Current perspective on the role of the interleukin-23/interleukin-17 axis in inflammation and disease (chronic arthritis and psoriasis)

Abstract: TH17 is a lymphocyte subset, which is characterized by its polarization to secrete interleukin (IL)-17. IL-23 is the pivotal mediator responsible for TH17 differentiation and the IL-23/IL-17 axis has been strongly implicated in the pathogenesis of several immune mediated diseases, in particular chronic arthritis and skin psoriasis. This review will summarize the basic immunology and the new monoclonal antibodies, which antagonize this pathway allowing a new therapeutic approach.

Keywords: TH17, IL-17, IL-23, psoriasis, psoriatic arthritis, ankylosing spondylitis

A T-cell subset on the stage: TH17

TH17 is a CD3+/CD4+ T lymphocyte subset, which is characterized by its polarization to secrete interleukin (IL)-17. The inflammatory cytokine IL-17 has been implicated in self-protection versus protozoa, bacteria, and fungi. The first description of IL-17 production by CD4 T was in 1995, but only in the last decade the concept of a separate CD4+ T subset producing IL-17, distinct from TH1 and TH2 subsets, has strongly emerged in the scientific literature. The old dichotomy in T lymphocyte classification pictured a scenario where antigen stimulation of naïve CD4+ T cells could determine the emergence either of TH1 lymphocytes secreting interferon-γ (IFN-γ) implicated in the mechanisms of protection to intracellular pathogens (also playing a major role in autoimmunity), or TH2 lymphocytes producing cytokines such as IL-4, IL-5, IL-6, and IL-13, implicated in the immune processes of defense versus extracellular organisms, humoral immunity, and allergy.

The development of the TH1 subset is triggered by various stimuli, in particular by the cytokine IL-12; an early innate immune reaction driven by natural killer cells is also able to activate the T-bet transcription factor through signal transducer and activator of transcription 1, thus enhancing response to IL-12; this is of importance because the therapeutic monoclonal antibody Ustekinumab is directed toward the IL-12p40 subunit that is shared by both IL-12 and IL-23, and therefore affects both TH1 and TH17 subsets. The pivotal cytokine IL-23, together with other mediators such as IL-1, tumor necrosis factor alpha (TNF-α), and IL-6, is fundamental in directing naïve CD4+ T cells toward the TH17 subset. The possible role of transforming growth factor-β in TH17 differentiation in the human immune system is still controversial, while this has been clearly demonstrated in mice models. In this regard it is relevant that, in naïve T lymphocytes, transforming growth factor-β and IL-6 induce retinoic acid orphan receptors (RORgt and RORa), triggering the upregulation of IL-23 receptor

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expression, the upregulation of colony stimulating factors and matrix metalloprotease expression.

**IL-23 and the TH17 subset in chronic arthritis**

For many years rheumatoid arthritis (RA), psoriasis, and psoriatic arthritis (PsA) were considered to be pathological processes driven by the TH1 subset, and IL-17 in the generation of the inflammatory cascade. In the recent past, emerging data have underlined the role of the TH17 subset and IL-17 in the pathological mechanisms leading to chronic arthritis such as PsA, AS, and RA, as well as inflammatory bowel diseases (IBDs) and skin psoriasis.

Strong evidence links these diseases to the TH17 subset; first of all the data arising from genome-wide association studies and genetic studies. The susceptibility to skin psoriasis and PsA is associated with alleles of the IL12B and IL23R. Moreover, AS and Crohn’s disease, belonging to the spectrum of SpA together with PsA, are also linked to IL23R alleles. This common genetic background easily suggests a common inflammatory pathway, which involves the receptor of IL-23. More data support the importance of the IL-23/TH17 axis in these diseases; IL23p19 and p40 (shared by IL-12p70 and IL-23 cytokines) subunits, but not IL-12p35 (present in IL-12 only), have been strongly detected in involved psoriatic skin as compared with non-lesional skin. Furthermore, serum levels of IL-12/23 p40 subunit have been detected at significantly higher levels in PsA patients compared with healthy controls. We have previously underlined the importance of the IL-23 cytokine and its receptor in TH17 maturation and function; the experimental data summarized support a primary role of the TH17 subset in SpA and skin psoriasis.

Several data also support the possible involvement of the IL-23/TH17 axis even in RA; both IL-17 and IL-23 have been detected in the synovial membrane, in the synovial fluid as well as in peripheral blood serum; moreover, IL-23 expression has been correlated with the expression of receptor activator of nuclear factor kappa B ligand at the mRNA level. IL-17 and TNF-α are able to induce receptor activator of nuclear factor kappa B ligand, which activates osteoclasts that are responsible for erosions at sites of articular inflammation. These data provide support to the concept that the IL-23/IL-17 axis is involved in the mechanisms of bone erosion and joint destruction. As previously outlined, IBDs are part of the SpA spectrum of diseases and therefore it is of importance to note the report of an overexpression of IL-17...
Monoclonal antibodies developed for use in human diseases which interfere with the interleukin (IL)-23/IL-17 axis

**IL-17 inhibitors**

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**IL-12 and IL-23 inhibitors**

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in the gut tissue and sera of these patients, as well as the finding of an increased number of TH17 cells in gut biopsies from Crohn’s patients.

The SpA spectrum of disease has been known for a long time to be associated with the HLA antigen B27. Genome-wide association studies have more recently demonstrated the association with IL-23R and the data previously summarized strongly underline the role of the TH17 subset. In 2011, the Oxford group of Bownes et al nicely summarized the evidence which arose from experimental work done in their laboratory, as well as data from the scientific community, and have linked together the HLA-B27 association with KIR receptors and the IL-23/TH17 axis. B27 is a hetero-trimeric molecule that has the tendency to dissociate from the bound peptide and the β2microglobulin component. This dissociation allows free heavy chains to form β2microglobulin-free heavy chain homodimers (B27), which are able to stimulate the proliferation, survival and IL-17 production of KIR3DL2+CD4+Th-17 cells; it has been also demonstrated that these effects are mediated by the KIR3DL2/B27 pair interaction. It is noteworthy that B27, responsive IL-17 producing CD4+ T cells were IL-23R positive and were also able to produce TNF-α and/or IFN-γ. Cells of the T lymphocyte lineage, showing an overlapping TH17 and TH1 phenotype (plasticity) can be detected in SpA patients widening the scenario of their possible role in disease as well as in physiologic functions.

**New emerging drugs that interfere with the IL-23/IL-17 axis**

The possibility that antagonism of this pathway may allow the key approach in the control of disease activity as well as disease damage in chronic arthritis and in other immune-mediated inflammatory diseases has been tested “in vivo” by means of several new biologic drugs, which target the IL-23/IL-17 axis, as summarized in Table 1. This review will focus on the three compounds, which have been more extensively studied at present, Ustekinumab, Secukinumab, and Brodalumab.

Ustekinumab is an IgG1k human monoclonal antibody that recognizes IL-17A. Two Phase III studies have been performed in psoriasis (ERASURE and FIXTURE). In the first one, patients were randomized to receive subcutaneous Ustekinumab at doses of 300 or 150 mg once weekly for 5 weeks and then every 4 weeks compared with placebo. PASI75 was reached at week 12 by 81.6%, 71.6%, and 4.5% of patients, respectively. In the FIXTURE study (which compared Ustekinumab versus Etanercept) PASI75 was reached by 77.1%, 67.0%, 44.0%, and 4.9% of patients on 300 mg or 150 mg of Ustekinumab, 50 mg twice weekly of Etanercept or placebo, respectively. Ustekinumab also demonstrated to be effective in nail disease, itch, and quality of life; serious side effects were infrequent and comparable among all arms. Candida infections were reported as mild-moderate in 4.7%,...
2.3%, and 1.2% of patients in the 300 mg or 150 mg Secukinumab or Etanercept groups, respectively.

In PsA, Secukinumab has been studied in two Phase III trials (FUTURE 1 and 2 trials). In FUTURE 1, patients were randomized to receive an intravenous loading dose of Secukinumab 10 mg/kg at baseline,43 weeks 2 and 4 and then 150 mg or 75 mg every 4 weeks starting from week 8 compared with placebo. At week 24, ACR20 was 50.0%, 50.5%, and 17.3%, Secukinumab 150 mg, 75 mg, or placebo, respectively. Other domains investigated included skin disease, dactylitis, enthesitis, function, quality of life, and inhibition of X-ray progression of damage, which all resulted statistically different from placebo. In the FUTURE 2 trial, patients did not receive an intravenous loading dose;44 results confirmed the efficacy in the same domains as in FUTURE 1 trial. Overall adverse effects in PsA patients were similar to psoriatic patients; the total infection rate was slightly higher in the Secukinumab arm compared with placebo, without opportunistic or tuberculosis infections.

Two Phase III trials have been also performed in AS: MEASURE 1 and MEASURE 2. In the first trial, patients were randomized in three arms after a 10 mg/kg weekly loading dose of Secukinumab for the first 4 weeks, followed by 75 mg or 150 mg or placebo subcutaneously every 4 weeks.45 The primary end point was ASAS20 response at week 16, which was reached by 59.7% and 60.8% of patients in the active arms and 28.7% in the placebo group, respectively. In the MEASURE 2 trial, patients did not receive the loading dose;46 the ASAS20 responses were 41.1%, 61.1%, and 28.4%, respectively. Side effects were in line with the previous studies.

It is remarkable that a Phase II study performed in RA was not able to separate the active drug arms compared with placebo in terms of ACR20 response,37 although Secukinumab-treated patients showed statistically lower DAS28 scores and lower high sensitivity C-reactive protein values.

Brodalumab is a human monoclonal antibody that blocks IL17A receptor, therefore inhibiting IL-17 signaling. Brodalumab has been proved to be effective in a Phase II study in psoriasis;47 patients were treated with 70, 140, 210, or 280 mg of Brodalumab subcutaneously and PASI75 response rates at 12 weeks were 45%, 85%, 86.3%, and 76%, respectively, compared with 16% of placebo controls. A Phase II study was also performed in PsA, aiming to an ACR20 response primary end point at 12 weeks; 37% and 39% of patients treated in the 140 and 280 mg active drug arms reached the primary end point compared with 18% in the placebo arm.48 Brodalumab has been studied also in RA, without benefit. In a Phase I ascending dose study, separation of active drug-treated patients compared with placebo was not demonstrated;49 furthermore in a Phase II study performed in methotrexate inadequate responders similar negative results were obtained.50

In this study, Pavelka et al reported a clear lack of therapeutic effect of IL-17 antagonism in RA, and the authors’ conclusion was that there is no reason to pursue further evaluation of Brodalumab in this disease. Although this is a negative study the lesson that arises from this publication is of value. Together with previously published data for Secukinumab, an anti-IL-17A antibody, the results of this trial strongly indicate that the IL-17 pathway is not an appropriate therapeutic target for RA while it is successful in PsA. This evidence is instructive and may help in clarifying the important pathogenic differences that characterize RA compared with PsA; similar disease in some features, so different in others.

Marketed or developing drugs that inhibit IL-17, IL-23, or the IL-12/IL-23 shared subunit IL-12p40 have demonstrated significant benefit in SpA and skin psoriasis. Further studies and post-marketing data will reveal the best approach in order to efficiently interfere in the pathogenetic mechanisms of TH17-mediated diseases.

Conclusion

The precise pathogenesis of chronic arthritis, skin psoriasis, and IBD, as well as the role of the TH17 subset in their inflammatory milieu, needs further in depth research. Experimental clinical work performed so far in patients with these diseases, thanks to the availability of new biologic compounds targeting the IL-23/IL-17 axis, suggests the important features that differentiate SpA and psoriasis from IBD and RA. These differences are reflected in the response to treatment and therefore deserve our greatest attention.

The availability of new effective drugs that target different mediators and inflammatory pathways is of great importance in order to increase opportunities for the physician to impact in disease activity and progression for the benefit of the patients.

Disclosure

The authors report no conflicts of interest in this work.

References


