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Mini review

TGFβ in T cell biology and tumor immunity: Angel or devil?

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ABSTRACT

The evolutionally conserved transforming growth factor β (TGFβ) affects multiple cell types in the immune system by either stimulating or inhibiting their differentiation and function. Studies using transgenic mice with ablation of TGFβ or its receptor have revealed the biological significance of TGFβ signaling in the control of T cells. However, it is now clear that TGFβ is more than an immunosuppressive cytokine. Disruption of TGFβ signaling pathway also leads to impaired generation of certain T cell populations. Therefore, in the normal physiological state, TGFβ actively maintains T cell homeostasis and regulates T cell function. However, in the tumor microenvironment, TGFβ creates an immunosuppressive milieu that inhibits antitumor immunity. Here, we review recent advances in our understanding of the roles of TGFβ in the regulation of T cells and tumor immunity.

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1. Introduction

TGFβ proteins are a family of pleiotropic cytokines that regulate diverse biological processes, including development of organs and tissues, carcinogenesis and immune responses. TGFβ is synthesized in a latent form with a homodimer of TGFβ that is noncovalently linked with the latency-associated protein (LAP). The activation of latent form TGFβ is promoted by a TGFβ activator *via* LAP degradation or conformational changes. Active TGFβ binds to TGFβ type 2 receptor (TGFβRII) and induces the assembly of the tetrameric TGFβ receptor complex composed of TGFβRII and TGFβ type 1 receptor (TGFβRI), which activates the kinase activity of TGFβRI. Activated TGFβRI phosphorylates transcription factors, mothers against decapentaplegic homolog (SMAD2) and SMAD3. Phosphorylated SMAD2 and/or SMAD3 form complexes with the common SMAD (SMAD4) that are translocated into the nucleus where they associate with DNA-binding cofactors to regulate the transcription of target genes [1]. In addition, TGFβ can also activate SMAD-independent pathway, including those mediated by mitogen-activated kinase (MAPK), Rho family proteins, Par6 and PP2A phosphatase to induce different cell type-specific SMAD-independent responses [2].

In mammals, three members of TGFβ family have been identified: TGFβ1, TGFβ2 and TGFβ3, with TGFβ1 being the major regulator in the immune system. TGFβ is involved in the regulation of development, survival and function of many types of immune cells. However, the role of TGFβ in T cell regulation has attracted the most interest due to the discovery of uncontrolled T cell activation and expansion in TGFβ1-deficient mice [3,4]. Given that TGFβ is produced in abundance by many types of tumor cells, it is without surprise that TGFβ facilitates evasion of immune surveillance by regulating T cells and other immune cell types in the tumor microenvironment [5]. In this review, we discuss the current understanding of TGFβ regulation of T cell biology and tumor immunity.

2. The role of TGFβ in T cell biology

TGFβ was initially defined as a negative regulator of T cells by early studies since addition of TGFβ to T cell culture inhibited T cell proliferation [6]. Consequently, mice that lack TGFβ1 and mice with T cell-specific deletion of either TGFβRI or TGFβRII die early of age from systemic autoimmune disorder caused by hyperactivation and enhanced proliferation of T cells [3,4,7–9]. These findings thus suggest TGFβ signaling to T cells is critically associated with the maintenance of T cell tolerance. Intriguingly, recent studies have provided evidence to demonstrate that TGFβ also promotes the differentiation, homeostasis and responses of certain T cell populations (Fig. 1). This section focuses on a major role of TGFβ in regulation of T cell differentiation and tolerance. We also address the potential of TGFβ-based therapeutics for the treatment of autoimmune disease.

2.1. T cell differentiation

TGFβ has been shown to implicate on the development of T cell precursors into mature T cells in the thymus, as well as differentiation of effector T cells in the periphery. In this section, we focus on a major role of TGFβ in the differentiation of

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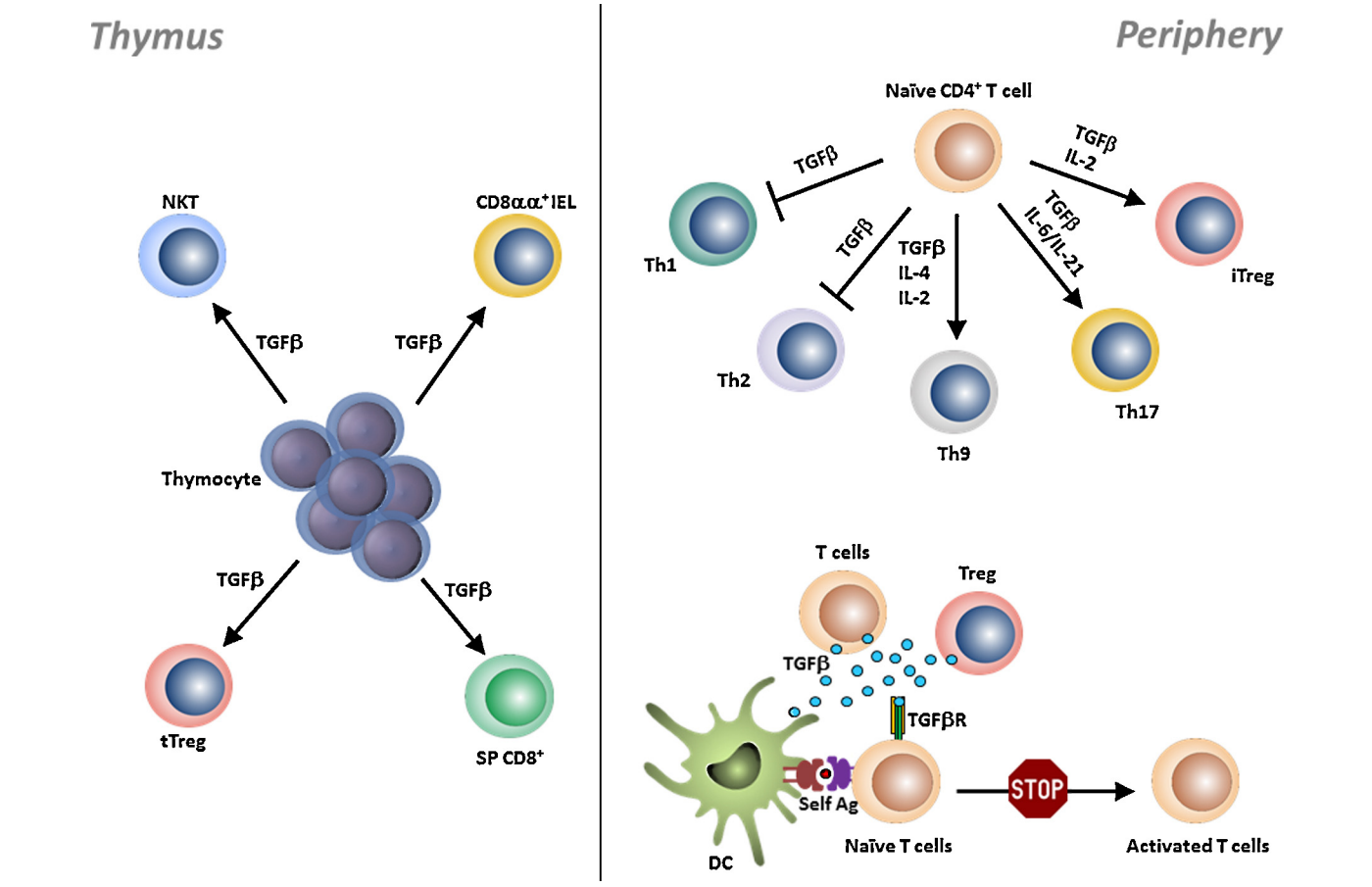

Fig. 1. TGFβ regulation of T cells in the thymus and periphery. During T cell development in the thymus, TGFβ supports the differentiation of thymocytes into tTreg cells, CD8 T cells, NKT cells and TCRαβ$^+$CD8αα$^+$ IEL precursors. In the periphery, TGFβ inhibits Th1 and Th2 cell differentiation by repressing T-bet and GATA-3 expression, respectively. In other scenarios, TGFβ acts synergistically with other cytokines to promote the differentiation of Th9, Th17 and iTreg cells. DCs, T cells and Treg cells serve as a source of TGFβ, which is critically required for the maintenance of peripheral T cell tolerance by inhibiting activation and proliferation of self-reactive T cells.

conventional T cells (CD4$^+$ and CD8$^+$), regulatory T (Treg) cells, and non-conventional T cells (natural killer T [NKT] cells, and CD8αα$^+$ intestinal intraepithelial lymphocytes [IELs]).

2.1.1. CD4$^+$ T cells

CD4$^+$ helper T (Th) cells play a major role in establishing and augmenting immune responses against pathogens. This is achieved through their production of cytokines that provide help to other cells in the innate and adaptive immune systems. After activation by engagement of TCR to peptide-MHC complex and co-stimulatory signals, naïve CD4$^+$ T cells undergo proliferation and differentiation into various effector Th subsets, which depends on the nature of antigens and cytokine environment. As TGFβ inhibits the differentiation and function of Th1 and Th2 cells (discussed later), we focus on the stimulatory role of TGFβ in the differentiation of Th17 cells, Treg cells and the recently identified Th9 cells.

2.1.2. Th17 cell differentiation

TGFβ has been shown to be required for the differentiation of Th17 cells from naïve CD4$^+$ T cells, as Th17 cells were profoundly diminished or absent in TGFβ-deficient mice [10]. Moreover, T cells that are deficient in TGFβ receptors, and therefore cannot respond to TGFβ, are impaired in Th17 cell differentiation resulting in mice that are protected from EAE [11]. It was found that TGFβ and IL-6 together induce the differentiation of Th17 cells from naïve CD4$^+$ T cell precursors [10,12,13]. In addition to IL-6, IL-21 together with TGFβ provided an alternative pathway for Th17 cell development in the absence of IL-6 [14].

However, some studies argue the necessity for TGFβ in driving Th17 differentiation under certain circumstances. For example, it was reported that TGFβ indirectly promotes Th17 cell differentiation by inhibiting STAT4 and GATA3 expression, which are required for Th1 and Th2 cell differentiation, respectively. Accordingly, IL-6 alone was sufficient to induce Th17 response in STAT6$^{-/-}$.Tbet$^{-/-}$ mice [15]. In another study, IL-6 or IL-23 in combination IL-1β was shown to induce Th17 cell differentiation from naïve T cells [16]. These results suggest that TGFβ is dispensable for generating Th17 cells under contain circumstances. Although TGFβ/IL-6 and IL-23/IL-6/IL-1β both induce T cells capable of producing IL-17, the pathogenicity of Th17 cells that arise from these two cytokine environments are strikingly different. Th17 cells generated by stimulation with IL-6/IL-1β/IL-23 efficiently caused severe EAE upon transfer, whereas TGFβ/IL-6-induced Th17 cells had no effect [16]. This was likely due to the high level of IL-10 produced by TGFβ and IL-6-induced Th17 cells [17]. Nevertheless, it is generally believed that TGFβ is critical for the differentiation of Th17 cells at least in rodents. The important questions ahead are the underlying molecular mechanisms downstream of TGFβ signaling that mediate IL-17 gene transcription in T cells.

As TGFβ is a differentiation factor for both Treg (discussed below) and Th17 cells, TGFβ synergizes with other cytokines to regulate Treg and Th17 cell development. It was shown that exposure of naïve CD4$^+$ T cells to TGFβ can result in expression of both Foxp3 and RORγt. However, Foxp3 drives the differentiation of Treg cells by inhibition of RORγt function. In contrast, IL-6, IL-21

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