ELSEVIER

Seminars in Immunology 19 (2007) 383–393

seminars in
IMMUNOLOGY

www.elsevier.com/locate/ysmim

Review

Targeting the development and effector functions of TH17 cells

Nico Ghilardi [a,*], Wenjun Ouyang [b]

[a] *Department of Molecular Biology, Genentech Inc., 1-DNA Way, South San Francisco, CA 94080, USA*
[b] *Department of Immunology, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA*

Abstract

T helper (TH) cells can assume different phenotypes characterized by the secretion of distinct effector molecules. Interferon-γ producing TH1 and IL-4 producing TH2 cells have long been recognized as important mediators of host defense, whereas regulatory T cells are known to suppress T cell responses. Recently, TH17 cells were characterized as a novel $CD4^+$ subset that preferentially produces IL-17, IL-17F, and IL-22 as the signature cytokines. TH17 cells appear to play a critical role in sustaining the inflammatory response and their presence is closely associated with autoimmune disease, which makes them an attractive therapeutic target. In this review, we focus on the mechanisms that regulate the differentiation of naive T cells into TH17 cells and on TH17 effector cytokines, as they represent opportunities for therapeutic intervention.

Keywords: TH17; Interleukin-17; Interleukin-6; Interleukin-23; Autoimmune disease

1. TH17 cells—a novel helper cell subset

It has long been appreciated that naive $CD4^+$ T cells can differentiate into T helper type 1 (TH1) cells or type 2 (TH2) cells [1]. In this classical scheme, T cells have two choices: Either they would react to type 1 signals such as IFNγ and IL-12 and turn into IFNγ secreting TH1 cells with a mission to fight intracellular pathogens, or, alternatively, they would react to IL-4 and evolve into TH2 cells, whose main function is to promote humoral and anti-helminth immunity. This simple dichotomy model successfully provided a mechanistic explanation of how $CD4^+$ T cells can exert a protective function in certain bacterial and nematode infections, but can also contribute to the pathogenesis of inflammatory and atopic diseases. For instance, the susceptibility to *Leishmania major* has been attributed to severely attenuated TH1 development in the *balb/c* mouse strain. Furthermore, the discovery of the links between TH2 cells, IgE production and atopic diseases such as asthma provided new insight into the pathogenesis of allergic diseases. However, the model could not explain some observations made in diseases that were clearly dependent on $CD4^+$ cells, but not TH1 or TH2 cytokines. In experimental autoimmune encephalomyelitis (EAE), for example, it was discovered that both IFNγ and IL-4 play a role in attenuating the severity of the disease, suggesting the presence of other types of disease-promoting helper cell subsets. A new candidate subset with potential to fill this gap was first described in 2000, when Infante-Duarte et al. published a seminal paper demonstrating a novel type of $CD4^+$ cell which was neither TH1 nor TH2 [2]. They stimulated antigen presenting cells (APC) with bacterial lipopeptides (blp) derived from the spirochete *Borrelia burgdorferi*, and T cells stimulated in their presence subsequently secreted IL-17, TNF-α, and GM-CSF, but neither IFNγ nor IL-4 [2]. It was also suggested that the APC derived cytokines IL-6 and IL-18 might mediate the IL-17 inducing effects of blp. Incidentally, these observations were made six years before the critical roles played by IL-6 and, to a lesser extent, IL-18 in the development TH17 cells were generally recognized.

Intrigued by this discovery, Gurney and co-workers sought to define the APC-derived signals that would trigger IL-17 production by T cells, and identified the novel cytokine IL-23 as a potent inducer of IL-17 as well as IL-17F, a closely related IL-17 family member [3]. IL-23 is a heterodimeric cytokine and shares the p40 subunit of IL-12 [4]. On the receptor side, IL-23 uses its proprietary IL-23R in combination with IL-12Rβ1 [5], whereas IL-12 uses IL-12Rβ1 in combination with IL-12Rβ2 (Fig. 1). Despite this overlap in subunit usage, IL-12 and IL-23 have very distinct biological effects. Based on the analysis of IL-23-deficient ($IL\text{-}23p19^{-/-}$) mice, this cytokine must be present in order to allow for sustained inflammation and many forms of autoimmune disease to occur *in vivo*. Specifically, $IL\text{-}23p19^{-/-}$ mice are

* Corresponding author. Tel.: +1 650 225 6907; fax: +1 650 225 6443.
E-mail address: ghilardi@gene.com (N. Ghilardi).

1044-5323/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smim.2007.10.016

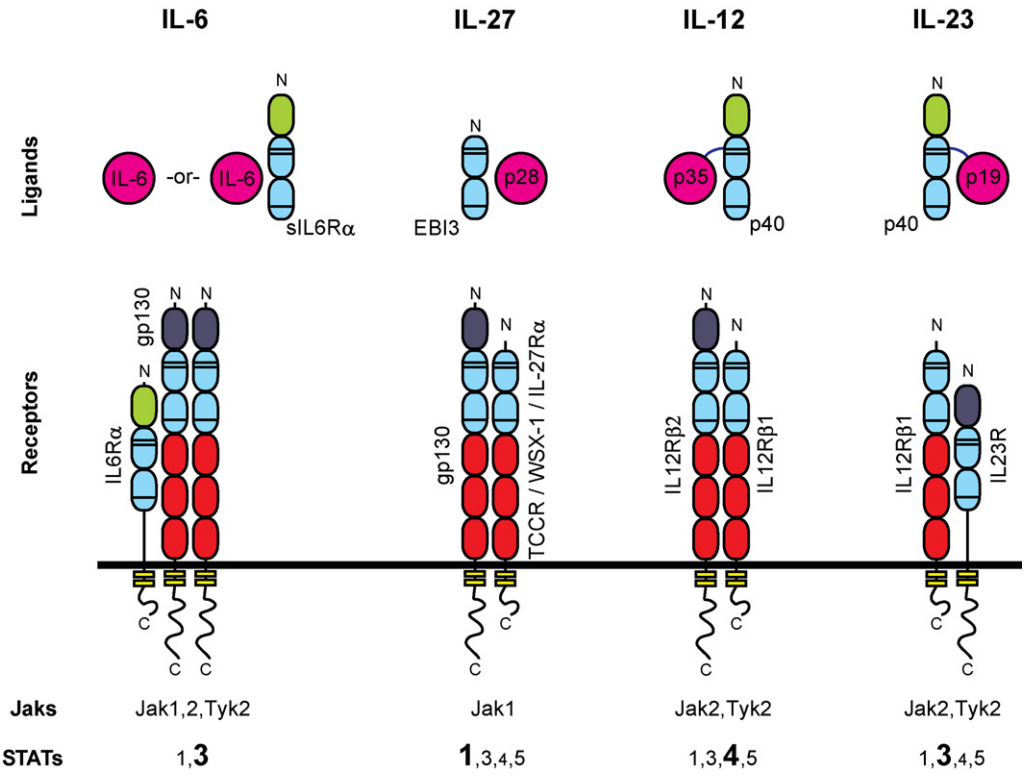

Fig. 1. Structural makeup of IL-6/12 family of cytokines and their receptors. Ligand/receptor complexes for IL-6, IL-27, IL-12 and IL-23 are shown schematically. Circles represent helical cytokines. The domain structure of receptors and receptor-like molecules is encoded as follows: CRH domains encoded by two modified FNIII domains are shown in blue, with two conserved cysteine bridges in the first module and a WSXWS motif in the second one indicated by lines. Red modules are FNIII domains. Immunoglobulin domains participating in ligand binding are colored dark gray, whereas Ig domains that do not bind ligands are colored green. The position of a disulfide bond in IL-12 and IL-23 is indicated by a blue line connecting the two subunits. IL-6Rα can either be membrane associated or soluble. Yellow boxes in the cytoplasmic portion of the receptors represent canonical box I and box II motifs required for Janus kinase association. JAKs and STATs known to be activated are indicated below each receptor complex, with the predominant STAT molecules shown in bold large numbers.

resistant to experimental autoimmune encephalomyelitis (EAE) [6], collagen-induced arthritis [7], and inflammatory bowel disease [8]. In all cases, resistance to disease in IL-23p19$^{-/-}$ mice is accompanied by the specific absence of TH17 cells, which are readily detected in wild-type mice suffering from these diseases. Furthermore, IL-23 treatment of *in vivo* PLP-primed CD4^{+} T cells from SJL mice results in a large proportion of IL-17^{+} cells, which are highly pathogenic for EAE when compared to cells treated with IL-12, which express IFNγ but not IL-17 [9]. Taken together, these early observations indicated a close link between IL-23, TH17 cells, and autoimmunity. They also questioned the role of IL-12 as the main culprit for autoimmunity, an assumption based primarily on work with IL-12p40$^{-/-}$ mice or IL-12p40 blocking antibodies. The discovery of IL-23 made it obvious that these reagents would assess the combined deficiency or neutralization of both IL-12 and IL-23. Careful comparison of IL-12p35$^{-/-}$, IL-12p40$^{-/-}$ and IL-23p19$^{-/-}$ mice has since revealed that IL-23 rather than IL-12 is required in many preclinical models of autoimmune disease, whereas IL-12 seems to exert some protective effects [6–8]. On the other hand, protective responses against intracellular bacteria such as *Mycobacterium tuberculosis* [10] and *Toxoplasma gondii* [11] were found to be predominantly dependent on IL-12 and TH1 cells.

2. Positive regulation of TH17 development

Fueled by the desire to better define this obviously very exciting new helper cell subset, several groups subsequently attempted to differentiate TH17 cells *in vitro*. Early efforts focused on the use of IL-23 as a driving stimulant, attempting to establish a differentiation pathway with symmetry to the IL-12–TH1 axis. In 2005, two groups demonstrated that IL-23 could indeed induce IL-17 production in about 10–20% of all CD4^{+} T cells as long as the signature TH1 and TH2 cytokines, IFNγ and IL-4, respectively, were neutralized by blocking antibodies [12,13]. Furthermore, Harrington et al. [12] demonstrated that STAT4 and STAT6, two transcription factors required for TH1 and TH2 development, respectively, were dispensable for TH17 development, although STAT4 was later shown to be required for IL-17 production induced by IL-23 in the absence of TCR stimulation [14]. Finally, T cells obtained under these conditions appeared to have a stable phenotype which could not be reversed to a TH1 or TH2 phenotype upon secondary stimulation [12].

However, subsequent investigations demonstrated that IL-23 failed to induce IL-17 production when the stimulation experiment was carried out in an APC-independent fashion, using FACS purified naive cells and agonistic antibodies directed against CD3 and CD28 [15–17]. This is easily explained by the