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Transforming Growth Factor-β: An Indirect Inducer of Th17 Cell Differentiation both in Human and Murine System

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Abstract: Since their first description only some years ago Th17 cells have become of vital importance in immunological research. However, the role of TGF-β in Th17 cell development is still a matter of controversial discussion. Predicted to have a key function in Th17 cell differentiation in the mouse TGF-β was shown to inhibit IL-17 production of human $CD4^+$ T cells. Moreover, recent data indicate TGF-β signaling in T cells to be dispensable for Th17 cell differentiation in the murine system. Hence, rather being a specie-specific factor TGF-β is likely to act as an indirect inducer of Th17 cell differentiation both in mice and men.

Key words: Transforming growth factor, T helper cell, mice and men, murine system

INTRODUCTION

Th17 cells are a subset of T helper cell lymphocytes producing IL-17, TNF-α and IL-6, but not IFN-γ or IL-4 (McKenzie *et al*., 2006; Iwakura and Ishigame, 2006). Via secretion of IL-17 Th17 cells enhance the expression of G-CSF (Fossiez *et al*., 1996; Cai *et al*., 1998; Schwarzenberger *et al*., 1998; 2001), IL-8 (Fossiez *et al*., 1996; Laan *et al*., 1999; Yao *et al*., 1995a; Kawaguchi *et al*., 2001; Katz *et al*., 2001; Jones and Chan, 2002; Prause *et al*., 2003) and ICAM-1 (Yao *et al*., 1995a; Albanesi *et al*., 1999) thereby promoting chemotaxis of neutrophils and monocytes to sites of inflammation. In addition, IL-17 stimulates the production of IL-6 (Fossiez *et al*., 1996; Yao *et al*., 1995a; 1995b; Katz *et al*., 2001; Chabaud *et al*., 1998), matrix metalloproteinases (Chabaud *et al*., 2000), prostaglandin E2 (Fossiez *et al*., 1996), NO (Shalom-Barak *et al*., 1998; Attur *et al*., 1997) as well as the complement components C3 and factor B (Katz *et al*., 2000). Hence, Th17 cells represent potent pro-inflammatory mediators crucial in the regulation of inflammatory responses.

In a number of inquiries using murine models of host defense Th17 cells have been described to be important in the pathogenesis of chronic inflammatory diseases including arthritis (Lubberts *et al*., 2005; Latham *et al*., 2005), colitis (Zhang *et al*., 2006; Ogawa *et al*., 2004), encephalitis (Komiyama *et al*., 2006; Hofstetter *et al*., 2005) as well as asthma and allergy (Hellings *et al*., 2003). In humans IL-17 producing T cells have been isolated from synovial membranes and synovial fluid of patients suffering from rheumatoid arthritis (Chabaud *et al*., 1999). At this, severity of inflammation is reported to be consistent to the IL-17 concentration detectable in serum and tissue of the arthritis patients. Furthermore, a correlation between IL-17 serum levels and the degree of inflammatory processes has been described in the context of autoimmune encephalomyelitis (Lock and Heller, 2003) and inflammatory bowel disease (Fujino *et al*., 2003). Thus, IL-17 especially if produced by T cells is a likely candidate for intervention in chronic inflammatory diseases in men.

Th17 cell differentiation: Proceeding specie-specific?

In the murine system the synergistic action of TGF-β and IL-6 has been considered to be essential for Th17 cell development, so far (Veldhoen *et al*., 2006; Mangan *et al*., 2006; Bettelli *et al*., 2006). In contrast, differentiation of human naïve T helper cells into Th17 cells has been reported not to depend on TGF-β (Chen *et al*., 2007; Wilson *et al*., 2007; Acosta-Rodriguez *et al*., 2007; Manel *et al*., 2008; Santarlasci *et al*., 2009; Cosmi *et al*., 2008). Moreover, TGF-β has been predicted to act suppressive on IL-17 production of human $CD4^+$ T cells (Acosta-Rodriguez *et al*., 2007; Manel *et al*., 2008). Due to the divergent observations made in murine and human systems Th17 cells development in mice and men has been assumed to be regulated differentially (Annunziato *et al*., 2009; Annunziato and Romagnani, 2009). However, recent data provide evidence that TGF-β is not directly required for the molecular orchestration of Th17 cell differentiation in

the mouse as well (Das *et al*., 2009; Schumann, 2008). Thus, the situation seen in the murine system is closer related to the human situation as previously thought.

What role for TGF-β in Th17 differentiation? TGF-β initially has been published as a growth factor (De Larco and Todaro, 1978). Thereinafter it was found, that TGF-β not only influences differentiation of cells but is also crucial in inflammatory processes (Kehrl *et al*., 1986a; 1986b). TGF-β regulates the innate and the adaptive immunity affecting macrophages (Ashcroft, 1999), dendritic cells (Strobl and Knapp, 1999), T cells (Cerwenka and Swain, 1999), B cells (Lebman and Edmiston, 1999) and NK cells (Horwitz *et al*., 1999). The cytokine acts both pro- and antiinflammatory depending on genetic background, cell type, state of differentiation, extracellular matrix as well as the presence of other regulatory factors (McCartney-Francis and Wahl, 1994; Wahl, 1994). Hence, TGF-β shows a distinctive pleiotropy playing a complex role in immunmodulation.

At present time the role of TGF-β in T helper cell differentiation has become of special interest. Depending on cytokine milieu naïve T helper cells differentiate into four known T helper cell subsets. TGF-β interacts in this process by several ways. Both Th1 (Gorelik *et al*., 2002; Lin *et al*., 2005) and Th2 cells (Chen *et al*., 2003a; Gorelik *et al*., 2000; Heath *et al*., 2000) are inhibited by TGF-β. Concomitantly, TGF-β represents the direct inducer of Treg cells, which themselves are considerable producers of the cytokine (Chen *et al*., 2003b).

Beside its clear role in Treg cell development conflicting data have been published concerning the relevance of TGF-β in Th17 cell generation in mice and men. In murine system cytokines critically for Th17 cell differentiation were propagated to be TGF-β and IL-6 (Veldhoen *et al*., 2006; Mangan *et al*., 2006; Bettelli *et al*., 2006). However, TGF-β has not been shown to directly promote the generation of IL-17 producing T cells from naïve precursors. Rather, a beneficial effect of TGF-β was seen, when naive $CD4^+$ T cells were co-cultivated with Treg cells plus dendritic cells and stimulated with anti-CD3-antibody as well as Lipopolysaccharid (LPS) (Veldhoen *et al*., 2006). LPS is known as strong inducer of Th1 reactions via a release of IL-12 by dendritic cells (Pearce *et al*., 2006). The effect of TGF-β in such a setting might therefore rather be based on the prevention of a Th1 cell development. Consistently to this assumption, using a mouse model unable to generate Th1 and Th2 cells, the cytokine IL-6 has been reported to be sufficient to drive Th17 cell generation (Das *et al*., 2009). In addition, TGF-β was shown not to affect the expression of the retinoic acid receptor-Related Orphan Receptor γt (ROR γt), a Th17 cell specific transcription factor (Das *et al*., 2009). Beyond that, Th17 cells could be detected in a transgene mouse strain T cell specific insensitive for TGF-β signaling (Schumann, 2008). Visualization of Th17 cells succeeded both *ex vivo* after re-stimulation of lymph node cells of *B. burgdorferi*-infected mice as well as *in vitro* after T cell specific stimulation of splenocytes and purified $CD4^+$ lymphocytes (Schumann, 2008). In contrast, stimulation of T cells over-expressing TGF-β resulted in decreased Th17 cell numbers in comparison to the wild type (Schumann, 2008). Hence, there is compelling evidence that TGF-β does not act as a direct inducer of Th17 cell development in the mouse.

The dispensability of TGF-β signaling on T cells for Th17 cell development in the murine system is consistent to publications dealing with effects of TGF-β on human T helper cell differentiation. In human system TGF-β has been shown to inhibit IL-17 production by T cells (Acosta-Rodriguez *et al*., 2007; Manel *et al*., 2008). According hitherto existing literature rather than TGF-β, cytokines such as IL-1β and IL-23 drive Th17 cell development from human $CD4^+$ precursors (Chen *et al*., 2007; Wilson *et al*., 2007; Acosta-Rodriguez *et al*., 2007).

TGF-β affects Th17 cell differentiation in an indirect way: TGF-β is part of a complex regulatory system critically in immune homeostasis. The cytokine is of vital importance in T helper cell differentiation influencing all four known T helper cell subsets. In addition to interference in T helper cell development TGF-β represents the main product of Treg cells thereby mediating the immunosuppressive and anti-inflammatory function of these cells (Chen *et al*., 2003b).

Of note, the cytokine accomplishes its effects both directly and indirectly. TGF-β directly induces Treg cell differentiation via promotion of the transcription factor FoxP3 (Chen *et al*., 2003b). TGF-β directly blocks Th1 as well as Th2 cell development via inhibition of T-bet (Gorelik *et al*., 2002; Lin *et al*., 2005) and GATA-3 (Chen *et al*., 2003a; Gorelik *et al*., 2000; Heath *et al*., 2000) expression, respectively. By contrast, Th17 cell differentiation is affected indirectly by TGF-β. IFN-γ and IL-4, the cytokines produced by Th1 and Th2 cells, are well known inhibitors of Th17 cell development. Hence, blocking of Th1 and Th2 cells linked with the absence of IFN-γ and IL-4 provides a milieu optimal for naïve $CD4^+$ precursors to

differentiate into Th17 cells (Veldhoen *et al*., 2006; Mangan *et al*., 2006; Bettelli *et al*., 2006; Infante-Duarte *et al*., 2000). Taken together, the impact of TGF-β in T helper cell specification both in human and murine system is due to its inhibitory action on Th1 and Th2 cells in addition to its direct promotion of Treg cell amplification.

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