β signaling do not show signs of overt autoimmunity, these cells show a more activated phenotype, are hyperresponsive to normally weak immunogens, and produce anti-dsDNA antibodies (Cazac and Roes 2000).

In contrast to TGF-β inhibiting IgG class switching, TGF-β promotes B-cell production of IgA antibodies (Coffman et al. 1989; Sonoda et al. 1989; Kim and Kagnoff 1990; Lebman et al. 1990; Ehrhardt et al. 1992; van Vlasselaer et al. 1992), which provide an important defense mechanism at mucosal barriers (Fig. 2) (Cerutti et al. 2011). Induction of IgA class switching by TGF-β is associated with increased transcription of α-germline transcripts (Lebman et al. 1990; Shockett and Stavnezer 1991) because of binding of activated Smads and Runx3 to a tandem-repeat element in the α-germline transcript promoter (Lin and Stavnezer 1992; Shi and Stavnezer 1998; Hanai et al. 1999; Pardali et al. 2000; Zhang and Derynck 2000; Park et al. 2001). Mice with B-cell-specific loss of TGF-β

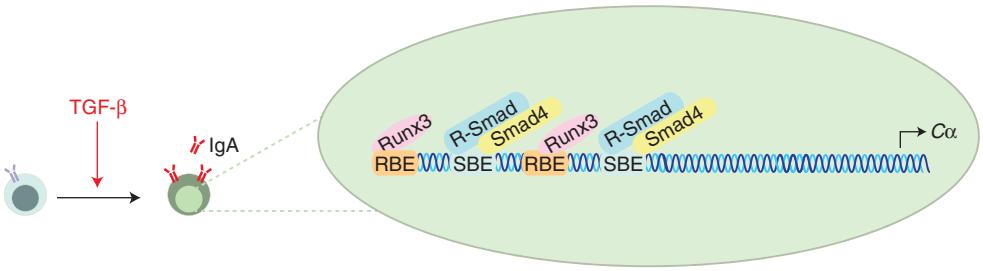

Figure 2. Regulation of IgA class switching by transforming growth factor β (TGF-β). TGF-β promotes the production of IgA antibodies by increasing the transcription of α-germline transcripts. Activated Smad3 in complex with Smad4, and Runx3 bind to Smad-binding elements (SBEs) and Runx-binding elements (RBEs), respectively, which are found in the promoter of the constant heavy chain α (*Cα*).

signaling also show dramatic reductions in serum and mucosal IgA levels (Cazac and Roes 2000; Borsutzky et al. 2004). Interestingly, whereas Smad3-deficient mice show relatively normal IgA production (Yang et al. 1999), B-cell-specific inactivation of Smad2 expression recapitulates the reduction in IgA observed in mice with TβRII-deficient B cells. This finding indicates that Smad2 has a nonredundant role in controlling responses of TGF-β-regulated IgA (Klein et al. 2006).

Dendritic Cells

Dendritic cells (DCs) are important effectors of both tolerogenic and pathogenic functions of TGF-β activity (Fig. 3A). Mice with myeloid or DC-specific loss of the αv integrins, which play key roles in integrin-mediated activation of TGF-β, develop colitis, showing that DCs play an important role in T-cell tolerance mediated by TGF-β (Lacy-Hulbert et al. 2007; Travis et al. 2007). A subset of mucosal $CD103^+$ DCs also specifically promote tolerance by inducing pTreg-cell differentiation (Coombes et al. 2007; Sun et al. 2007) likely by enabling integrin-mediated activation of TGF-β (Paidassi et al. 2011; Worthington et al. 2011). From a pathogenic perspective, DC-mediated activation of latent TGF-β also contributes to Th17-cell differentiation in vivo and the development of experimental autoimmune encephalomyelitis (EAE) (Acharya et al. 2010; Melton et al. 2010).

In addition to a role for DCs in maintaining T-cell tolerance through integrin-mediated activation of TGF-β, studies show that DCs themselves can acquire a tolerogenic phenotype on exposure to TGF-β in cell culture. TGF-β promotes the tolerogenic properties of plasmacytoid DCs (pDCs) by inducing pDC expression of the tryptophan-catabolizing enzyme indoleamine 2,3 dioxygenase (IDO) (Pallotta et al. 2011). TGF-β appears to induce expression of this enzyme in pDCs through activation of noncanonical NF-κB signaling, which promotes IDO expression in DCs (Tas et al. 2007). Besides TGF-β, culture of pDCs with IFN-γ also induces IDO expression (Mellor and Munn 2004). However, although pDCs treated with IFN-γ and TGF-β together show short-term tolerogenic functions, only pDCs cultured with TGF-β alone show long-term IDO-dependent tolerogenic activity (Pallotta et al. 2011).

TGF-β also has an inhibitory effect on DC function. Indeed, exposure of DCs to TGF-β in culture represses the antigen presentation capabilities and maturation status of developing DCs (Nandan and Reiner 1997; Yamaguchi et al. 1997; Piskurich et al. 1998; Geissmann et al. 1999; Zhang et al. 1999b). TGF-β may also exert control over DC function in part by regulating DC responses to inflammatory stimuli. Whereas TGF-β treatment of human monocyte-derived DCs that are not exposed to other inflammatory stimuli has no effect on DC-induced T-cell proliferation, human monocyte–derived DCs exposed to TGF-β be-

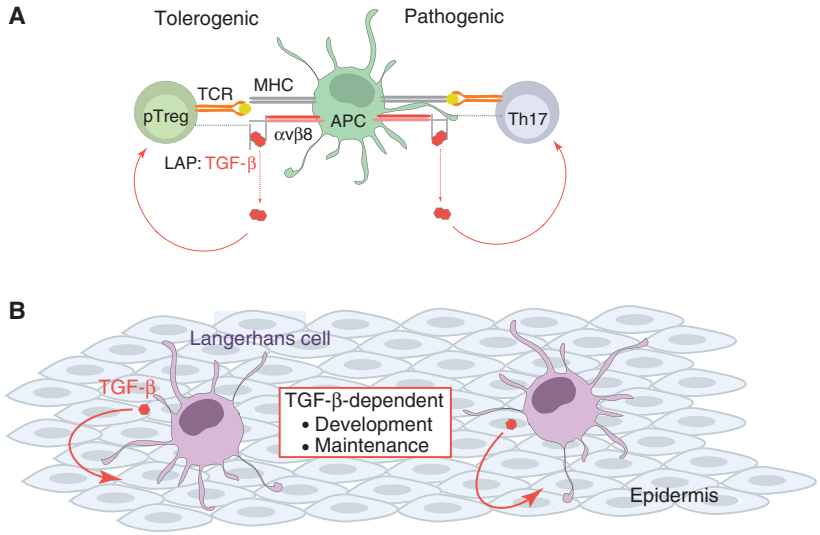

Figure 3. Regulation of dendritic cells by TGF-β. (*A*) Dendritic cells (DCs) are key effectors of TGF-β activity. TGF-β is produced in a latent form in which the mature TGF-β is noncovalently associated with the latency-associated peptide (LAP). Release of TGF-β from its association with LAP is a critical step in activation of the cytokine. Integrin-mediated activation of TGF-β by DCs promotes the generation of peripheral Treg (pTreg) cells that possess important tolerogenic functions, and induces the differentiation of pathogenic Th17 cells. (*B*) Langerhans cells are specialized DCs of the epithelia that depend on TGF-β for their development and maintenance. Autocrine TGF-β signaling is required for the maintenance of this cell population.

fore lipopolysaccharide (LPS) stimulation induce a lower degree of T-cell proliferation than LPS-only-treated counterparts (Fogel-Petrovic et al. 2007). Furthermore, human monocyte-derived DCs pretreated with TGF-β also produce reduced levels of a variety of inflammatory mediators in response to Toll-like receptor (TLR) or cytokine stimulation (Fogel-Petrovic et al. 2007). Notably, the ability of TGF-β to modulate the activation of a DC is determined by the stimulation conditions. Although TGF-β can inhibit DC maturation induced by cytokines, TLR ligands, or Fc-receptor engagement, engagement of the costimulatory CD40 receptor overrides the suppressive effect of TGF-β on DC maturation (Geissmann et al. 1999).

Efforts to unravel how TGF-β signaling regulates DC function in vivo have yielded less clear conclusions. Despite evidence supporting the inhibitory effects of TGF-β on DC function in culture, TβRII-deficient splenic DCs showed no difference in their activation status, based on the expression of MHC class II and costimulatory molecules when compared with their wild-type counterparts (Ramalingam et al. 2012). Yet, mice with CD11c-Cre-mediated deletion of *Tgfbr2* in DCs succumbed to a systemic autoimmune disorder, the major manifestation of which is gastritis. Gene-expression analyses of TβRII-deficient splenic and mesenteric lymph node DCs indicated some changes in cytokine, chemokine, and chemokine receptor expression patterns, but whether and how these phenotypic alterations contribute to the manifestation of autoimmunity remains unknown. In addition, how TGF-β signaling affects DCs in nonlymphoid tissues, such as the stomach or intestines, has not been examined, and a major question that remains is whether the sensitivity of DCs to TGF-β regulation is determined by the identity and/or location of DCs.

TGF-β plays an important role is the biology of Langerhans cells, which are specialized DCs of the epithelia that possess important immunological and tolerogenic functions (Roma-

ni et al. 2010). TGF-β was first implicated as a regulator of Langerhans cells by the observation that mice with global inactivation of *Tgfb1* expression lack this specific DC population (Borkowski et al. 1996). Cell-culture studies subsequently showed that TGF-β induces Langerhans cell differentiation of a variety of human-derived precursor cells (Strobl et al. 1996; Geissmann et al. 1998; Zhang et al. 1999b). The role of TGF-β in Langerhans cell biology is further supported by studies using mouse lines with conditional deficiency of TβRI or TβRII, which established that TGF-β directly regulates the development and maintenance of Langerhans cells (Kaplan et al. 2007; Kel et al. 2010; Zahner et al. 2011). Additionally, mice in which TβRII or TGF-β1 were deleted specifically in Langerhans cells phenocopied each other, showing that this pathway, and specifically autocrine TGF-β signaling, is critical for the development or maintenance of Langerhans cells (Fig. 3B) (Kaplan et al. 2007). In addition, TGF-β signaling increases recruitment of the transcription factor PU.1 to the promoter and intronic regions of the *Runx3* gene (Chopin et al. 2013), which encodes a critical transcription factor in Langerhans cell development (Fainaru et al. 2004).

It has been proposed that, in the intestinal lamina propria, a combination of TGF-β and bacterial sensing regulates the tolerogenic properties of gut DCs, largely by controlling DC production of TGF-β, which is suggested to direct pTreg-cell generation (Kashiwagi et al. 2015). Notably, although autocrine TGF-β signaling confers enhanced TGF-β expression in DCs, the TGF-β-activated Smads appear to play opposing roles in this regulation with Smad3 promoting and Smad2 inhibiting TGF-β production. DCs that lack only Smad2 express higher levels of mRNA for TGF-β1 and IL-10, and lower levels of mRNA for inflammatory cytokines, for example, TNF-α, IL-6, and IL-12, and show tolerogenic activity. However, despite the indication that autocrine TGF-β signaling promotes TGF-β production in DCs, whether DCs represent the critical source of TGF-β for pTreg-cell differentiation, as proposed (Kashiwagi et al. 2015), remains to be validated by genetic methods, for example, using CD11c-Cre-mediated deletion of floxed *Tgfb1*. Indeed, it has been shown that T cells themselves are the essential source of TGF-β for Th17 differentiation (Li et al. 2007; Gutcher et al. 2011).

NK Cells

TGF-β has a general inhibitory effect on the development and function of NK cells. In neonates, blocking TGF-β signaling on NK cells promotes faster NK maturation and reduces susceptibility of neonates to viral infection (Marcoe et al. 2012). In adults, TGF-β inhibits IFN-γ and T-bet expression in NK cells, thus inhibiting type 1 immunity (Laouar et al. 2005; Yu et al. 2006). Reciprocally, proinflammatory cytokines can down-regulate TβRII expression and inhibit TGF-β signaling in NK cells (Yu et al. 2006). Additionally, TGF-β expressed by T cells may inhibit proliferation of NK cells in vivo after they become activated by infection with acute lymphocytic choriomeningitis virus (LCMV) (Su et al. 1991, 1993), or by hepatitis B virus (HBV) infection in humans (Sun et al. 2012). NK cells express activating receptors at their surface, including NKG2D and NKp30, whose expression is suppressed by TGF-β (Castriconi et al. 2003; Lee et al. 2004; Crane et al. 2010). The expression of NKG2D at the cell surface requires its association with the intracellular adaptors DAP10 or DAP12 to stabilize the complex. Although IL-2 signaling stabilizes the cell-surface expression of activating NKG2D–DAP10 receptor complexes, TGF-β prevents this interaction by inhibiting the expression of DAP10 (Park et al. 2011; Sun et al. 2012). TGF-β also induces miR-183 expression to repress DAP12 expression, which destabilizes the NKG2D receptors at the surface of NK cells and inhibits their downstream signals (Donatelli et al. 2014).

Monocytes and Macrophages

Early work examining TGF-β regulation of myeloid cells showed that TGF-β largely inhibits the proinflammatory response of macrophages activated by TLR ligands or cytokine stimula-

tion (Li et al. 2006b). However, stimulation with TGF-β alone, in the absence of TLR ligands or other cytokines, promotes myeloid cell production of several inflammatory cytokines (Wahl et al. 1987; Chantry et al. 1989; Musso et al. 1990; Turner et al. 1990). TGF-β also induces migration of monocytes and macrophages isolated from human peripheral blood (Wahl et al. 1987), and enhances the adherent properties of monocytes (Bauvois et al. 1992; Wahl et al. 1993b). The distinct effects of TGF-β on myeloid cell function, which depend on the specific nature of the activating conditions, reflect the complex and pleiotropic nature of this cytokine. Furthermore, the regulation of myeloid cells by TGF-β appears to be influenced by the identity of the cell. For example, depending on their anatomic origin, some subsets of macrophages show more sensitivity to TGF-β signaling than others (Fan et al. 1992). In addition, in chemotaxis studies, blood monocytes, but not intestinal macrophages, were found to traffic in response to TGF-β signaling (Smythies et al. 2006). Nevertheless, determining whether and how TGF-β regulates distinct myeloid cell populations in vivo remains elusive.

The intestine may be an anatomic location where regulation of myeloid cells by TGF-β is of particular importance. The intestine is a unique tissue in which the maintenance of resident macrophages relies on continuous input from circulating monocytes (Ginhoux and Jung 2014). In this context, TGF-β may induce trafficking of monocytes and promote their differentiation into noninflammatory macrophages that reside in the tissue. Indeed, after prolonged exposure to TGF-β, human blood monocytes begin to acquire a less activated phenotype, illustrated by down-regulation of innate response receptor expression and reduced cytokine production (Smythies et al. 2005). Notably, this altered phenotype resembles the less inflammatory profile that characterizes human intestinal macrophages. These macrophages produce no or only limited amounts of inflammatory cytokines in response to a variety of stimuli, despite maintaining their phagocytic and bacteriocidal functions (Smythies et al. 2005). The ability of these macrophages to perform the functions needed for tissue health, while tightly regulating inflammatory cytokine secretion, is likely an essential feature in maintaining intestinal tolerance and homeostasis. Indeed, mice with expression of dnTβRII from the CD68 promoter, which is primarily expressed in monocytes and macrophages, show loss of TGF-β inhibition of LPS-induced cytokine production. These mice are also more susceptible to dextran sulfate sodium (DSS)-induced colitis, showing that TGF-β controls monocytes and/or macrophages to regulate intestinal inflammation (Rani et al. 2011).

The exact mechanism by which TGF-β regulates the inflammatory response of myeloid cells in vivo remains largely unknown. However, TGF-β may promote suppression of TLR signaling. For example, in myeloid cells, TGF-β induces and maintains expression of Axl (Bauer et al. 2012), a member of the Tyro3, Axl, and Mer (TAM) receptor tyrosine kinase family that inhibits innate immune inflammatory responses (Sharif et al. 2006; Rothlin et al. 2007). Indeed, blocking Axl increased cytokine production after TLR stimulation (Bauer et al. 2012).

In addition, several cell-culture studies indicate that TGF-β may also control myeloid cell activation by directly inhibiting NF-κB signaling activated by innate receptors or cytokines (Naiki et al. 2005; Choi et al. 2006; Hong et al. 2007; Lee et al. 2011). TLR engagement is a major pathway of microbial recognition, and multiple adaptor proteins, including MyD88 (myeloid differentiation primary response protein 88), TRIF (Toll/IL-1R [TIR] domain-containing, adaptor-inducing interferon-β), and TRAM (TRIF-related adaptor molecule) mediate signal transduction downstream from these innate receptors. Studies using the RAW macrophage cell line show that TGF-β represses MyD88-dependent, but not TRIF- or TRAM-dependent, TLR signaling (Naiki et al. 2005). TGF-β inhibits this pathway by promoting the ubiquitylation and degradation of MyD88 (Naiki et al. 2005; Lee et al. 2011), which involves Smad6 and the E3 ubiquitin ligases Smurf1 and Smurf2 (Lee et al. 2011). TGF-β also impedes NF-κB activation by sequestering the adaptor protein pellino-1 and, consequent-

ly, disrupting the formation of a signaling complex containing IRAK1 (IL-1-receptor-associated kinase 1), TRAF6, and MyD88 downstream from IL-1R/TLR activation (Choi et al. 2006). Both Smad6 and Smad7 can interact with pellino-1 through discrete sequences in their respective MH2 domains, which allows simultaneous interactions with the adaptor protein (Choi et al. 2006; Lee et al. 2010). In addition to controlling the responses of receptors that recognize microbial patterns, TGF-β inhibits NF-κB activation downstream from TNF-α signaling by promoting interactions between Smad7 and the adaptor proteins TAB2 (TAK1 binding protein 2) and TAB3. These components are part of the signaling complex that forms after activation of the TNF-α pathway (Hong et al. 2007). These findings indicate important cross talk between TGF-β and NF-κB signaling. How these interactions shape myeloid cell biology in vivo remains to be determined.

Granulocytes

Granulocytes are innate immune cells that are identified by the presence of dense granules in their cytoplasm, and are also termed polymorphonuclear leukocytes for their distinctly shaped nuclei. This subset of innate immune cells has important functions in infection and inflammation, and includes neutrophils, eosinophils, and basophils. TGF-β induces chemotaxis of both neutrophils (Brandes et al. 1991; Fava et al. 1991; Reibman et al. 1991) and eosinophils (Luttmann et al. 1998). At the molecular level, Smad3 may be required for TGF-β-induced neutrophil migration, as *Smad3*$^{-/-}$ neutrophils show impaired chemotactic responses (Yang et al. 1999). However, TGF-β can also inhibit neutrophil migration by suppressing TNF-α–induced endothelial cell production of IL-8, a known neutrophil chemoattractant (Smith et al. 1996). Under some conditions, TGF-β may also promote neutrophil oxidant production (Brandes et al. 1991; Balazovich et al. 1996). Alternatively, TGF-β can act as a negative regulator of granulocytes, and inhibits the survival of human eosinophils by promoting apoptosis and inhibiting cytokine production (Alam et al. 1994). Despite these observations, the extent to which TGF-β regulates the granulocytic arm of the innate immune system remains poorly understood.

Mast Cells

Mast cells have been predominantly associated with allergy responses, but a growing understanding of mast cell functions has identified additional roles for these cells in wound healing, tissue repair, and infections. Similar to other innate immune cells, TGF-β can induce chemotaxis and enhance the adherent properties of mast cells (Gruber et al. 1994; Olsson et al. 2000; Rosbottom et al. 2002). TGF-β has been reported to promote or suppress mast cell function. As part of its negative regulatory functions, TGF-β inhibits the expression of the high-affinity IgE receptor FcεRI, a mechanism that activates mast cells (Gomez et al. 2005). TGF-β was also reported to inhibit mast cell proliferation, degranulation, and production of several effector molecules (Broide et al. 1989; Bissonnette et al. 1997; Gebhardt et al. 2005; Gomez et al. 2005). However, in mast cells, TGF-β can also promote expression of inflammatory mediators, such as IL-6 and lymphotactin (Rumsaeng et al. 1997; Miller et al. 1999; Ganeshan and Bryce 2012).

TGF-β CONTROLS IMMUNE RESPONSES

Fetal–Maternal Tolerance

Treg cells are essential for suppressing destructive alloantigenic immunity during pregnancy (Zenclussen 2006; Munoz-Suano et al. 2011; Robertson et al. 2013). These cells are peripherally induced, as their differentiation depends on both paternal antigens and the conserved noncoding sequence-1 (CNS1) enhancer element that contains a Smad-binding site at the *Foxp3* locus (Zheng et al. 2010; Rowe et al. 2012; Samstein et al. 2012). Female mice that lack CNS1 have higher rates of embryo resorption when mated with allogeneic, but not syngeneic, males, confirming that pTreg cells modulate

maternal immune responses to paternal alloantigens during pregnancy (Samstein et al. 2012). In addition, during secondary pregnancy, these fetal-specific Treg cells are maintained as a memory pool with accelerated expansion, which provides more resistance to embryo resorption if Treg cells are partially ablated (Rowe et al. 2012). The importance of pTreg-cell generation in fetal–maternal tolerance has prompted much interest in understanding the biological source of TGF-β in this process.

The female reproductive tract (FRT) is a rich environment for TGF-β production and responsiveness (Zhao et al. 1994; Polli et al. 1996). TGF-β production is regulated by ovarian sex hormones and enables several aspects of immunosuppression in the FRT at different stages of the menstrual cycle (Chegini et al. 1994; Takahashi et al. 1994; Wira and Rossoll 2003; Kim et al. 2005; Maurya et al. 2013). Accordingly, hormone-regulated fluctuations occur in systemic and uterine Treg-cell populations, with an estrogen-regulated increase at the time of ovulation (Arruvito et al. 2007). Additionally, in vaginal cells, estradiol regulates tolerance induction and antigen presentation by mediating the local production of TGF-β (Wira et al. 2002; Wira and Rossoll 2003). Furthermore, endogenous TGF-β in the human endometrium suppresses the activity of uterine NK cells (Eriksson et al. 2004, 2006).

Several studies have linked Treg-cell expansion in early pregnancy with exposure to male seminal fluid. Semen provides both male alloantigens and immunomodulatory factors that sufficiently exert biological influences in the FRT, such as activating cytokine gene expression and eliciting changes in the abundance and behavior of infiltrating leukocyte populations. These responses promote tolerance and receptivity for embryo implantation (Robertson 2005; Robertson et al. 2013). The mechanisms underlying immunological suppression by semen are not clearly defined but appear related, at least in part, to extremely high concentrations of TGF-β and prostaglandin (PG)E_2 (Robertson et al. 2002, 2009b). Seminal plasma contains high concentrations of TGF-β, nearly 500 ng/ml, which is approximately fivefold higher than that of serum (Saito et al. 1993; Nocera and Chu 1995; Loras et al. 1999). In seminal fluid, TGF-β induces Treg-cell expansion and promotes tolerance to paternal alloantigens in mice (Robertson et al. 2009a). Exogenous TGF-β delivered at conception also boosts the numbers of vaginal Treg cells and helps reduce fetal loss in the CBA/J × DBA/2J spontaneous abortion model (Clark et al. 2008). Thus, seminal TGF-β has been implicated as a key factor in initiating the remodeling events and immunological changes that occur in the uterus during the preimplantation period of pregnancy (Robertson et al. 2002, 2013).

Mucosal Immune Responses

Development of the Gut Barrier

After leaving the sterile intrauterine environment, neonates enter a world full of innocuous environmental antigens, as well as harmful pathogens. Gradual and age-dependent maturation of the immune system fulfills several demands, such as preparing the skin and intestine for colonization by commensal bacteria, tolerizing the host for exposure to food and environmental antigens, and protecting against pathogenic infections (PrabhuDas et al. 2011). TGF-β preserves the intestinal barrier function (Planchon et al. 1994, 1999; Jarry et al. 2008), and its production in the intestine is age-dependent (Zhang et al. 1999a; Maheshwari et al. 2011). For example, rodent pups initially produce low levels of endogenous intestinal TGF-β, which increase during the weaning period (Penttila et al. 1998).

Although still controversial, mammalian milk is thought to provide an important exogenous source of TGF-β to the infant until it can fully produce endogenous TGF-β (Prokesova et al. 2006; Oddy and Rosales 2010; Penttila 2010). In mammalian milk, TGF-β is present at high concentrations and may be a key immunoregulatory factor for promoting intestinal maturation (Rautava et al. 2012), IgA production, and tolerance induction (Letterio et al. 1994; Hawkes et al. 1999; Kalliomaki et al. 1999; Lebman and Edmiston 1999; Donnet-

Hughes et al. 2000; Saarinen et al. 2000; Ogawa et al. 2004; Verhasselt et al. 2008; Verhasselt 2010; Arnold et al. 2011).

Microbiome

The composition of the intestinal microbiota regulates the balance between Th17 and Treg cells in the lamina propria and influences intestinal homeostasis (Honda and Littman 2012). Treg-cell numbers are increased in the colonic lamina propria compared with other organs, and these numbers are reduced in germ-free or antibiotics-treated mice, suggesting that the nature of the microbiota affects colonic pTreg-cell differentiation (Atarashi et al. 2011; Honda and Littman 2012). A cocktail of 17 strains of bacteria, belonging to the clusters of *Clostridium* species, isolated from the stool of a healthy human provided bacterial antigens and a TGF-β-rich environment to support the expansion of Treg cells in germ-free mice (Atarashi et al. 2013). Th17 cells are also induced in the small intestinal lamina propria in the presence of members of the cytophaga–flavobacter–bacteroides phylum, which requires TGF-β activity (Ivanov et al. 2008).

Inflammatory Bowel Disease

IL-10 and TGF-β play nonredundant roles in maintaining intestinal homeostasis (Fiocchi 2001; Izcue et al. 2009; Feagins 2010; Jarry et al. 2011; Biancheri et al. 2014). IL-10 functions both upstream and downstream in TGF-β signaling (Fuss et al. 2002; Kitani et al. 2003). For example, IL-10 can induce TGF-β expression and secretion in T cells of the lamina propria (Zhou et al. 1998; Fuss et al. 2002). Additionally, it cooperates with TGF-β to promote differentiation of Treg cells (Weiner 2001; Di Giacinto et al. 2005), which produce more TGF-β and IL-10 (Harrison and Powrie 2013). Mutations in genes encoding components of TGF-β and IL-10 signaling pathways have been implicated in human inflammatory bowel disease (IBD) (Glocker et al. 2009; Franke et al. 2010; McGovern et al. 2010; Naviglio et al. 2014). Indeed, when both of these pathways are simultaneously genetically blocked, mice develop severe fulminant ulcerative colitis caused by the microbially induced proinflammatory cytokines IFN-γ and TNF-α (Kang et al. 2008).

Similarly, in IBD patients, Smad7 overexpression in mucosal T cells inhibits TGF-β signaling, causing uncontrolled production of inflammatory cytokines (Fiocchi 2001; Monteleone et al. 2001). In IBD patients, Smad7 protein is more highly stabilized by p300-mediated posttranslational acetylation compared with healthy controls (Monteleone et al. 2005), potentially making the cells more resistant to Treg-cell-mediated suppression (Fantini et al. 2009). Indeed, overproduction of TGF-β has been reported (Feagins 2010), which may cause the loss of protective cells that produce IL-22 (Leung et al. 2014). Regardless of the abundance of environmental TGF-β, high Smad7 levels block TGF-β signaling in pathogenic T cells (Fiocchi 2001). IL-25 can limit proinflammatory cytokine production and chronic intestinal inflammation (Owyang et al. 2006). TGF-β induces, whereas TNF-α inhibits, IL-25 production in the human gut, and knockdown of Smad7 increases IL-25 production (Fina et al. 2011). Oral administration of Smad7 antisense oligonucleotides can restore TGF-β signaling and ameliorate inflammation in hapten-induced colitis (Boirivant et al. 2006), suggesting that blocking Smad7 may be a promising and safe method to dampen inflammation in IBD patients (Monteleone et al. 2008, 2012; Marafini et al. 2013).

Autoimmune Diseases

Arthritis

Rheumatoid arthritis (RA) is an inflammatory disorder that targets the joints and is driven by aberrant responses in T and B cells. The effects of TGF-β on RA development appear to be determined by the anatomical context of cytokine signaling, as local versus systemic modulation of TGF-β activity has opposing effects on disease development in rodent models of RA. For example, injecting TGF-β into the joints of Lewis rats induces synovial inflammation and

joint swelling associated with macrophage infiltration and increased expression of IL-1β (Allen et al. 1990). Correspondingly, administering a TGF-β blocking antibody into a joint ameliorates group A streptococci–induced arthritis (Wahl et al. 1993a). In contrast, studies in the collagen-induced arthritis model indicate that systemic TGF-β signaling protects against disease development (Kuruvilla et al. 1991; Thorbecke et al. 1992). These protective effects are, in part, mediated by direct regulation of T cells, as mice with T-cell-specific expression of the dnTβRII subunit develop more severe arthritis (Schramm et al. 2004).

Diabetes

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease driven by immune-mediated destruction of pancreatic islet β cells. Multiple models of pancreas-specific overexpression of active TGF-β show that TGF-β inhibits diabetes development (King et al. 1998; Moritani et al. 1998; Grewal et al. 2002). Protection against T1D is associated with the induction of tolerogenic T-cell responses, suggesting that TGF-β regulates diabetogenic T cells to prevent disease (King et al. 1998; Moritani et al. 1998). Indeed, coadministering a TGF-β blocking antibody reverses the protective effects of CD3-specific antibody treatment in the nonobese diabetic (NOD) model (Belghith et al. 2003). Studies using a model of diabetes in which $CD4^+$ T cells express a transgenic TCR that recognizes a pancreas-specific peptide clearly show the importance of TGF-β in directly regulating the response of effector T cells to prevent diabetes (Ishigame et al. 2013b). Whereas deleting TβRII expression in activated effector T cells induces diabetes development, Treg-cell-specific loss of TGF-β signaling has no effect on disease pathogenesis (Ishigame et al. 2013b).

Multiple Sclerosis

EAE is the animal model system that is commonly used to study the central nervous system disorder multiple sclerosis (MS). Administering TGF-β has a protective effect in several murine models of EAE (Johns et al. 1991; Kuruvilla et al. 1991; Racke et al. 1991), suggesting that TGF-β inhibits disease development. Indeed, two models of EAE showed that suppression of disease by tolerogenic $CD4^+$ T cells depends on TGF-β activity (Chen et al. 1994, 2008). In accordance, T-cell lines derived from patients with stable MS produce more TGF-β than those from patients with active MS, suggesting that disease severity may associate inversely with levels of TGF-β production (Mokhtarian et al. 1994).

Interestingly, TGF-β signaling also promotes differentiation of Th17 cells that induce EAE development. $CD4^+$ T cells that express a dnTβRII do not differentiate into Th17 cells, and mice expressing a dnTβRII under the control of the CD4 promoter are resistant to EAE, indicating that TGF-β signaling is critical for the in vivo generation of pathogenic Th17 cells and EAE development (Veldhoen et al. 2006b). Furthermore, genetic studies show that autocrine TGF-β signaling is required for in vivo Th17 differentiation, as mice with T-cell-specific deletion of *Tgfb1* do not develop Th17 cells and are resistant to EAE (Li et al. 2007; Gutcher et al. 2011). In contrast, cell-culture studies suggest that treatment of $CD4^+$ T cells with TGF-β1 produces nonpathogenic Th17 cells that fail to induce EAE (McGeachy et al. 2007; Ghoreschi et al. 2010), whereas treatment with TGF-β3 induces a pathogenic Th17 population that causes disease (Lee et al. 2012). However, the ability of TGF-β3 to induce pathogenic Th17 cells in vivo (e.g., by using T-cell-specific *Tgfb3* knockouts) has not been explored.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by autoantibody production that affects multiple organs. Administering a vector that encodes TGF-β1 enhances survival and ameliorates disease severity in a murine model of lupus, suggesting that TGF-β plays a protective role in disease (Raz et al. 1995). In general, SLE patients produce lower levels of TGF-β when compared with healthy individuals (Ohtsuka et al.

1998, 1999; Becker-Merok et al. 2010). Total TGF-β levels were lowest in hospitalized patients with active disease, suggesting that TGF-β production may be associated with disease severity (Ohtsuka et al. 1999). This is supported by a survey of 102 SLE patients in which TGF-β levels associate inversely with disease severity (Becker-Merok et al. 2010).

Infection

Bacterial

The route by which a pathogen infects its host can determine the arm of protective immunity that the host elicits against that pathogen. For example, oral infection with *Yersinia enterocolitica* promotes Th17-mediated immunity, whereas systemic infection promotes Th1-mediated immunity (DePaolo et al. 2012). Vaginal *Neisseria gonorrhoeae* induces TGF-β production, which inhibits a protective Th1-cell response while promoting a Th17 response (Liu et al. 2012). Other mucosal pathogens, such as *Citrobacter rodentium,* induce Th17-cell responses by promoting apoptosis of intestinal epithelium, and producing TLR-containing apoptotic cells that induce both IL-6 and TGF-β production (Torchinsky et al. 2009; Brereton and Blander 2010). However, without normal production of inflammatory cytokines, high TGF-β levels produced by infected intestinal epithelium can also lead to defects in proper activation of T cells against mucosal pathogens, as apparent during *Helicobacter pylori* infection (Beswick et al. 2011).

Viral

Influenza virus neuraminidase activates latent TGF-β (Schultz-Cherry and Hinshaw 1996), which protects the host from influenza pathogenesis and virus-mediated pathology in the lung (Carlson et al. 2010). Although TGF-β protects against excessive pathology during acute viral infections, it can have a detrimental effect on T-cell immunity during chronic viral infections. For example, during LCMV infection, sustained TGF-β expression and Smad2 activation cause apoptosis of virus-specific $CD8^+$ T cells, and genetic blockade of TGF-β signaling using dnTβRII rapidly eradicates the virus (Tinoco et al. 2009). However, blocking the TGF-β receptor during the early memory phase failed to substantially enhance the antiviral T-cell response or reduce viral titers in vivo (Boettler et al. 2012), suggesting that TGF-β may exert its apoptotic effect on clonally expanding effector cells rather than on exhausted T cells (Sanjabi et al. 2009; Tinoco et al. 2009). Therapeutically blocking TGF-β signaling before viral infection significantly increases viral-specific T cells; however, it also fails to improve T-cell function or the ability of T cells to clear chronic LCMV infection. These findings suggest that the inflammatory environment and the potential difference in T-cell repertoire in mice expressing a dnTβRII in T cells may contribute to their ability to clear chronic viral infection, as originally reported by Tinoco et al. (2009). In a fourth study of chronic LCMV infection, TβRII expression was increased in $CD8^+$ T cells, but conditionally inactivating *Tgfbr2* expression in peripheral T cells decreased the expansion of $CD8^+$ T cells yet did not affect their function or exhaustion (Zhang and Bevan 2013). Thus, the exact role of TGF-β signaling on the expansion, function, and exhaustion of $CD8^+$ T cells during chronic viral infection remains unclear.

In human studies, serum TGF-β levels are increased in patients with HBV or hepatitis C virus (HCV), which contributes to the liver fibrosis often seen with these chronic viral infections (Alatrakchi et al. 2007; Khorramdelazad et al. 2012; Karimi-Googheri et al. 2014). Furthermore, *TGFB1* genetic polymorphisms have been associated with higher systemic TGF-β levels and worse outcome in hepatic viral infections (Dai et al. 2008; Pereira et al. 2008). Viral-specific proteins have also been shown to enhance TGF-β production and its cellular activity. The HBV-encoded pX oncoprotein enhances transcriptional activity of TGF-β by stabilizing the Smad complex on the transcriptional machinery (Lee et al. 2001), whereas the HCV nonstructural protein 4 (NS4) induces TGF-β expression in monocytes (Rowan et al. 2008). The HCV core protein can also activate TGF-β, and mice that overexpress HCV core

protein through transgenic expression in the liver, show deregulated expression of TGF-β target genes (Benzoubir et al. 2013). Finally, TGF-β produced by hepatic cells can induce Treg-cell generation, which can further dampen antiviral immunity and contribute to chronic hepatic viral infections (Dunham et al. 2013; Karimi-Googheri et al. 2014).

TGF-β1 expression is also increased in HIV-infected patients and correlates with disease progression (Lotz and Seth 1993; Wiercinska-Drapalo et al. 2004). HIV tat protein has been linked to high TGF-β secretion in infected cells (Wahl et al. 1991; Zauli et al. 1992; Lotz et al. 1994; Sawaya et al. 1998; Reinhold et al. 1999). The association of viral gp160 with CD4 on monocytes can also induce TGF-β production (Hu et al. 1996). TGF-β induces C-X-C chemokine receptor type 4 (CXCR4) expression on macrophages, contributing to enhanced tropism of HIV for both CD4 T cells and macrophages (Chen et al. 2005). TGF-β1 production by monocytes may also cause HIV-induced apoptosis of $CD4^+$ T cells and consequent depletion in vivo (Wang et al. 2001). Conversely, TGF-β represses CD4 and C-C chemokine receptor type 5 (CCR5) expression, and inhibits NF-κB activation, thus limiting HIV replication in intestinal macrophages (Shen et al. 2011). Interestingly, TGF-β induces the expression of CD169, which is a main HIV-1 receptor expressed on mucosal DCs that captures virus and transmits it to target cells; thus, TGF-β found in semen may contribute to sexual transmission of the virus (De Saint Jean et al. 2014). Infecting human $CD4^+$ T cells with HIV induces TGF-β production that further promotes Treg-cell generation specific to the gp120 surface viral antigen (Amarnath et al. 2007; Stevceva et al. 2008). However, infection of Treg cells with HIV represses Foxp3 expression, reduces the generation of TGF-β, and increases IL-4 production, thus limiting Treg-cell function (Pion et al. 2013) and likely contributing to chronic inflammation seen in HIV-infected patients. TGF-β produced in the mucosal lymph nodes during HIV infection can also induce apoptosis of activated $CD8^+$ T cells (Cumont et al. 2007), whereas promoting the generation of NKT cells, which share properties of both T cells and NK cells, which produce IL-17 (Campillo-Gimenez et al. 2010). Furthermore, the HIV envelope protein gp120 can bind to α4β7 integrins on naïve B cells to induce TGF-β and Fc receptor-like 4 (FcRL4) expression, which causes B-cell dysfunction and inhibits their proliferation (Jelicic et al. 2013). Furthermore, TGF-β is an important mediator of pathological fibrosis, and promotes collagen deposition in lymphoid organs in response to HIV- or SIV (simian immunodeficiency virus)-induced inflammation. This effect disrupts IL-7 production in lymph nodes, which can eventually contribute to depletion of $CD4^+$ T cells (Estes et al. 2007; Zeng et al. 2011).

When rhesus macaques are infected with SIV, they develop AIDS-like syndromes that are accompanied by massive inflammation, similar to HIV-infected patients; however, African green monkeys (AGM) infected with SIV remain healthy and do not show this chronic inflammation (Chahroudi et al. 2012). SIV-infected AGMs show early and strong increases in IL-10, TGF-β, and Foxp3 expression, which oppose findings in infected macaques that show diminished sensitivity to TGF-β signaling in T cells (Kornfeld et al. 2005; Ploquin et al. 2006).

One of the hallmarks of AIDS is HIV-mediated immunodeficiency against other pathogenic and nonpathogenic organisms. TGF-β may play an active role in this process. In HIV and HCV coinfections, HIV-induced TGF-β expression promotes both HCV replication and advanced liver fibrosis (Lin et al. 2008). Similarly, HIV-infected macrophages produce high levels of TGF-β and permit the survival and multiplication of otherwise nonpathogenic parasites (further discussed below) (Barreto-de-Souza et al. 2008).

Parasitic

During acute *Trypanosoma cruzi* and *Leishmania* infection, TGF-β production inhibits macrophage function, including IFN-γ production and increased pathogen replication (Silva et al. 1991; Barral-Netto et al. 1992; Barral et al. 1993). Conversely, malaria infection leads to ac-

tivation of latent TGF-β, whose production correlates with protective immune responses. This effect results in slowed parasite growth early on, and less pathology late in infection (Omer and Riley 1998; Omer et al. 2003). TGF-β-mediated induction of Treg-cell differentiation is also associated with higher rates of parasite growth after malaria infection in humans (Walther et al. 2005; Scholzen et al. 2009), and inhibiting TGF-β activity results in more robust $CD8^+$ T-cell responses and protection against reinfection in mice (Ocana-Morgner et al. 2007). As helminth parasites stimulate TGF-β production and Treg-cell induction, they may, in fact, protect the host from allergic diseases (Dittrich et al. 2008; Grainger et al. 2010).

CONCLUDING REMARKS

Studies in the past three decades have revealed the remarkably diverse and important functions of TGF-β in the immune system, and its penetrating control of immune responses under pathophysiological conditions. These discoveries support the notion that immune regulatory mechanisms, established by coopting cell signaling pathways that are evolutionarily conserved, work in concert with mechanisms of both innate and adaptive immune recognition to ensure well-ordered immune activities. Future investigations will define the precise cellular and molecular mechanisms of immune regulation by TGF-β, and will explore targeting this pleiotropic cell signaling pathway for therapies to treat pathogenic immune disorders.

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