The IL-23/Th17 Axis in the Immunopathogenesis of Psoriasis

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Abnormal production of inflammatory mediators is believed to play an important role in the pathogenesis of psoriasis. Emerging data, both in mice and in humans, put the spotlight on a new subset of T helper (Th) cells, in part characterized by their production of IL-17 and accordingly named Th17 cells. Here, we review the development, characterization, and function of human Th17 cells as well as the crucial role of IL-23 in the context of Th17-cell-dependent chronic inflammation in psoriasis. We further discuss recent clinical trials targeting the IL-23/Th17 axis in psoriasis.

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease, evolving over time during a complex interplay between environmental and genetic factors. Although, in the past, psoriasis has been considered a primary keratinocyte (KC) disorder, the successful treatment of psoriasis patients with cyclosporin A suggested a potential role of the immune system in the pathogenesis of the disease (Mueller and Herrmann, 1979). The identification of activated CD4+ and CD8+ lymphocytes in psoriatic plaques and blood of psoriatic patients (Bos *et al.*, 1989; De Panfilis *et al.*, 1989; Ferenczi *et al.*, 2000), the detection of clonally expanded T cells (Vollmer *et al.*, 2001), and studies of human skin xenografts in mice (Wrone-Smith and Nickoloff, 1996; Nickoloff and Wrone-Smith, 1999; Boyman *et al.*, 2004) supported the growing evidence that activated T cells are the primary modulators in the pathogenesis of psoriasis. Clinical studies on the therapeutic efficacy of T-cell-targeted drugs further substantiated the role of T cells in psoriasis (Abrams *et al.*, 2000; Goedkoop *et al.*, 2004). Characterization of cells and cytokines involved in the initiation and maintenance of psoriasis showed elevated levels of IFN-γ, tumor necrosis factor (TNF) -α, and IL -12, but not IL-4, IL-5, or IL-10, at both mRNA and protein levels (Nestle *et al.*, 1994; Schlaak *et al.*, 1994; Austin *et al.*, 1999). These observations led to the new definition of psoriasis as a T helper (Th) 1-type disease (Lew *et al.*, 2004).

Recently, a new population of IL-17-producing Th cells, accordingly named Th17, has been described and its involvement in model systems of autoimmunity shown (Weaver *et al.*, 2007). Furthermore, the development and maintenance of Th17 cells have been linked to IL-23, a key initiating cytokine in the development of autoimmunity (Bettelli *et al.*, 2007; Kastelein *et al.*, 2007).

The findings of elevated levels of IL-23 and Th17-related cytokines in cutaneous lesions and in the serum of psoriatic patients, the association of *IL23R* gene variants with psoriasis, and the evidence of a functional role of Th17 cells in autoimmunity, provide the basis for a rising interest in the IL-23/Th17 axis in psoriasis (Blauvelt, 2008). In this review, we will discuss the biology and function of the IL-23/Th17 pathway, its potential dysregulation in psoriasis, and the exciting perspective of novel therapeutics targeting the IL-23/Th17 axis.

BIOLOGY OF IL-23 AND Th17 CELLS

IL-23 and the IL-23 receptor

IL-23 was discovered in 2000 by Oppmann and co-workers while searching sequence databases for members of the IL-6 cytokine family (Oppmann *et al.*, 2000). They identified a new protein designed as IL-23p19, which had no biological activity but, when combined with the IL-12p40 subunit of IL-12, formed a novel heterodimeric cytokine that they named IL-23.

IL-23 was found to be expressed by activated mouse and human monocytes, macrophages, dendritic cells (DCs), T cells, B cells, and endothelial cells (Oppmann *et al.*, 2000; Pirhonen *et al.*, 2002). IL-23 binds to and signals through its heterodimeric receptor complex composed of IL-12Rβ1 and IL-23R subunits (Parham *et al.*, 2002) (Figure 1). Whereas IL-12Rβ1 is also part of the IL-12 receptor, IL-23R is unique to the IL-23 receptor complex. IL-23R expression on memory T cells, natural killer T cells, monocytes, and DCs correlates with cellular responsiveness

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Abbreviations: Ab, antibody; CD, Crohn's disease; CIA, collagen-induced arthritis; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; KC, keratinocyte; MS, multiple sclerosis; PASI, psoriasis area and severity index; RA, rheumatoid arthritis; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor

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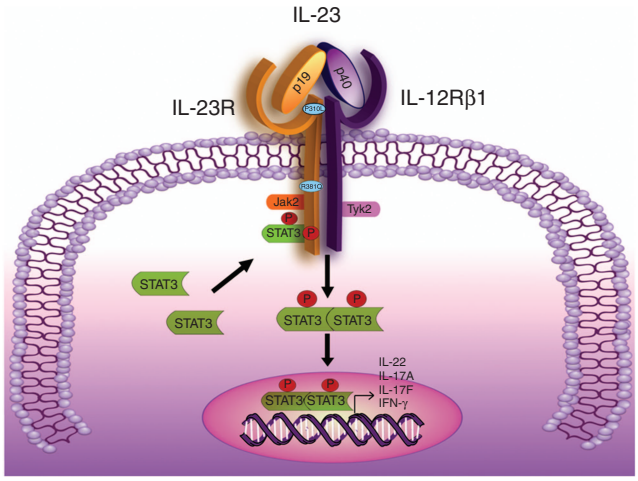

Figure 1. IL-23 signaling pathway. IL-23 is a heterodimeric cytokine composed of p40 and p19 subunits. It binds to its IL-23 receptor complex composed of IL-12Rβ1 and IL-23R subunits, which are associated with the Jak family members, Tyk2 and Jak2, respectively. IL-23 binding to its receptor complex results in Jak2-mediated phosphorylation of tyrosine residues located in the intracellular domain of the IL-23R subunit. Phosphorylated tyrosine residues serve as a docking site for STAT3 molecules, which in turn get phosphorylated. Phospho-STAT3 proteins homodimerize and translocate into the nucleus inducing transcription of cytokines, such as IL-17A, IL-17F, IL-22 and IFN-γ. Amino acid substitutions, arginine to glutamine (R381Q) and leucine to proline (L310P), in the IL-23R subunit, conferring protection against psoriasis, are shown.

to IL-23 (Belladonna *et al.*, 2002; Parham *et al.*, 2002; Rachitskaya *et al.*, 2008).

Both the IL-12Rβ1 and IL-23R chain lack intrinsic signaling activity and are associated with intracellular proteins to induce downstream signaling. IL-12Rβ1 binds to the Jak family member, Tyk2, whereas IL-23R associates with Jak2 (Zou *et al.*, 1997; Parham *et al.*, 2002). IL-23 stimulation results in ligand-induced autophosphorylation and transphosphorylation of receptor-associated Jaks. Jaks in turn phosphorylate tyrosine residues located in the intracellular domain of the receptor subunits. These phosphorylated tyrosine residues serve as docking sites for the signal transducer and activator of transcription (STAT) molecules, which in turn also get phosphorylated. Notably, IL-23 activates a similar spectrum of STATs as IL-12: STAT1, STAT3, STAT4, and STAT5 (Parham *et al.*, 2002); however, STAT3 is the main player in the IL-23 signaling pathway, whereas STAT4 is the main player in the IL-12 pathway. Once activated, STAT3 homodimers translocate into the nucleus, where they bind to the DNA in the promoter region of the target genes.

Since its discovery, IL-23 has been linked to the pathogenesis of autoimmune inflammation. Early studies showed that expression of IL-23p19 in multiple tissues of transgenic mice induced systemic inflammation, runting, infertility, and premature death (Wiekowski *et al.*, 2001). Interestingly, mice lacking IL-23p19 and IL-12p40 subunits, but not those lacking the IL-12p35-specific subunit, are resistant to animal models of autoimmunity, including experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA) (Cua *et al.*, 2003; Murphy *et al.*, 2003). Furthermore, the development of spontaneous colitis in IL-10-deficient mice is completely prevented by crossing them with IL-23p19-deficient mice (Yen *et al.*, 2006). These data, together with the observation that IFN-γ-producing cells are present in EAE-resistant, IL-23-deficient mice (Langrish *et al.*, 2005), showed that IL-23-driven immune responses are IFN-γ pathway independent and that IL-23, rather than IL-12, is critical for the development of autoimmune disease in these model systems. The expression of IL-23p19 in clinical samples of Crohn's disease (CD) (Schmidt *et al.*, 2005), rheumatoid arthritis (RA) (Sato *et al.*, 2006), and multiple sclerosis (MS) patients (Vaknin-Dembinsky *et al.*, 2006; Li *et al.*, 2007, 2008) supports a possible role of IL-23 in common human autoimmune diseases.

Robust evidence for a role of the IL-23 pathway in autoimmune diseases comes from recent genetic studies. Taking advantage of recently introduced high-throughput genotyping technologies, a number of genome-wide association studies have been carried out to identify novel susceptibility genes for common complex genetic diseases. We and others have conducted such studies in psoriasis and have identified a non-synonymous nucleotide substitution in exon 9 of the *IL23R* gene, which results in an arginine to glutamine exchange (Arg381Gln) in the cytoplasmic domain of the receptor, showing a protective role of the variant against psoriasis (Capon *et al.*, 2007; Cargill *et al.*, 2007; Nair *et al.*, 2008). The same effect has also been clearly documented in CD, ulcerative colitis, (Duerr *et al.*, 2006), ankylosing spondylitis (Rueda *et al.*, 2008), graft-versus-host disease (Elmaagacli *et al.*, 2008), and, with less significant results, also in celiac disease and MS (Nunez *et al.*, 2008). Additional variants in the *IL23R* gene have been associated with psoriasis (Cargill *et al.*, 2007; Nair *et al.*, 2008), RA (Farago *et al.*, 2008), Graves' disease (Huber *et al.*, 2008), and MS (Illes *et al.*, 2008), thus suggesting that variants in the *IL23R* gene, may be common determinants of autoimmunity. In addition, we and others have also shown that the *IL12B* gene, coding for the IL-12p40 subunit of IL-12 and IL-23, is associated with psoriasis (Capon *et al.*, 2007; Cargill *et al.*, 2007).

Th17 cells and cytokines

Initial studies showed that IL-23 is involved in the proliferation of human and murine memory T cells (Oppmann *et al.*, 2000); in contrast, naïve T cells do not respond to IL-23 as they express little or no IL-23R subunit (Parham *et al.*, 2002). Subsequent studies showed that IL-23 promotes the expansion of the novel Th17 population characterized by the production of IL-17A and other related proinflammatory cytokines (Aggarwal *et al.*, 2003; Harrington *et al.*, 2005; Langrish *et al.*, 2005; Park *et al.*, 2005). CD4+ Th cells are essential regulators of adaptive immune responses and inflammatory diseases. After activation by professional antigen-presenting cells, antigen-specific CD4+ T cells differentiate into effector cells according to the cytokine milieu, and specialize in terms of their secreted cytokines. Th1 cells produce IFN-γ as well as lymphotoxin, and are

involved in cell-mediated immunity against intracellular bacteria and viruses. Their development from naïve T cells depends on the presence of IL-12 and on the activation of the master regulator transcription factor, T-bet. Th2 cells produce IL-4, IL-5, IL-13, and IL-25 (IL-17E), and are implicated in humoral immunity against parasites and helminthes. IL-4 and the transcription factor GATA-3 are the key regulators of Th2 differentiation. Interestingly, each subset promotes its own development, whereas it inhibits that of other subsets through cytokine secretion. Immune activation that results from dysregulated Th1 responses to self or commensal antigens can promote autoimmune-type tissue destruction, whereas dysregulated Th2 responses can cause allergy and asthma.

Th17 cells represent the first new lineage of effector CD4+ T cells to be described since the original report of Th1 and Th2 subtypes by Mosmann *et al.* (1986) (Figure 2). IL-17A was originally described as a product of activated memory CD4+ T cells (Fossiez *et al.*, 1996), but Infante-Duarte *et al.* (2000) provided a first indication in 2000 that IL-17A-producing cells cannot be categorized according to the classical Th1/Th2 paradigm. In fact they showed that CD4+ T cells, primed with a synthetic peptide in the presence of the spirochete *Borrelia burgdorferi*, express IL-17A at significantly higher levels than do CD4+ T cells primed in the presence of IL-12, whereas Th2 cytokines, IL-4 and IL-10, were inhibited under the same conditions (Infante-Duarte *et al.*, 2000). The concept that the IL-17-producing T cell may be of a distinct T-cell lineage was further strengthened by the discovery of the IL-23 function (Aggarwal *et al.*, 2003) and by gene-targeted mice studies. In IL-23-deficient mice, CIA and EAE resistance correlates well with the absence of IL-17-producing T cells, despite normal induction of IFN-γ-producing Th1 cells, thus suggesting that the former are essential for the establishment of autoimmunity (Murphy *et al.*, 2003; Langrish *et al.*, 2005). Finally, the gene expression analysis of IL-17-producing cells identified a unique expression pattern of proinflammatory mediators, including IL-17A, IL-17F, IL-6, CCL20, and GM-CSF (Langrish *et al.*, 2005). Definitive arguments pointing toward IL-17-producing cells as a distinct T-cell lineage arose simultaneously from two laboratories, showing that the development of murine Th17 cells from naïve T cells is potently inhibited by IFN-γ and IL-4 (Harrington *et al.*, 2005; Park *et al.*, 2005). During recent years, cytokines and signaling pathways involved in Th17 differentiation have been widely investigated in both mice and humans. Expanding the initial *in vivo* observations (Aggarwal *et al.*, 2003; Cua *et al.*, 2003; Langrish *et al.*, 2005), it has been shown later that, in mice, IL-23 alone is not sufficient to drive *in vitro* Th17 differentiation from naïve T cells as they do not express IL-23R; rather, it acts on the already committed Th17 population. In fact, transforming growth factor (TGF)-β1, together with IL-6, IL-21, and subsequently IL-23, promotes differentiation of Th17 cells from naïve CD4+ T cells (Bettelli *et al.*, 2006; Mangan *et al.*, 2006; Veldhoen *et al.*, 2006; Korn *et al.*, 2007). This finding was initially surprising as TGF-β1 is known to induce the development of regulatory T cells with a potent suppressor function (Chen *et al.*, 2003). Consistent with their definition as a *bona fide* distinct T-cell lineage, the development of Th17 cells does not involve any of the transcription factors implicated in Th1/Th2 differentiation. On the contrary, both *in vitro* and *in vivo* differentiation of Th17 cells required the TGF-β1-induced upregulation of the unique lineage-specific transcription factor, ROR (retinoid-related orphan receptor)γt, an orphan nuclear receptor (Ivanov *et al.*, 2006; Zhou *et al.*, 2007). Furthermore, activation of STAT3 (Mathur *et al.*, 2007; Yang *et al.*, 2007), as well as involvement of the orphan nuclear receptor RORα (Yang *et al.*, 2008b) and of the aryl hydrocarbon receptor (Quintana *et al.*, 2008; Veldhoen *et al.*, 2008) have been suggested to be important in Th17 development.

A paucity of data regarding Th17 differentiation in humans has been recently rectified by several publications addressing key issues pertinent to possible differences between mouse and human Th17 biology (Chen and O'Shea, 2008).

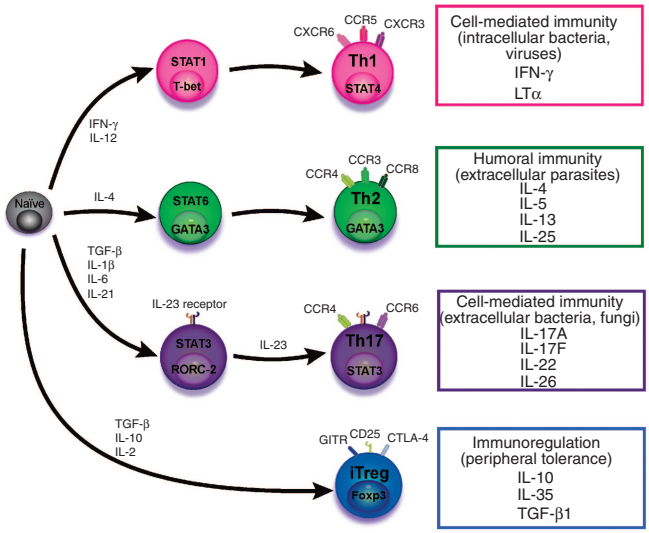

Figure 2. Model for T helper (Th) or T regulatory (Treg) differentiation from naïve CD4+ T cells. Th1 cells differentiate in the presence of IL-12, and require activation of the master regulator transcription factor, T-bet, through STAT1. Fully committed Th1 cells express chemokine receptors, CXCR6, CXCR3, and CCR5, and produce IFN-γ and lymphotoxin through STAT4. They are involved in cell-mediated immunity against intracellular bacteria and viruses. Th2 cells depend on the presence of IL-4, STAT6, and GATA-3, and release IL-4, IL-5, IL-13, and IL-25. Th2 cells express chemokine receptors, CCR3, CCR4, and CCR8, and are important in humoral immunity against parasites and helminthes. Th17 cells require a combination of TGF-β1 and proinflammatory cytokines (IL-1β, IL-6, and/or IL-21) to differentiate from naïve CD4+, and RORC-(variant) 2 acts as the key transcriptional regulator. Upregulation of the IL-23 receptor makes these cells responsive to IL-23. Human Th17 cells produce, for example, IL-17A, IL-17F, IL-22, and IL-26, and are important in host protection against extracellular pathogens and in autoimmunity. Their surface markers include chemokine receptors, CCR4, CCR6, and CD161 (not shown). In addition to effector T cells, naïve CD4+ T cells can also differentiate into induced Treg (iTreg) in the presence of IL-2 and TGF-β1 or IL-10. iTreg produces immunosuppressive cytokines, TGF-β1, IL-10, and IL-35, and express surface markers, GITR, CD25, and CLTA-4. Similar to thymus-derived naturally occurring Treg (nTreg, not shown), iTreg also expresses the master regulator transcription factor, Foxp3.

Early studies had shown that *in vitro* polarization of human Th17 cells from naïve CD4+ cells occurs in the presence of toll-like receptor-activated monocytes (Evans *et al.*, 2007) and also that proinflammatory cytokines, such as IL-1β and IL-6, alone or in combination with IL-23, were able to drive Th17 differentiation (Chen *et al.*, 2007; Wilson *et al.*, 2007; Acosta-Rodriguez *et al.*, 2007a). In particular, IL-1β was sufficient to induce the expression of RORC variant 2, the human ortholog of mouse RORγt, and the production of both IL-17A and IFN-γ (Acosta-Rodriguez *et al.*, 2007a), whereas a combination of IL-6 and IL-1β promoted the differentiation of T cells producing IL-17A, but not IFN-γ (Acosta-Rodriguez *et al.*, 2007a). Surface phenotype analysis of these cells showed that IL-17A-producing cells express the chemokine receptors, CCR6 and CCR4, whereas IFN-γ/IL-17-producing cells express CCR6 and CXCR3 (Acosta-Rodriguez *et al.*, 2007b). Recently, CD161 has been found to be expressed in IL-17A-producing cells and has been suggested as a novel surface marker for human Th17 cells (Cosmi *et al.*, 2008).

However, the most challenging aspect of human Th17 biology is the role of TGFβ-1. Although dismissed for a while, an absolute need for TGFβ-1 in human Th17 differentiation is now being recognized (O'Garra *et al.*, 2008). Initial studies showed that TGFβ-1 does not promote Th17 differentiation but rather inhibits IL-17A production in a dose-dependent manner (Chen *et al.*, 2007; Wilson *et al.*, 2007; Acosta-Rodriguez *et al.*, 2007a). However, recent reports have shown that in humans also, low concentrations of TGFβ-1 are necessary to differentiate human naïve CD4+ T cells into Th17 cells, either in combination with IL-21 (Yang *et al.*, 2008a), with IL-1β and IL-23 (Manel *et al.*, 2008) or with IL-1β, IL-23, and IL-6 (Volpe *et al.*, 2008). Although these studies differ slightly in their conclusions about the relative role of proinflammatory mediators, they have collectively shown that, similar to that in mice (Zhou *et al.*, 2008), TGF-β1 concentration and the concomitant presence of at least one proinflammatory cytokine are key factors in human Th17 differentiation. In fact, low concentrations of TGF-β1 synergizes with proinflammatory cytokines such as IL-1β, IL-6, IL-21, and IL-23 (Manel *et al.*, 2008; Yang *et al.*, 2008a) to promote IL-23R expression, thus favoring the differentiation of naïve cells into the Th17 effector lineage, whereas, high levels of TGF-β1 and the absence of inflammatory cytokines would rather inhibit Th17 differentiation, shifting the balance toward regulatory T cell development (Manel *et al.*, 2008). The presence of a discrete amount of TGF-β1 in the human and bovine serum used in earlier studies probably accounts for the inability to observe TGF-β-induced Th17 differentiation. Finally, using a different approach on the basis of particular genetic traits affecting putative Th17-relevant signals, de Beaucoudrey *et al.* (2008) have recently confirmed that, among other cytokines, IL-23 is indeed required for an optimal development of human Th17 cells.

In parallel to factors required for Th17 commitment, natural inhibitors of Th17 development have also been identified. As mentioned, both Th1 (IFN-γ) and Th2 (IL-4) cytokines inhibit Th17 differentiation (Harrington *et al.*, 2005; Park *et al.*, 2005). More recently, IL-25, a member of the IL-17 family earlier known as IL-17E and involved in Th2 response (Angkasekwinai *et al.*, 2007), has been found to negatively regulate Th17 cells by inhibiting the expression of IL-1β and IL-23 by DC (Kleinschek *et al.*, 2007). Likewise, IL-27, belonging to the IL-6 family (Pflanz *et al.*, 2002), also acts as a Th17 inhibitor, consistent with its capacity to drive a Th1 cell response (Batten *et al.*, 2006; Stumhofer *et al.*, 2006).

In addition to IL-17A, Th17 cells have been collectively shown to also produce IL-17F, IL-22, and IL-26, as well as IL-6, IL-21, TNF-α, and IFN-γ (Chen *et al.*, 2007; Wilson *et al.*, 2007; Acosta-Rodriguez *et al.*, 2007a; Manel *et al.*, 2008; Volpe *et al.*, 2008). To date, IL-17A, IL-17F, and IL-26 are considered to be specific Th17 cytokines (Manel *et al.*, 2008), whereas the others, including IL-22, can be produced by Th1 cells also (Volpe *et al.*, 2008). In this review, we will focus our attention on those cytokines produced by Th17 cells that have been shown to be of potential relevance to cutaneous inflammation.

Human IL-17A is the founding member of the IL-17 cytokine family, which includes six members, IL-17A to F. Very little is known about IL-17B, IL-17C, and IL-17D, which are produced by non-T-cell sources, whereas IL-17E has been renamed IL-25 and IL-17F shares many features with IL-17A (Weaver *et al.*, 2007). Although Th17 cells are the major source of IL-17A, other IL-17A-producing cells have also been reported, including CD8+ cells (Shin *et al.*, 1999), γδ-TCR cells (Roark *et al.*, 2008), and natural killer T cells (Rachitskaya *et al.*, 2008). IL-17F shares 50% sequence homology with IL-17A and both cytokines can exist either as IL-17A and IL-17F homodimers or as IL-17A-IL-17F heterodimers (Liang *et al.*, 2007). They all induce the expression of diverse proinflammatory cytokines (for example, IL-1β and IL-6), colony-stimulating factors (for example, GM-CSF and granulocyte colony-stimulating factors), and chemokines (for example, CXCL8, CXCL1, and CXCL10) from a variety of cells, including monocyte/macrophages, and epithelial cells. Accordingly, IL-17A and IL-17F have potent activity to mobilize, recruit, and activate neutrophils, thus linking adaptive and innate immunity (Weaver *et al.*, 2007).

IL-22 is a member of the IL-10 cytokines family, and is mainly produced by T and natural killer cells (Wolk *et al.*, 2002). Neither resting nor activated immune cells respond to IL-22. In contrast, tissue cells at outer body barriers, that is, of the skin, kidney, and the digestive and respiratory systems are targets of this cytokine. IL-22 functions by promoting antimicrobial defense mechanisms, protecting against tissue damage, and re-organizing non-immune tissues, such as epithelia, thus regulating terminal differentiation of KCs (Wolk and Sabat, 2006).

Functional analysis of Th17 cytokines has revealed an important and unique role for these cytokines in host protection against infections with extracellular pathogens. IL-17R-deficient mice are highly susceptible to infection by the Gram-negative bacterium, *Klebsiella pneumoniae,* and the fungus, *Candida albicans* (Ye *et al.*, 2001; Huang *et al.*, 2004). In addition, the preferential production of IL-17 by T cells during infection by *Bacteroides fragilis* (Chung *et al.*,

2003), *Borrelia burgdorferi*, *Mycobacterium tuberculosis* (Infante-Duarte *et al.*, 2000), and the fungal species (LeibundGut-Landmann *et al.*, 2007), suggests that Th17 responses are triggered by specific pathogens and are required for their clearance. These data are supported by recent findings showing that null mutations in *IL12B* and *IL12RB1* genes lead to impaired IL-17-producing T-cell development in patients with autosomal-recessive susceptibility to mycobacterial diseases (de Beaucoudrey *et al.*, 2008). A number of autoimmune disorders have been associated with overproduction of Th17 cytokines, and interference with their production or action attenuate autoimmune diseases. IL-17-deficient mice are resistant to adjuvant-induced arthritis (Nakae *et al.*, 2003) and develop EAE with delayed onset and reduced severity (Komiyama *et al.*, 2006). Similarly, IL-17R antagonists (Bush *et al.*, 2002) and IL-17A-blocking antibodies (Abs) (Hofstetter *et al.*, 2005; Langrish *et al.*, 2005) prevent the development of autoimmune diseases.

Under homeostatic conditions, IL-17A is present in extremely low or undetectable concentrations in human sera but has been reported to be overproduced at the both serum and tissue level in inflammatory bowel diseases, MS, and RA; (Kotake *et al.*, 1999; Matusevicius *et al.*, 1999; Lock *et al.*, 2002; Fujino *et al.*, 2003). Similarly, IL-22-expressing T-cells are present in inflamed regions of the gut in patients with inflammatory bowel diseases but not in the normal colonic mucosa (Andoh *et al.*, 2005). IL-22 expression was also described in both synovial tissues and in mononuclear cells of the synovial fluid from RA patients (Ikeuchi *et al.*, 2005).

ROLE OF IL-23 AND TH17 CELLS IN PSORIASIS

IL-23 and the IL-23 receptor in psoriasis

The role of IL-23 and IL-23R in cutaneous inflammation has been investigated both in mice and in humans. Intradermal injection of IL-23 in mice led to erythema, induration, and prominent dermal papillary blood vessels with histopathological features resembling psoriasis (Chan *et al.*, 2006). The morphological features of the IL-23-induced skin lesions were more severe than the ones induced by IL-12 (Zheng *et al.*, 2007). Furthermore, IL-23 was shown to mediate epidermal hyperplasia, acanthosis, hyperparakeratosis, and orthohyperkeratosis through TNF-α and IL-20R2 (Chan *et al.*, 2006). In a transgenic mouse model of skin inflammation overexpressing the common IL-12/IL-23 subunit, IL-12p40, under the influence of the keratin 14 promoter, it was shown that IL-12p40 and IL-23p19, but not IL-12p35, were constitutively produced by basal KCs (Kopp *et al.*, 2003). These data were complemented in humans by Lee *et al.* (2004) showing overexpression of IL-23p19 and IL-12p40, in the absence of IL-12p35, at the mRNA level in psoriatic skin lesions, when compared with that in uninvolved skin. IL-23p19 was mostly localized in the papillary dermis, and it was strongly expressed in monocytes, monocyte-derived DCs, and in mature DCs. Collectively, these data indicate that production of IL-23 occurs at inflammatory skin sites and is mediated by tissue-resident and/or recruited immune cells, such as DCs, and possibly KCs (Piskin *et al.*, 2006).

Little is known about the immediate downstream effects of IL-23 in psoriasis. IL-23 signals through the IL-23 receptor complex expressed on DCs, lymphocytes, natural killer T cells, and KCs. It has been recently shown that IL-23, in synergy with IL-1β, is able to enhance production of human-β-defensin-2, an antimicrobial peptide increased in psoriasis, in normal human KCs (Kanda and Watanabe, 2008). Further evidence supporting a pathogenic role of IL-23 in psoriasis comes from the clinical data. Zaba *et al.* (2007) have shown that anti-TNF-α agents are able to modulate IL-23p19 and IL-12p40 mRNA levels, and the inflammatory infiltrate in the psoriatic skin. Furthermore, modulation of IL-23 by cyclosporin A, UV therapy, and by biological agents has been correlated to the clinical benefit in psoriatic patients (Piskin *et al.*, 2004; Gottlieb *et al.*, 2005; Lowes *et al.*, 2008; Haider *et al.*, 2008b).

Finally, detailed genetic studies of the *IL23R* gene in psoriasis have recently shown that at least two non-synonymous single nucleotide polymorphisms, Arg381Gln and proline to leucine (Pro310Leu), independently contribute to a psoriasis phenotype (Capon *et al.*, 2007; Cargill *et al.*, 2007; Nair *et al.*, 2008). These convincing genetic data, in combination with data showing an association between *IL-12B* and psoriasis, support the importance of the IL-23 (and possibly IL-12) pathway in psoriasis.

Th17 cells and cytokines in psoriasis

Consistent with the described role of Th17 cells in a variety of chronic inflammatory autoimmune-type diseases, there is a growing body of evidence supporting a major role of Th17 cells and Th17-related cytokines in psoriasis. The first observation that IL-17 could be a relevant cytokine in psoriasis was found in the late 1990s. Teunissen *et al.* (1998) showed detectable levels of IL-17 mRNA in lesional psoriatic skin, but not in non-lesional skin, and showed that CD4+ and CD8+ clones derived from lesional psoriatic skin were able to produce IL-17 after stimulation with CD3/CD28 Abs. IL-17 was also shown to promote the production of IL-6, IL-8, GM-CSF, and ICAM-1 in KCs, synergizing with IFN-γ (Albanesi *et al.*, 2000; Koga *et al.*, 2008). IL-17-producing cells have been isolated from the dermis of psoriatic lesions (Lowes *et al.*, 2008). Dermal localization of Th17 cells has also been documented in atopic dermatitis, with a higher percentage of IL-17-producing cells present in acute rather than in chronic lesions (Koga *et al.*, 2008). Surface phenotypic analysis of IL-17-producing T cells derived from psoriatic skin as well as from intestinal biopsies of patients affected with CD, showed a predominantly CD161+ phenotype (Cosmi *et al.*, 2008). DCs isolated from psoriatic skin are able to increase the percentage of IL-17A production in allogenic T cells (Zaba *et al.*, 2009).

Interestingly, in contrast to other potential Th17-type autoimmune diseases such as RA (Chabaud *et al.*, 1999; Kohno *et al.*, 2008), CD (Fujino *et al.*, 2003), MS (Matusevicius *et al.*, 1999), systemic lupus erythematosus (Wong *et al.*, 2000), and systemic sclerosis (Kurasawa *et al.*, 2000), no statistically significant differences in peripheral levels of IL-17A have been found in psoriatic patients when

compared with that in controls (Arican *et al.*, 2005). This suggests that the major site of production of IL-17A in psoriasis may be the lesional skin infiltrated by Th17 cells. This concept is strengthened by the data derived from studies on cytokine profiles after various immunomodulatory treatments in RA and psoriatic patients. In RA, the efficacy of both cyclosporin A and anti-TNF-α therapies has been correlated to modulation of proinflammatory cytokines, both in peripheral blood and in synovia (Cho *et al.*, 2007; Kageyama *et al.*, 2007). In contrast, in psoriasis, the use of cyclosporin A and anti-TNF-α agents has been reported to decrease cutaneous, but not peripheral, levels of proinflammatory cytokines, such as IFN-γ, IL-17A, IL-23p19, and CCL20 (Zaba *et al.*, 2007; Lowes *et al.*, 2008; Haider *et al.*, 2008a, b).

A key cytokine produced by Th17 cells is IL-22. The role of IL-22 in the pathogenesis of psoriasis has been extensively examined because of its peculiar activities in immune innate response and functions on epithelial cells (Wolk *et al.*, 2006). IL-22, as well as IL-17, TNF-α, IL-1β, IL-6, IL-12p40, and IL-12, has been found elevated in ear tissues of a psoriasiform mouse model, that is, transgenic K14/VEGF mice treated with 12-O-tetradecanoyl phorbol-13-acetate (Hvid *et al.*, 2008). IL-23 injection in rodents induces IL-22-dependent dermal inflammation, KC hyperproliferation, and epidermal acanthosis (Wolk *et al.*, 2006; Zheng *et al.*, 2007). In a CD4 T-cell-dependent psoriasis mouse model, an IL-22-neutralizing Ab was able to modulate the cutaneous expression of S100A8, S100A9, defensin β1, and cathelicidins, as well as prevent the development of skin lesions (Ma *et al.*, 2008).

In vitro studies have shown that IL-22 synergizes with IL-17A and IL-17F to enhance the KC expression of antimicrobial peptides (Liang *et al.*, 2006; Wilson *et al.*, 2007). IL-22 can also drive epithelial cell release of chemokines, such as IL-8 (Brand *et al.*, 2006; Liang *et al.*, 2006; Koga *et al.*, 2008), a key factor for neutrophil recruitment into psoriatic lesions. Moreover, in reconstituted human epidermis, KCs express genes involved in tissue repair and wound healing responses on stimulation with IL-22 (Sa *et al.*, 2007).

Finally, increased IL-22 mRNA and protein levels have been found both in the skin and blood of psoriatic patients (Wolk *et al.*, 2006; Boniface *et al.*, 2007). IL-22 mRNA levels were higher in lesional skin than in psoriatic peripheral monocytes (Boniface *et al.*, 2007).

From these data, a concept emerges that IL-17A and IL-22 are key mediators of cutaneous inflammation, linking Th17 pathology with epithelial pathology, thus contributing to the pathogenesis of psoriasis (Figure 3). The IL-23/Th17 axis model for psoriasis integrates the well-defined type-1 inflammatory pathway model, in which Th1, Tc1 (cytotoxic T cell type-1) lymphocytes, and DCs are the central orchestrators of the events leading to psoriasis (Lew *et al.*, 2004). The molecular spectrum of the type-1 model of psoriasis is dominated by IL-12, produced by DCs, TNF-α, and IFN-γ, released by Th1 and Tc1 lymphocytes, which act on KCs by increasing their proliferation rates and stimulating their ability to release proinflammatory mediators. Typically, in the psoriatic plaque, Th1 lymphocytes are localized in the dermis, whereas Tc1 lymphocytes are mainly found in the epidermis expressing α1β1 integrin (VLA-1, very late antigen-1), which binds to basement membrane collagen IV (Conrad *et al.*, 2007). Therefore, it can be postulated that, in the psoriatic plaque, dermal dendritic cells produce both IL-12 and IL-23, driving a mixed type-1/Th17 infiltrate that interacts with KCs, fibroblasts, endothelial cells, and neutrophils to create a psoriatic plaque.

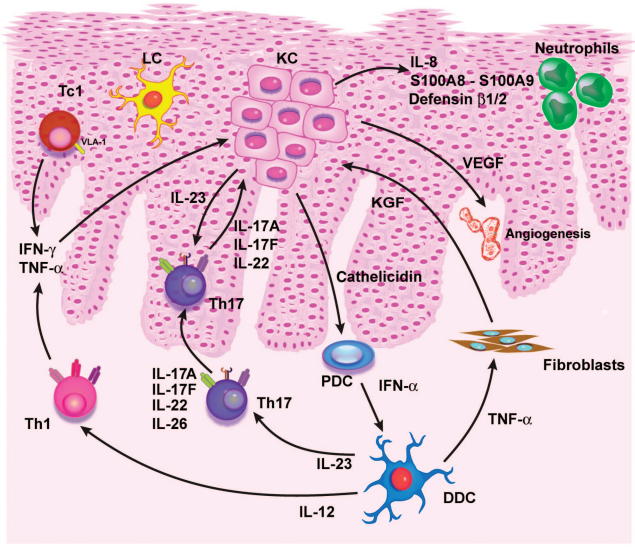

Figure 3. Th17 lymphocytes and psoriasis: cellular and molecular interactions with skin-resident cells. In the 'IL-23/Th17 axis' model for psoriasis, Th17 lymphocytes (Th17) interact with skin-resident cells, contributing to the psoriatic phenotype. In the dermis, IL-23, secreted by dermal dendritic cells (DDC), is able to induce Th17 lymphocyte activation with the consequent release of proinflammatory cytokines, such as IL-17A, IL-17F, IL-22, and IL-26. IL-17A, IL-17F, and IL-22 act on keratinocytes (KC) leading to epidermal hyperplasia, acanthosis, and hyperparakeratosis. Dermal CCR5 + CXCR3 + CXCR6 + Th1 and epidermal VLA-1 + Tc1 lymphocytes are activated by DDCs and produce TNF-α and IFN-γ, contributing to the pathogenesis of the disease. KC hyperproliferation might also be influenced by fibroblasts, which can release keratinocyte growth factor (KGF) through TNF-α stimulation. In the context of this proinflammatory milieu, activated KCs might produce IL-23, which could mediate a cross-talk with Th17 lymphocytes in synergy with IL-23 coming from DDC. Th17 cells induce KC to produce IL-8 and antimicrobial peptides (for example, S100A8, S100A9, and defensin β1/2) for recruitment of neutrophils, cathelicidin for activation of plasmacytoid dendritic cells (PDC), and vascular endothelial growth factor (VEGF) with resulting angiogenesis.

Targeting the IL-23/Th17 pathway in the treatment of psoriasis

Novel insights into the immunopathogenesis of psoriasis have led to the development of new effective therapies, characterized by highly selective mechanisms of action, targeting key immune cytokines and receptors.

With regard to the IL-23/Th17 axis, targeting the common subunit, p40, of IL-12 and IL-23 has shown clinical benefits in autoimmune-type diseases, such as CD and psoriasis. Two anti-IL-12p40 monoclonal Abs have been developed, namely, CNTO-1275/ustekinumab and ABT-874. An oral IL-12/23 inhibitor has been tested in early clinical trials in CD (Burakoff *et al.*, 2006).

Both CNTO-1275 and ABT-874 are human IgG1 MAbs that bind to the p40 subunit of human IL-12 and IL-23, and prevent its interaction with IL-12Rβ1. Preclinical analyses in cynomolgus monkeys, in the monkey asthma model and in the marmoset model for MS, and *in vitro* studies have been conducted to evaluate the safety of anti-IL-12p40 (Brok *et al.*, 2002; t Hart *et al.*, 2005). It has also been shown that anti-IL-12p40 can lead to a decrease in disease activity in the mouse models of MS (Leonard *et al.*, 1997) and CD (Neurath *et al.*, 1995). Anti-IL-12p40 successfully abolished psoriatic lesions in mice, even when administered after transfer of the T-cell subset that induced the psoriasis-like condition (Hong *et al.*, 1999; Ma *et al.*, 2008).

In humans, results from phase I (Kauffman *et al.*, 2004) and phase II studies (Krueger *et al.*, 2007; Kimball *et al.*, 2008) have shown that both CNTO-1275 and ABT-874 can be appropriate treatments for moderate-to-severe psoriasis (Nestle and Conrad, 2004), being able to modulate IL-8, IL-18, IFN-γ, cutaneous lymphocyte antigens (CLA), IL-12R, CD40L, and IL-2Rα expressions and to inhibit the secretion of cytokines induced by IL-12, and IL-23 in psoriasis as well as in CD (Fuss *et al.*, 2006; Toichi *et al.*, 2006; Gottlieb *et al.*, 2007; Reddy *et al.*, 2007). Indeed, clinical data from phase II studies on anti-IL-12p40 in CD further support IL-12p40 as an appropriate target for CD therapy (Mannon *et al.*, 2004). Notably, an oral treatment, STA-5326, which acts as a selective transcription inhibitor with potent anti-IL-12 and anti-IL-23 activity, has been reported as effective in preclinical studies on rat and murine models of CD and in a phase I/IIA trial in active moderate-to-severe CD (Burakoff *et al.*, 2006; Wada *et al.*, 2007).

Currently, several phase III trials have been published or are ongoing to evaluate the efficacy and safety of the anti-IL-12p40 MAb versus placebo or etanercept (anti-TNF-α therapy) in the treatment of moderate-to-severe chronic plaque psoriasis.

Leonardi *et al.* and Papp *et al.* have published the results of the PHOENIX 1 (Leonardi *et al.*, 2008) and PHOENIX 2 (Papp *et al.*, 2008), phase III, randomized, placebo-controlled trials evaluating the efficacy and safety of ustekinumab in moderate-to-severe psoriasis.

The PHOENIX 1 trial assessed the efficacy and safety of ustekinumab 45 and 90 mg, administered subcutaneously at weeks 0, 4, and then every 12 weeks over 76 weeks of treatment. Overall, a larger number of patients in the ustekinumab arm (both 45 and 90 mg) achieved PASI (Psoriasis Area and Severity Index)-75 at week 12 when compared with those in placebo (PASI-75 response in 67.1, 66.4, and 3.1%, respectively). Efficacy increased over time with the maximum effect at week 24 (PASI-75 response observed in 76.1% of patients treated with 45 mg and in 85% of patients in the 90 mg group) and improvement in the PASI score remained stable up to at least week 76. The occurrence of adverse events was similar during the whole duration of the study; it was not statistically different from the placebo group, and did not require treatment adjustment. The most commonly reported adverse events were mild and considered non-serious, and mostly consisted of upper respiratory tract infections, nasopharyngitis, headache, and arthralgia.

The aim of the PHOENIX 2 trial was to assess whether dosing intensification would increase the response to treatment in partial responder patients (between PASI-50 and PASI-75). The results up to week 28 were comparable with the ones reported in PHOENIX 1. At week 28, patients who responded to ustekinumab continued to receive the study agent every 12 weeks and maintained a good response up to week 52. Partial responders at week 28 (22.7 and 15.8% of patients in the 45 and 90 mg group, respectively) were randomly assigned to continue treatment every 12 weeks or, through an intensified regimen, every 8 weeks. Dosing intensification did result in increased clinical efficacy only in patients receiving 90 mg, and not 45 mg, of ustekinumab every 8 weeks (PASI-75 in 68.8% of patients receiving 90 mg every 8 weeks versus 33.3% of patients receiving 90 mg every 12 weeks). The incidence and the kind of adverse events that occurred during the PHOENIX 2 study did not differ from those reported in the PHOENIX 1 trial.

Overall, the results of the clinical studies on the efficacy of anti-IL-12p40 Abs observed so far are promising, suggesting that ustekinumab and possibly ABT-874 could provide a new and effective treatment for moderate-to-severe psoriasis, thus stressing the important role of IL-12/IL-23 in the pathogenesis of the disease. Moreover, anti-IL-12p40 Abs have so far shown a good safety profile during treatment periods of up to 76 weeks. Nevertheless, long-term safety issues are to be considered given the relevant part played by IL-12p40 in host defense (Trinchieri, 1998), potentially leading to increased susceptibility to infections in patients treated with anti-IL-12p40. In humans, mutations in the IL-12p40 subunit or in its receptor have been associated with susceptibility to tuberculosis and salmonella infections, but not to viral or fungal infections (Altare *et al.*, 1998; de Jong *et al.*, 1998; Oxenius *et al.*, 1999).

Taken together, targeting both IL-12 and IL-23 is a highly effective therapeutic approach in chronic plaque-type psoriasis. Future studies will show if targeting IL-23 on its own will be effective. Longer follow-up periods with the establishment of treatment registries are necessary to confirm the safety of anti-IL-12p40 Abs in the treatment of moderate-to-severe chronic plaque psoriasis.

CONCLUSIONS

A significant amount of both clinical and experimental data have established Th17 cells as key players in chronic inflammatory conditions, such as psoriasis, providing an exciting advance in our understanding of psoriasis immunopathogenesis and novel therapeutic targets.

This puts the spotlight on IL-23, which is secreted by skin DCs, and induces production of proinflammatory mediators by Th17 cells such as IL-17A, IL-17F, and IL-22. These mediators will act on KCs leading to their activation and hyperproliferation. In the cross-talk between KC and Th17 cells, activated KCs produce key proinflammatory cytokines, chemokines, and antimicrobial peptides, which are able to recruit and activate immune cells in the inflamed skin. These events result in amplification of the immune response, leading to the clinical features of the disease.

Integration of the IL-23/Th17 axis into a revised concept of psoriasis pathogenesis has been already translated into novel therapeutic strategies, which are proving to be effective and safe in the treatment of chronic plaque psoriasis. Future investigations will further clarify the role of key components of the IL-23/Th17 axis, and their interplay with other relevant cellular and molecular pathways of the innate and adaptive immune system in psoriasis.

CONFLICT OF INTEREST

Dr Nestle has provided consultant activity to Centocor, Abbott, and Janssen Cilag. The other authors state no conflict of interest.

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