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Review

TGF-β: A Master of All T Cell Trades

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A functional adaptive immune system depends on a diverse and self-tolerant population of T lymphocytes that are generated in the thymus and maintained in the peripheral lymphoid organs. Recent studies have defined the cytokine transforming growth factor-β (TGF-β) as a critical regulator of thymic T cell development as well as a crucial player in peripheral T cell homeostasis, tolerance to self antigens, and T cell differentiation during the immune response. The unique mechanism of TGF-β activation and the plasticity of TGF-β signaling create a stage for TGF-β to integrate signals from multiple cell types and environmental cues to regulate T cells.

Introduction

The defining feature of a functional immune system is the ability to correctly discern foreign pathogenic antigens from self- or other innocuous antigens and to mount an effective immune response. T lymphocytes are the key components of the cellular arm of the adaptive immune system. Elucidation of the mechanisms underlying T cell regulation during the immune system steady state and pathogen invasion is fundamental to the understanding of immune system function. Studies of T cell regulation have begun to shed light on the pervasive and essential role that the regulatory cytokine transforming growth factor-β (TGF-β) plays in T cell development, homeostasis, tolerance, and the immune response, thereby providing a means to grasp the underlying principles of T cell biology. This review will discuss recent progress in understanding the regulation of T cells by TGF-β.

T lymphocytes express T cell receptors (TCRs) that recognize antigens in association with molecules of the major histocompatibility complex (MHC) (Box 1). The stochastic process by which a pool of TCRs with different antigen-binding specificities is generated creates the inherent problem that some receptors have a high affinity for self-antigens or for innocuous environmental antigens such as those from commensal organisms. Thus, to ensure immune system homeostasis and to prevent an autoimmune response provoked by T cell recognition of self-antigens, T cells are subjected to selection in the thymus before they migrate to the peripheral lymphoid organs. T cells bearing TCRs with low affinity for MHC–self-antigen complexes are favored in this thymic selection, whereas T cells expressing TCRs with high affinity for MHC–self-antigen are eliminated through apoptosis (Starr et al., 2003). This purge of high-affinity T cell clones from the T cell repertoire is not an infallible process. As a consequence of incomplete presentation of self-antigens in the thymus and the plasticity of TCR recognition of antigens, autoreactive T cells are present in the peripheral lymphoid organs of healthy individuals (Danke et al., 2004). Therefore, other regulatory mechanisms in addition to thymic selection must hold these autoreactive T cells in check and keep them from triggering autoimmune disease. Once low-affinity T cell clones have undergone the maturation process in the thymus, they relocate to the peripheral lymphoid organs, where they are maintained as a nonproliferating, diverse population of naive T cells with a half-life of at least 6 months in mice (Jameson, 2005). Should infection occur, naive T cells that recognize foreign antigens derived from the invading pathogen are preferentially activated and then differentiate into effector T cells ($CD4^+$ helper T cells or $CD8^+$ cytotoxic T cells) to combat the invading pathogen. These crucial processes of T cell development, tolerance, homeostasis, and differentiation are highly dependent on a regulatory network that is modulated by TGF-β.

Box 1. Abbreviations

CIA: collagen-induced arthritis
CTL: cytotoxic T lymphocyte
DC: dendritic cell
DNRII: dominant-negative mutant of TGF-βRII
EAE: experimental autoimmune encephalomyelitis
ECM: extracellular matrix
eTh17: effector Th17
GALT: gut-associated lymphoid tissue
IL: interleukin
iTreg: induced $CD4^+Foxp3^+$ regulatory T
LAP: latency-associated protein
LTBP: latent TGF-β-binding protein
MHC: major histocompatibility complex
NKT: natural killer T
nTreg: natural $CD4^+Foxp3^+$ regulatory T
RA: retinoic acid
RAG: recombination activating gene
rTh17: regulatory Th17
TA: TGF-β activator
TCR: T cell receptor
TF: transcription factor
TGF-β: transforming growth factor-β
TGF-βRI: TGF-β type I receptor
TGF-βRII: TGF-β type II receptor
Th: helper T lymphocyte

TGF-β belongs to a family of regulatory cytokines that have pleiotropic functions in a broad range of cell lineages involved in numerous physiological and pathological processes such as embryogenesis, carcinogenesis, and the immune response (Blobe et al., 2000). In mammals, three members of the TGF-β family (TGF-β1, TGF-β2, and TGF-β3) have been identified, with TGF-β1 being the predominant form expressed in the immune system (Li et al., 2006b). TGF-β is synthesized as a precursor: the pre region contains a signal peptide, and pro-TGF-β is processed in the Golgi by a furin-like peptidase that removes the N terminus of the immature protein. A homodimer of this new protein, called the latency-associated protein (LAP), is noncovalently associated with a homodimer of mature TGF-β (Figure 1). This latent complex can be secreted, or may associate with latent-TGF-β-binding protein (LTBP), which plays an important role in targeting TGF-β to the extracellular matrix. TGF-β cannot bind to its receptors in its latent form—it needs to be liberated from the constraints of LAP and LTBP by a TGF-β activator (TA) through LAP proteolysis or a conformational change (Annes et al., 2003) (Figure 1). Notably, the cells that produce TA can be different from those that secrete TGF-β. This unique activation step for TGF-β provides a means for this secreted molecule to integrate signals from multiple cell types to regulate cellular responses.

Active TGF-β mediates its biological functions by binding to TGF-β type I (TGF-βRI) and type II (TGF-βRII) receptors, both of which are serine/threonine kinases. TGF-β engagement with a tetrameric receptor complex consisting of two TGF-βRI molecules and two TGF-βRII molecules activates these receptor kinases, allowing them to phosphorylate downstream targets and to activate different signaling pathways (Figure 1). The signaling output of TGF-β elicits diverse cellular responses that are primarily mediated through the actions of Smad transcription factors (Massague and Gomis, 2006; Shi and Massague, 2003). Active Smad protein complexes bind to DNA weakly; high-affinity DNA binding is achieved by the association of Smad proteins with a large number of transcription factor partners (Massague and Gomis, 2006). In addition, TGF-β activates various cell type-specific Smad-independent signaling pathways, including those mediated by mitogen-activated protein kinase (MAPK), PI3K kinase, PP2A phosphatase, Rho family proteins, and the epithelial polarity protein Par6 (Derynck and Zhang, 2003; Ozdamar et al., 2005). The plasticity of Smad proteins in transcriptional regulation and the diversity of Smad-independent pathways enable TGF-β to exert its pleiotropic actions.

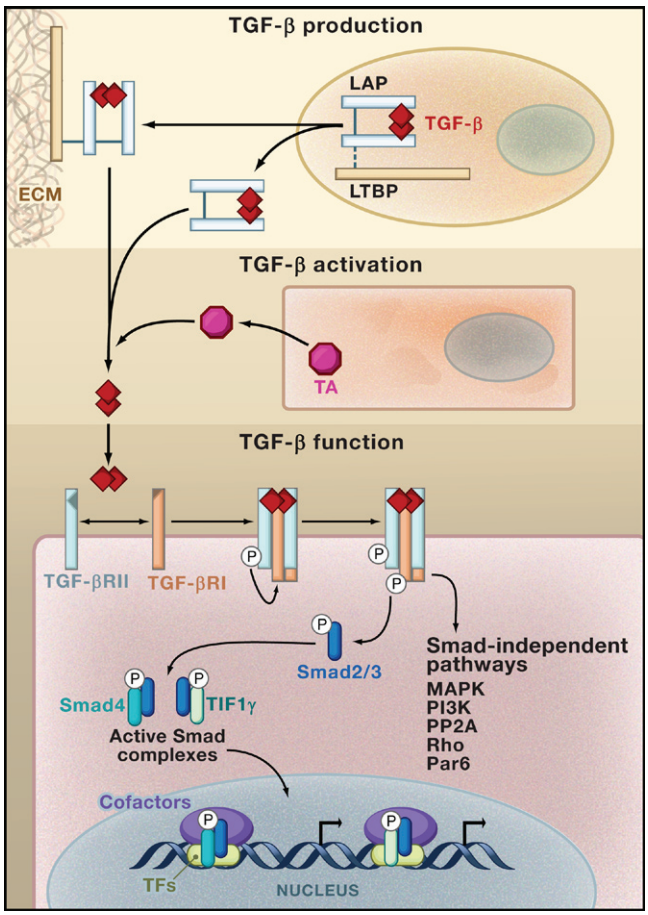

Figure 1. The TGF-β Module of Cellular Regulation

TGF-β is synthesized in an inactive form composed of a TGF-β dimer in association with the latency-associated protein (LAP). This latent TGF-β molecule can be secreted as such, or can form a complex with latent-TGF-β-binding protein (LTBP) that mediates its deposition to the extracellular matrix (ECM). TGF-β becomes activated after the engagement of a TGF-β activator (TA) that triggers LAP degradation or alters LAP's conformation in response to environmental cues. Active TGF-β binds to a tetrameric complex composed of TGF-β receptor II (TGF-βRII) and TGF-β receptor I (TGF-βRI) and initiates signaling pathways that are dependent on the kinase activity of the receptors. Activated TGF-βRI phosphorylates the transcription factors Smad2 and Smad3, triggering their translocation into the nucleus in complex with the proteins Smad4 or TIF1γ. Smad complexes in association with additional transcription factors (TFs) bind to the regulatory sequences in target genes and regulate gene expression by recruiting transcription cofactors. In addition, TGF-β activates Smad-independent pathways such as those mediated by mitogen-activated protein kinase (MAPK), PI3K kinase, PP2A phosphatase, Rho family proteins, and the epithelial polarity protein Par6, which trigger different cell type-specific responses.

TGF-β Regulates T Cell Development

Thymic T precursor cells undergo a series of molecular and phenotypic changes before they differentiate into mature T cells. One critical event in T cell differentiation occurs at the stage when immature T cells expressing both CD4 and CD8 cell surface markers ($CD4^+CD8^+$) as well as αβ TCRs are subjected to selection and lineage diversification.

$CD8^+$ T Cell Differentiation

TGF-β may play a role at the $CD4^+CD8^+$ stage in T cell development to promote thymic $CD8^+$ T cell differentiation, but this remains unresolved. The initial implication of TGF-β in this process came from a study that found a 2-fold reduction in conventional mature $CD8^+$ T cells ($CD8^+TCR^{high}$) in mice lacking the *Tgfbr2* gene in $CD4^+CD8^+$ T cells (Li et al., 2006a). However, a related study using the same mouse model system (Marie et al., 2006) reported normal thymic $CD4^+$ and $CD8^+$ T cell differentiation in these mutant mice. Another study of mice reconstituted with TGF-βRII-deficient bone marrow cells demonstrated the opposite effect, that is, increased proliferation of $CD8^+$ thymocytes in the absence of TGF-β signaling with no effect on overall $CD8^+$ T cell number (Leveen et al., 2005). The