Immunopathogenesis of Psoriasis: Emphasis on
the Role of Th17 Cells

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Introduction

Psoriasis is a chronic inflammatory disease that occurs in genetically susceptible individuals and affects 2% to 3% of the population worldwide. Hereditary predisposition, environmental factors and immunological mediators are all involved in the pathogenesis of psoriasis (Fig.1). Several studies have demonstrated the familial association of the disease thanks to concordance rates among twins affected with psoriasis. Such investigations have shown the concordance rate for dizygotic twins is only 22% compared with a high rate of 72% for monozygotic twins.[1] In addition, HLA class I and II antigens such as HLA-B13, -B17, -B39, -B57, -Cw6, -Cw7, -DR4 and -DR7 also have been shown to be positively associated with the pathogenesis of psoriasis.[2,3]

Different environmental factors have been shown to trigger the first episode of psoriasis in those individuals who already have a genetic predisposition. These triggers are physical trauma, psychological stress, sunburn, surgery, infections and medications such as β-blockers, angiotensin-converting enzyme inhibitors, antimalarials and lithium.[4] Behind hereditary factors and external triggers, important mediators for the formation of lesions in psoriasis are: a) IFN-γ, which promotes hyper-proliferation of keratinocytes by inhibiting apoptosis and increases ICAM-1 expression in the endothelial cells, facilitating lymphocyte circulation;[5] and b) IL-17, which, interacting with IFN-γ, increases the synthesis of proinflammatory cytokines by keratinocytes such as IL-6 and IL-8.[6] This increase the chemoattraction of T cells into the skin maintaining the psoriasis plaque.[7] Early concepts of the pathogenesis of psoriasis focused primarily on keratinocyte hyperproliferation. However, in the last decade data have been accumulated on the pivotal role of dysregulation of the immune system this disease. It appears that psoriasis is a complex immune-mediated disease in which T-lymphocytes and dendritic cells play a central role. Novel CD4+ T-helper (Th) cells, called Th17 cells, are recognized to be important in the pathogenesis of psoriasis.[8] The dependence of these diseases on Th17 cells rather than Th1 cells has led some to reclassify psoriasis and similar diseases as Th17 diseases.[9] Here we discuss the pathophysiology of psoriasis focusing on the emerging role of Th17 cells.

![Fig.1: Multifactorial immunopathogenesis of psoriasis ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon γ; IL, interleukin.](image)

T cells as main actor in psoriasis

In the last years psoriasis has been included both into the autoinflammatory diseases group as well as in autoimmune skin disorders. This is true and wrong at the same time. Indeed, psoriasis is chronic and relapse after triggers stimuli as seen in
autoinflammatory diseases, on the other hand several evidences show autoimmune mechanisms in the skin. The antigen in psoriasis has never been discovered nonetheless the enormous economical and scientific efforts. Keratinocytes are probably the antigenic target but most of the attention has been focused on T cells.\[10\] The Th1 response was first taken in consideration driving attentions on the TNF-α molecule.\[11,12\] The central role of this cytokine has opened a new world in the treatment of psoriasis since anti TNF-α mAb has been considered the gold standard for most patients non responders to conventional therapies.\[13\] A typical Th1 response does not explain several aspects of T cell activation in psoriasis, so recently due to implication of other cytokines we now should consider psoriasis a complex interaction between T reg, Th1 and Th17.\[14,15\] From this network of chemical mediators IL-23 and IL-17 looks like the most interesting molecules to be investigated.\[16\] Recently IL-36 driven the attention of several investigators on its role in triggering psoriasis\[17\] and is a good candidate as target molecule for new therapies in the future. IL-36 is a key molecule for innate immunity dysfunction in psoriasis.\[18\] Furthermore is able to cross-talk with keratinocytes and dendritic cells producing TNF-α and has regulatory functions on IL-23/IL-17/IL-22\[19\] the main pathways investigated in psoriasis in the last years (Fig.2). Naïve T cells are induced to differentiate into Th1, Th17, or T-regulatory cells based on T-cell receptor stimulation, costimulation signals and the specific cytokines released by antigen presenting cells.\[20\] Differentiation of Th17 cells may be induced by IL-1β plus IL-23, and possibly by TGFβ in the presence of inflammatory cytokines (IL-6, IL-21, and/or IL-23). By contrast, TGF-β in the absence of IL-6 promotes development of anti-inflammatory T-regulatory cells.\[21\] Recent data indicate that IL-1 and not TGF-β is critical in the differentiation of naïve T cells into Th17 in humans.\[22\] Human Th17 cells express RORc, and produce IL-17A, IL-17F, IL-22, IL-26, and the chemokine CCL20. They are also characterized by expression of CCR4 and CCR6, the latter being the receptor for CCL20.\[23\] In addition, human CD4+ cells may exhibit some plasticity in what they can differentiate into a Th1/Th17phenotype and produces both IL-17A and IFNγ.\[24\] The presence of IL-12 or IL-23 mediates further differentiation of these cells into Th1 or Th17 cells, respectively. IL-23, a heterodimeric cytokine produced by dendritic cells and macrophages, consists of a unique IL-23p19 subunit and a common IL-12/23 p40 subunit, which shares with IL-12.\[25\] When IL-23 binds its receptor, janus kinase-2 and tyrosine kinase-2 are activated. This lead to the phosphorylation of the receptor complex and consequently to the activation of the transcription factors STAT-3 and STAT-4 which up regulate IFN-γ and allow Th17 differentiation, with its downstream secretion of IL-17A and other Th17 products.\[26\] Therefore,

**IL-23 induces immune inflammatory pathologies via Th17 effector pathway.**

**IL-17A**

IL-17A is a proinflammatory cytokine now recognized as a member of a unique cytokine family that includes five other members (IL-17B–IL-17F) with different capacity in activating genes expression. It is a disulfide-linked glycoprotein with 155 aminocacids which acts on multiple cell types, including macrophages, dendritic cells, chondrocytes, neutrophils, osteoblasts, fibroblasts, endothelial cells, epithelial cells, keratinocytes, and lymphocytes.\[21\] Its receptor is composed by 5 subunits termed IL17RA-IL17RE. The link between IL-17 and its receptor leads to the activation of the nuclear transcription factor-kB which promotes gene expression.\[20\] IL-17A plays an important function in host defense, mediated through several mechanisms that involve upregulation of cytokine, chemokine, and antimicrobial peptide production. In psoriasis IL-17 plays different roles: 1. acts on keratinocytes to induce expression of CCL20, thereby recruiting CCR6+ Th17 cells and dendritic cells to the skin;\[28\] 2. recruits neutrophils that accumulate within subcorneal micro-abscesses in the epidermis of psoriatic lesions by upregulating expression of other chemokines on keratinocytes (e.g., CXCL1,CXCL3, CXCL5,CXCL6, and CXCL8\[29\]); 3. upregulates the expression of keratin 17 in keratinocytes.\[26\] 4. upregulates β-defensins and S100A family members, which provides a potential stimulus for the innate immune system; 5. downregulates filaggrin and

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<td>Merk</td>
<td>Tildrakizumab</td>
<td>Humanized IgG1</td>
<td>IL-23 p19 subunit</td>
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Recognition of the importance of the IL-23-Th17 in the pathogenesis of psoriasis has opened the door to new therapeutic options, as illustrated in Table 1. One IL23 p19 subunit, tildrakizumab, and three IL-17 based therapies are undergoing phase III clinical evaluation, the latter including the anti-IL-17A monoclonal antibody (mAb) secukinumab and ixekizumab and the anti-IL-17RA monoclonal antibody brodalumab.

Tildrakizumab (Merk) is a humanized IgG1 targeting the IL23 p19 subunit that blocks binding of IL23 to its receptor, thereby inhibiting, differentially from ustekinumab, selectively the IL23 signaling pathway. The mAb is undergoing evaluation in two phase 3 studies in patients with moderate to severe chronic plaque psoriasis. The first, initiated in December 2012, is a 64-week study to evaluate the efficacy and safety/tolerability of tildrakizumab, injected subcutaneously. Patients receive 100 mg or 200 mg at week 0 and week 4, and every 12 weeks. The comparator is placebo. In the second study, patients receive the same doses of mAb, but the study include 50 mg etanercept as well as placebo as comparator. The two trials are a 64-week and 54-week studies, respectively. They both have an estimated primary completion dates of half 2015.

The phase III studies of brodalumab (Amgen) in patients with moderate to severe plaque psoriasis are almost completed. The first study is evaluating, either of two doses (140 mg or 210 mg) or placebo administered subcutaneously every two weeks. In case of return of disease the patient are retreated. In the second e third studies, four different regimens of brodalumab are compared with placebo and ustekinumab.

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<td>Brodalumab</td>
<td>Human IgG2</td>
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<td>Novartis</td>
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<td>Eli Lilly</td>
<td>Ixekizumab</td>
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Table 1. Therapeutic antibodies in Phase 3 clinical studies of psoriasis indication

Other factors involved in cell adhesion, which may contribute to skin barrier disruption.[31] Despite its protective effects, IL-17A can be dysregulated in some individuals and thereby contribute to the pathogenesis and/or maintenance of autoimmune and immune inflammatory disorders. Levels of Th17 cells are increased in the circulation of psoriatic patient compared to healthy subjects and their level is strictly related to disease severity measured by Psoriasis Area and Severity Index score. As consequence, recent studies demonstrate that also IL-17A levels are an index of psoriasis severity since patients with higher PASI score have higher IL-17A serum levels.[32]

Emerging new biologic treatment and their effect on Th17 cells

The human IgG1 sekukinumab (Novartis) and the humanized IgG4 ixekizumab (Eli Lilly) are currently being evaluated in phase III trials in patient with moderate to severe psoriasis, which are exploring their efficacy and safety during induction and maintenance therapy, as well as their long-term effects (NCT01365455, NCT01406938, NCT01358578, and NCT001412944 for sekukinumab; NCT01236118 for ixekizumab). These studies includes placebo as well as etanercept as comparators.

Target for psoriasis treatment have evolved in accordance with our evolving understanding of psoriasis pathogenesis and have led to new mAbs known as biologic agents, which in turn, showing clinical efficacy, confirm the pivotal role of the IL-23-Th17 pathways. The first introduced was ustekinumab, which is a fully human IgG1 mAb directed against the p40 subunit common to IL-12 and IL-23 and prevents these cytokines from binding to the IL-12R1 receptor on the surface of immune cells.[33] The efficacy of this mAb against psoriasis have been shown in several large Phase III studies, which lead approval of this drug for treatment of psoriasis. The newer mAbs acts more selectively, since tildrakizumab targets only the IL-23 p19 subunit; brodalumab, sekukinumab and ixekizumab inhibit the IL-17RA and IL-17A, respectively. Overall, the magnitude of clinical response observed in the above phase III trials appears at least as high or greater than that reported for existing therapies, including ustekinumab. This preliminary data are consistent with the more selective mechanism of action of the IL-17 based therapies, which rapidly inhibit the cytokine directly or via receptor blockade, rather than modulating IL-17 activity via effects on turnover and activity of Th17 cells. However, data from large-scale clinical trials are needed before any definitive conclusion can be drawn.

Conclusions

In the last decade the new discoveries on psoriasis pathogenesis opened new therapeutic opportunities. Selected target therapy starting from anti TNFa, toghether with the understanding of cytokine networks in psoriasis drove to new specific target biologic therapies such as anti IL-23/IL-17. This is a perfect example of transitional research with a goal to the best treatment of our patients.

References


