

Immunology of Psoriasis Part I

The Th17 Cytokine Nexus: A New Target for Psoriasis Therapy

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In a recent issue of the New England Journal of Medicine, Krueger et al. (1) published the results of a successful treatment of psoriasis, using a novel monoclonal antibody directed against p40 protein. A single injection of this antibody (CNT01275) resulted in a significant response in 2/3 patients (PASI75-response) whereas four repeated weakly application resulted in PASI75-response in >80% of the patients. These results are comparable with the responses obtained using potent TNF α blockers, infliximab and adalimumab.

Obviously, the results of the CNT01275 trial are significant from the clinical point of view, since this antibody is the first non-TNF α targeted biological therapy of high potency. But even more importantly, the successful therapeutic targeting of the p40 protein has modified our understanding of the pathogenesis of psoriasis and is likely to lead to the identification of new therapies in the near future.

Psoriasis is an autoimmune disease. Until very recently the pathogenesis of psoriasis was explained in the terms of disturbed Th1-Th2 balance. Traditional immunopathology teaches us that naïve CD4 cells differentiate during the course of the immune response into two effector

cell population. This differentiation process is regulated by the nature of the antigen and the soluble cytokines released by the dendritic cells. In case of parasitic infection the dendritic cell will release IL-4 and the T-cell will differentiate into the Th2 cell. The immune system is confronted with bacterial infections, and the dendritic cells react by producing interferon γ (IFN- γ) and IL-12 which results in an emergence of Th1 cells. Autoimmune diseases have also been interpreted in the context of the disturbed Th1/Th2 balance. Allergic disorders such as asthma or atopy has been thought to be caused by an exaggerated Th2 response whereas psoriasis, Crohn's disease and rheumatoid arthritis are examples of awry Th1 response. Some clinical observations seemed to confirm this scenario. Firstly, atopic dermatitis is underrepresented in the patients with psoriasis suggesting that Th1 and Th2 responses are mutually exclusive. Secondly, psoriasis is known to be associated with other Th1 diseases, such as Crohn's disease. Thirdly, administration of Th1 cytokines to patients with psoriasis (such as alpha interferon) results in an exacerbation of the disease

(2). Reversely, IL-10, a Th2 cytokine, seems to ameliorate the disease after subcutaneous injection (3). Moreover, the p40 subunit of the dimeric IL-12 protein was found to be over-expressed in psoriasis skin.

However, it turned out in the meantime, that another cytokine, IL-23 is structurally similar to IL-12, and both interleukins share a common p40 subunit. A more detailed investigation revealed that in fact the elevated p40 in psoriasis skin seems to be entirely derived from IL-23 (4). Convincing evidence that IL-23 is important came from studies on mice where intracutaneous injection of IL-23 caused a psoriasis phenotype, but IL-12 did not.

Why are these data important? The very significant issue is that IL-23 does not play any significant role in either Th1 or Th2 responses, but is a key mediator of a third differentiation pathway into the so-called Th17 lymphocytes. Fig. 1 depicts our current understanding of the differentiation of CD4+ T cells. The name of Th17 is derived from their ability to release

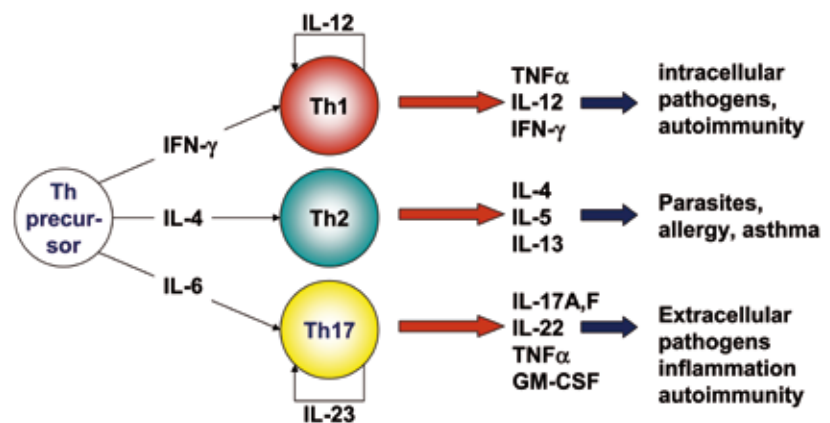


Fig. 1. Known subtypes of Th cells.

high amounts of IL-17. In addition these cells produce IL-22, TNF α , GM-CSF (all three cytokines involved in psoriasis pathogenesis) and their development is mediated by a concerted action of IL-6 and TGF β .

The Th17 cells are under very intensive scrutiny, since they are also supposed to be centrally involved in pathogenesis of rheumatoid arthritis and Crohn's disease (5). Interestingly, the development and expansion of Th17 depends on 3 crucial cytokines (Fig. 2): IL-6 which is essential for the differentiation of the precursor T-cell to Th17 and the already mentioned IL-23 which is released by dendritic cells and allows for Th17 proliferation in response to the antigen (5). In turn the IL-23-induced psoriasiform phenotype requires the activity of IL-20 and IL-22 (4, 6) (Fig. 2). In that way

4 other possible therapeutic targets (interleukins 6, 20, 22, 23) in psoriasis are identified. There are already promising early data suggesting the usefulness of anti-IL-20 approach in psoriasis. Also anti-IL-6 has been synthesized (tocilizumab) and gained promising results in rheumatoid arthritis (7). It is likely that we soon will see the development of anti-IL-6 for psoriasis.

The story of anti-p40 IL12/IL23 antibody is a fascinating example of the interaction between basic and clinical research. Translational research in psoriasis, taking both hands from the vast knowledge on immunology of autoimmune diseases led to the idea of Th1/Th2 imbalance due to excessive IL-12 signalling. Clinical research with CNTO1275 seemed to confirm this assumption. However,

the concept has been a victim of its own success. Very promising clinical results precipitated an avalanche of basic research that revealed that the success with the anti-IL12 approach was solely to the cross-reactivity of the antibody with IL-23. In consequence the Th1 cell was dethroned, the Th17 cell reigns now in the realm of immunopathogenesis of psoriasis.

References

1. Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, et al.; CNTO 1275 Psoriasis Study Group. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007; 356: 580-592.
2. Quesada JR, Gutterman JU. Psoriasis and alpha-interferon. *Lancet*. 1986; 1: 1466-1468.
3. Asadullah K, Sterry W, Stephanek K, Jasulaitis D, Leupold M, Audring H, et al. IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. *J Clin Invest* 1998; 101: 783-794.
4. Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004; 199: 125-130
5. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007; 25: 821-852.
6. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W. Interleukin-22, a Th17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007; 445: 648-651.
7. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al.; CHARISMA Study Group. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; 54: 2817-2829.

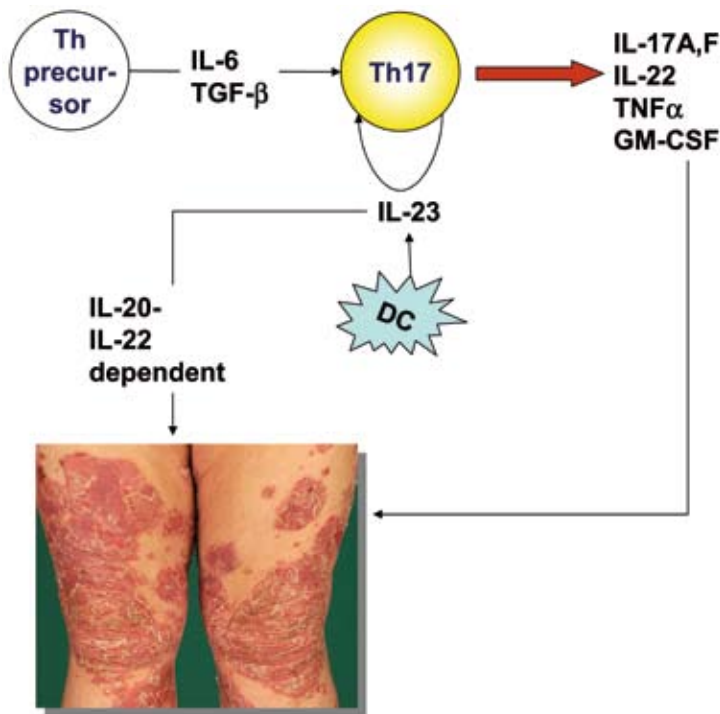


Fig. 2. Role of Th17 cells in psoriasis.