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The IL-12 Family Member p40 Chain as a Master Switch and Novel Therapeutic Target in Psoriasis

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Psoriasis is one of the most prevalent T cell-mediated inflammatory disease in humans. It is also listed among the most common autoimmune diseases (Davidson and Diamond, 2001). It, however, shares with chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease the absence of a known autoantigen. The pathogenesis of psoriasis is thought to depend on the activation of lesional and/or circulating T cells and their secreted products leading to keratinocyte hyperproliferation and angiogenesis with marked ectasia of blood vessels (Lew *et al*, 2004; Nickoloff and Nestle, 2004). There is convincing *in vitro* and *in vivo* evidence in clinically relevant mouse models and humans that tumor necrosis factor-α (TNF-α) is a master cytokine relevant to the disease process (Chaudhari *et al*, 2001; Boyman *et al*, 2004). Yet, the presence of TNF-α does not fully account for the known T helper (Th) 1-dominated cytokine milieu including the presence of ample amounts of interferon-γ (IFN-γ) in lesional psoriatic skin. A key question in psoriasis research relates therefore to factors orchestrating the Th1-immune response *in situ*. Potential candidates include the interleukin (IL)-12 family members IL-12 and the recently described cytokine IL-23. IL-12 p40 and p35 mRNA as well as p70 protein has been detected in psoriasis lesions (Yawalkar *et al*, 1998). Recent evidence, however suggests that IL-23, rather than IL-12, might be a key cytokine in psoriatic lesions based on the finding that p19 and p40, but not p35mRNA are increased in psoriatic lesions (Lee *et al*, 2004).

Both IL-12 and IL-23 are members of the IL-12 family of cytokines sharing a common p40 subunit. p40 forms heterodimers with p35 in IL-12 and p19 in IL-23. IL-12 and IL-23 bind to IL-12Rβ1/IL-12Rβ2 and IL-12Rβ1/IL-23R, respectively. Engagement of IL-23 with its receptor activates a similar spectrum of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) molecules as IL-12 but in contrast to IL-12, the most prominent STAT induced by IL-23 are STAT3/STAT4 heterodimers rather than STAT4 homodimers (Trinchieri *et al*, 2003). The physiological source of IL-12 and IL-23 are similar. Many cell types express p19 or p35 mRNA, but the relatively restricted expression of p40 subunits limits potential IL-12- and IL-23-producing cells to B cells, monocytes/macrophages and dendritic cells (DC). The receptor complex for IL-12/IL-23 is expressed or upregulated on T and NK cells, as well as on cells of the myelomonocytic lineage including DC. The effects of IL-12 and IL-23 on the immune response are comparable but distinct. Whereas IL-12 mainly stimulates IFN-γ production in naïve Th cells, IL-23 preferentially stimulates IFN-γ production and proliferation of memory Th1 cells. On the basis of the early known biology of these two cytokines it has been suggested that IL-12 would play a role in the expansion and stabilization of the Th1 response, and IL-23 would sustain proliferation of memory T cells, thus maintaining a Th1-committed memory response (Trinchieri *et al*, 2003).

Novel insight into the pathogenesis of psoriasis has spurred the development of biologic therapies selectively targeting key cytokines and receptor–ligand interactions (Kupper, 2003; Lew *et al*, 2004; Nickoloff and Nestle, 2004). The vision of a single cytokine as potential therapeutic target for the treatment of psoriasis has been validated with the triumphant march of anti-TNF-α based therapies. Fusion proteins or antibodies blocking the biological effects of TNF-α have demonstrated potent anti-psoriatic activity in phase I and II trials (Chaudhari *et al*, 2001; Leonardi *et al*, 2003). Based on these promising data the search is open for other master cytokines with therapeutic potential in the pathogenesis of psoriasis. One such candidate are members of the IL-12 family of heterodimeric proteins sharing the p40 chain.

In this issue, Kauffmann *et al* demonstrate in a phase I, first in human, nonrandomized open label study that a single intravenous infusion of a human neutralizing monoclonal antibody to the human IL-12 family member p40 subunit (anti-IL-12p40) is generally well tolerated and induces concentration-dependent improvements of psoriatic lesions. The rationale for the study is that interruption of the IL-12p40/IL-12Rβ1 interaction will prevent the biological activity of IL-12, IL-23 and potentially other IL-12 family members with concomitant interference of the pathogenic Th1 environment in psoriasis. Eighteen patients with body surface area ranging from 3% to 35% and at least two plaques located on either the trunk or extremities were treated with a single intravenous infusion. Doses ranged from 0.1 to 5.0 mg per kg. There were no serious adverse events related to the study drug. The most commonly reported adverse events included transient decreases in CD4+ and CD16/56+ cells, headache, common cold symptoms and pain at the biopsy site. Twelve of 18 subjects (67%) achieved at least 75% improvement in psoriasis activity and severity index (PASI) between 8 and 16 wk after study administration. Clinical improvements were concentration dependent.

Abbreviations: DC, dendritic cell; IFN-γ, interferon-γ; IL, interleukin; Th1, T helper 1; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor-α

This phase I study suggests that anti-IL-12p40 represents an exciting new therapeutic target in plaque-type psoriasis. It, however has to be mentioned that, as a result of the early nature of clinical compound development, several caveats remain and important questions are yet to be answered. Long-term safety will be a primary concern in future studies taking into account IL-12p40 knockout mice data showing increased susceptibility to bacterial, parasitic and especially mycobacterial infections (Lankford and Frucht, 2003). Repeated infusions and their impact on safety and antibody induction need to be studied. Moreover, solid clinical data on kinetics and duration of clinical response are needed. It is too early to speculate about the future place of anti-IL-12p40 in the arsenal of biologic agents for psoriasis. Nonetheless, members of the IL-12 family of cytokines clearly have the potential to represent the next master cytokine(s) in the pathogenesis and therapy of psoriasis. One apparent difference compared with the gold standard in anti-cytokine therapy, i.e., anti-TNF-α treatment, is a potentially later onset of the therapeutic response with anti-IL-12p40. This fact could be explained by the interference of anti-IL-12p40 with effector molecules relevant in later phases of the autoimmune response in psoriasis.

How can we integrate the findings of Kauffmann *et al* in our current view of the pathogenesis of psoriasis?

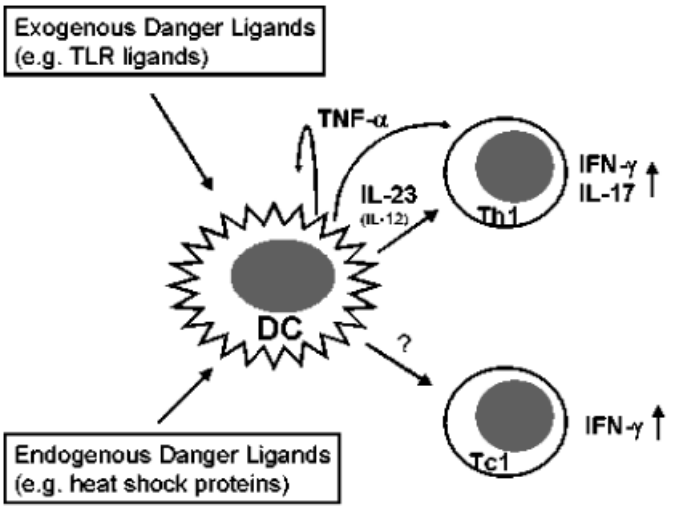

Figure 1
Integrating interleukin (IL)-12 family members IL-12 and IL-23 in the pathogenesis of psoriasis. Dendritic cell (DC)–T cell interactions are at the center stage of the psoriatic disease process. DC secrete IL-12 family members such as IL-12 and IL-23 which share the common IL-12p40 chain. Engagement of their respective receptors leads to proliferation of lesional psoriatic Th1 memory cells as well as the secretion of interferon (IFN)-γ. This will turn on an IFN-dependent transcriptional program typical for psoriasis and the downstream activation of psoriasis-specific chemokines, inducible nitric oxide synthetase, and IL-8. Tumor necrosis factor-α (TNF-α) is mainly produced by lesional myelomonocytic cells and acts on DC as well as T cells. Open questions remain: the definition of ligands activating lesional DC in psoriasis such as endogenous (e.g., heat shock proteins) or exogenous danger ligands (pathogen derived products) as well as factors activating lesional Tc1 T cells.

The ménage a trois between DC, T cells and keratinocytes provides the basis for the unique molecular signature defining a typical psoriatic lesion. More specifically, signals exchanged at the immunological synapse between lesional myeloid DC and T cells as shown in Fig 1 are at the center stage of the chronic inflammatory disease process. The central role of TNF-α in shaping the psoriatic disease process is well appreciated (Boyman *et al*, 2004); however, signals driving the Th1-biased effector response need to be defined in an *in vivo* setting in humans. The findings by Kauffmann *et al* provide supportive evidence for a major role of IL-12 family members such as IL-23 and IL-12 in the pathogenesis of psoriasis, most likely by driving IFN-γ production by Th cells. The obvious cellular source of IL-12 family members are lesional DC activated by endogenous (e.g., heat shock proteins) or exogenous (e.g., toll like receptor ligands) danger ligands, TNF-α or CD40L derived from activated T cells. Future research needs to focus on a better understanding of signals activating lesional DC and also has to to investigate in more detail factors which drive the prominent epidermal Tc1 response in psoriasis. Such work will undoubtedly lead to novel molecular therapeutics for the benefit of the numerous patients suffering from psoriasis.

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