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Mini-review

TGF-β as a promising option in the treatment of multiple sclerosis

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ABSTRACT

Transforming growth factor-β (TGF-β) is a potent regulatory cytokine with diverse effects on hemopoietic cells. The pivotal function of TGF-β in the immune system is to maintain tolerance via the regulation of lymphocyte proliferation, differentiation, and survival. Among T cells, $CD4^+CD25^+FOXP3^+$ T regs contain the main source of TGF-β that suppresses immune responses in inflammatory sites. Defects in TGF-β1 expression or its signaling in T cells correlate with the onset of several autoimmune diseases. Thus, understanding the function and regulation of TGF-β during immune responses offers therapeutic promise for the control of autoimmune diseases such as multiple sclerosis. However, the main mechanism by which TGF-β exerts its protective effects on the experimental model of multiple sclerosis remains to be elucidated. Paradoxically, TGF-β1 also acts as a pro-inflammatory cytokine and induces interleukin 17-producing pathogenic T helper cells (Th IL-17 cells) synergistically during an inflammatory response in which interleukin 6 is produced. In this review, we will describe the regulatory and therapeutic effects of TGF-β in multiple sclerosis.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by recurrent episodes of demyelination and axonal injury mediated primarily by CD4-positive T-helper cells with a pro-inflammatory Th1 phenotype, macrophages, and soluble mediators of inflammation (Trapp et al., 1998; Mirshafiey, 2007a). Cytokines released by macrophages, lymphocytes, microglia and astrocytes play an important role in the pathogenesis of the disease characterized by periods of exacerbations and remissions. Among them there are pro-inflammatory cytokines like interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α) or interferon-γ (IFN-γ) produced by Th1 cells and cytokines with immunosuppressive properties like IL-4, transforming growth factor-β1 (TGF-β1) and/or IL-10 (Olsson, 1995).

TGF-β1 has an important role in suppression of the immune system in autoimmune diseases. This cytokine regulates the differentiation, growth and function of a wide range of cells and has been implicated in many different disease processes (Goris et al., 2007). Its role in negative regulation of the immune system raises speculations that it might be involved in the etiology of immune-related disorders such as multiple sclerosis in terms of influencing either susceptibility to disease or rate of progression (Kim et al., 2005). There is ample evidence that TGF-β1 protects against relapsing experimental autoimmune encephalomyelitis (EAE), a mouse model of human multiple sclerosis. TGF-β1 plays a role in preventing sensitized T cells from entering into the CNS. It can inhibit expression of pro-inflammatory cytokines and block cytokine induction of adhesion molecules. The production of endogenous TGF-β has been demonstrated to be one of the factors involved in protecting against multiple sclerosis, as shown by the adverse effect of neutralizing anti-TGF-β on the course of acute and relapsing EAE and collagen-induced arthritis (Johns and Sriram, 1993; Racke et al., 1992; Kuruvilla et al., 1991).

2. TGF-β and its role in immune system

The dominant role of TGF-β1 in the immune system is to induce tolerance. TGF-β consists of a family of pleiotropic cytokines that regulates multiple pathways of cellular functions, such as proliferation, differentiation, migration, and survival (Li et al., 2006a,b).

The TGF-β superfamily comprises over 30 members that include TGF-β and a number of related factors (e.g. activins, nodals, bone morphogenetic proteins/growth and differentiation factors). The mature active forms of the family are typically dimers of 12–15 kDa subunits linked mainly by a single disulfide bond. TGF-β consists of three isoforms: TGF-β1, TGF-β2 and TGF-β3. Although each of these is derived from distinct genes, they display greater than 70% sequence homology and have similar properties at least in vitro and are collectively assigned the generic term TGF-β (Ramji et al., 2006). This cytokine is synthesized as a homodimeric pro-protein (pro-TGF-β; molecular mass 75 kDa), which is cleaved in the Golgi

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apparatus (Annes et al., 2003). The cleaved TGF-β is then secreted as a small latent complex, which is unable to bind to the cytokine receptor. TGF-β is produced by most cells in a latent form, attached to a latency-associated protein (LAP) which requires removal to uncover the receptor-binding region of active TGF-β (Wakefield et al., 1988). Removal of LAP in the lymphoid tissue is believed to be accomplished by thrombospondin, plasmin and acidification in macrophages within the inflammatory process (Hugo et al., 1998).

The diverse effects of TGF-β could be categorized to the down-regulation of tumor necrosis factor (TNF) and lymphotoxin (LT) production (Stevens et al., 1994a), responses to IL-12 (Murano et al., 2006; Malyak et al., 1998), macrophage and microglia activation (Nelson et al., 1991), cytokine-enhanced class II expression (Epstein et al., 1991), and migration into the CNS (Santambrogio et al., 1993b). A number of studies have shown that immunoregulatory effects of T cells in humans and animals are partly a result of TGF-β production. A crucial function of TGF-β was shown by its anti-proliferative activity on T cells in vitro. TGF-β uses multiple pathways to suppress T cell proliferation mainly via inhibition of IL-2 transcription (Li et al., 2006a,b). Also, an inhibitory role has been demonstrated for TGF-β1 in blocking nuclear factor-B activation and pro-inflammatory cytokines in which the nuclear factor-B and the cytokines are stimulated by Toll-like receptor (TLR) 2, 4, and 5 ligand-induced responses involving MyD88 (Naiki et al., 2005). Among the three TGF-β isoforms, TGF-β1 is strongly chemotactic for monocytes, neutrophils, and T cells and induces the production of chemokines such as monocyte chemoattractant protein 1 (MCP-1) and several chemokine receptors (Lúethvíksson and Gunnlaugsdóttir, 2003; Wahl et al., 1987; Adams et al., 1991). Besides the effect on chemotaxis, TGF-β1 might increase homing to the brain by increasing adhesion molecules on infiltrating cells and the vasculature (Luo et al., 2007).

In addition to a direct role for TGF in regulating effector T cell differentiation, proliferation and apoptosis, TGF signaling was found to be required for the maintenance of the peripheral CD4+ regulatory T (TReg) cell subset that expresses the transcription factor forkhead box P3 (FOXP3) (Fantini et al., 2004; Marie et al., 2006). As it was referred, TGF-β1 is initially produced in a latent inactive form which subsequently undergoes activation and this results in the release of the active cytokine. In T cells, TGF-β1/TGF-β-receptor interaction also send signals through *Caenorhabditis elegans* Sma and *Drosophila* Mad proteins (SMAD)-independent Ca^{2+}-calcineurin-nuclear factor of activated T cells (NF-AT) cascade that inhibits naive T cell activation (Lúethvíksson and Gunnlaugsdóttir, 2003). TGF-β receptor consists of two different proteins, TGF-β receptor type I (TGF-βRI) and TGF-β receptor type II (TGF-βRII), which signal through a serin/threonine kinase domain that phosphorylates transcription factor of SMAD (Fig. 1). Active TGF-β1 binds to the TGF-β receptor type II (TGF-βRII) subunit on the cell surface. The binding of TGF-β1 induces the assembly of the activated receptor–ligand heteromeric complex, which results in autophosphorylation of the receptor followed by phosphorylation of R-SMAD (receptor-regulated SMAD), as shown in Fig. 1. Phosphorylated R-SMADs form homooligomeric and heterooligomeric complexes with the co-mediator SMAD (Co-SMAD). These complexes are translocated to the nucleus where they associate with DNA-binding co-factors, transcriptional co-activators (Co-A) and co-repressors to regulate transcriptional activity of the target genes (Rubtsov and Rudensky, 2007). TGF-β1 prevents abnormal T cell activation through the modulation of $Ca2^{+}$-calcineurin signaling in a SMAD3 and SMAD4-independent manner; however, in Treg cells, its effects are mediated, at least in part, through SMAD signaling (Bommireddy and Doetschman, 2007).

TGF-β-treated dendritic cells (DC) are resistant to LPS-induced maturation and may be related to the down-modulation of TLR4 expression. TGF-β1-treated murine dendritic cells are maturation resistant and down-regulate Toll-like receptor 4 expression. TGF-β1 might increase the generation of tolerogenic DC with the expression of CD14. Myeloid DC over-expressing TGF-β inhibited T cell proliferation in allostimulatory experiments. Infusion of TGF-β1 gene-modified immature DC prolongs the survival of the allograft through the effective induction of donor-specific T cell hyporesponsiveness. The studies show that TGF-β slightly increases the number of HLA-DR+CD11c+ cells with lower capacity to stimulate T cells and higher endocytosis, indicating that TGF-β1 maintains antigen presenting cells (APC) in an immature state (Xiao et al., 2007). In this study, TGF-β1-APC exhibited lower expression of HLA-DR and CD86, especially in CD86, revealing that T cell hyporesponsiveness may be related to lower expression of HLA-DR and CD86. A role for TGF-β has also been shown in the induction of IL-10 production by macrophages and the inhibition of production of TNF- and IL-1 (Takayama et al., 2002; Fogel-Petrovic et al., 2007; Mou et al., 2004).

It should be noted that, primarily, the family of effectors CD4+ T cell lineages included only two main types, TH1 and TH2 cells, the differentiation of which is negatively regulated by TGF-β1. Numerous in vitro studies of both human and mouse CD4+ T cell differentiation have suggested the existence of two additional types of CD4+ T cell that have suppressive properties. These cells are known as TR1 and TH3 cells, which produce IL-10 and TGF-β1, respectively (Thomas and Massagué, 2005; Roncarolo et al., 2006). Recently evidence shows that TGF-β1 plays an essential role in the differentiation of a distinct lineage of pro-inflammatory CD4+ T cells that produce IL-17, known as TH17 cells. In vitro stimulation of naive T cells in the presence of TGF-β1 leads to the induction of FOXP3 expression in peripheral T cells; however, a combination of TGF-β1 and IL-6 results in up-regulation of expression of the transcription factor retinoic-acid-receptor-related orphan receptor-t (RORt), which serves as a key regulator of the TH17 cell differentiation program (Weaver et al., 2007; Ivanov et al., 2006; Harrington et al., 2005; Veldhoen et al., 2006a).

3. TGF-β in autoimmune diseases

Studies of animal models and human patients have revealed a critical function for TGF-β in regulating leukocyte functions in autoimmune diseases. Mouse models in which TGF-β signaling is disrupted develop cell-autonomous autoimmune disease, suggesting an important physiological role for TGF-β1-dependent Treg cells (Gil-Guerrero et al., 2008). TGF-β is produced by several immune and non-immune cell types and functions in both autocrine and paracrine manner, but T reg cells are the primary source of TGF-β1 in the control of autoimmune disease (Bommireddy and Doetschman, 2007; Cao et al., 2008; Schmidt-Weber and Blaser, 2004). In the adaptive immune system TGF-β signaling has a non-redundant essential role which includes limiting the elaboration of T cell and natural killer (NK) cell responses, facilitating IgA class switching, promoting the development of certain lymphocyte subsets and limiting T cell-mediated autoimmunity (Rubtsov and Rudensky, 2007; Veldhoen and Stockinger, 2006). Specifically, however, TGF-β signaling is involved in the inhibition of cytolytic processes and T helper 1 (TH1) cell differentiation and effector functions of T cells. In support of this notion, aggressive autoimmune lesions were observed following abrogation of TGF-β signaling in mice (Li et al., 2006a,b). Immune regulation is achieved by tightly controlled interactions among cytokines, surface receptors and transcription factors. Deficiency in all or several of these, such as TGF-β1, CTLA-4 or FOXP3, leads to severe autoimmune disease, whereas over-expression of either TGF-β1 or FOXP3 protects mice from autoimmune diseases (Gil-Guerrero