

# New insights into IL-17/IL-23 signaling in ankylosing spondylitis (Review)

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**Abstract.** Ankylosing spondylitis (AS) is a progressive common autoimmune inflammatory disease, part of the spondylarthrititis group, characterized, besides clinical spinal and peripheral joint inflammation, by enthesitis and new bone formation, that can lead to severe functional impairment. Beyond intensive and continuous research on the pathogenic process extensively performed in recent years, their impact on therapeutic management remains open to future development. Better knowledge of AS pathogenesis have shown results progressively and studies are being performed to advance our current understanding of the disease. It is well known that tumor necrosis factor (TNF) exerts a central role, along with interleukin-17 (IL-17) and interleukin-23 (IL-23), demonstrated by several clinical studies. Similar to other rheumatic inflammatory conditions, SA is associated with an early process of systemic bone loss, both trabecular and cortical, consecutive osteopenia, osteoporosis, and high fracture risk. Current personalized therapeutic options benefit from new published data, to prevent future complications and to improve quality of life.

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## 1. Introduction

Ankylosing spondylitis (AS) is a progressive common inflammatory disease, part of the spondylarthrititis group (SpA), characterized, besides enthesitic inflammation, by new bone formation, that can be associated with both spinal and peripheral involvement. The burden of the disease is dependent on the degree of acute inflammation causing pain and stiffness and on new bone formation causing a reduction in spinal mobility and extra-articular features. Recent scientific publications have shown important advances in understanding new genetic associations and immune mediated processes, by studying genes that encode cytokine receptors, several transcription factors, or disturbances in antigen-presentation phenomenon (1-3).

Intestinal microbiota exerts a role in the pathogenic process, with no proven to little input, so far, on therapeutic management (4). Although important data have been published regarding genetic, cellular, and molecular pathways that regulate SpA pathogenesis, no new promising results came from new therapeutic options. Beyond intensive and continuous research performed in recent years, the input on therapeutic management remains opened to future development (1-4).

It is well known that tumor necrosis factor (TNF) exerts a central role, along with interleukin-17 (IL-17) and interleukin-23 (IL-23), demonstrated by several clinical studies. Furthermore, experimental research has proven that several autoimmune diseases, including AS, psoriatic arthritis (PsA), psoriasis, rheumatoid arthritis (RA), and Crohn disease (CD), can be triggered by activation of the IL-17/IL-23 pathway (5,6).

AS also shows a strong hereditary background, related mostly, but not exclusively, to the presence of human leukocyte

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antigen-B27 (HLA-B27). Several theories have been proposed concerning the role of HLA-B27, the major one stating that changes in its amino acid sequences determines specificity for some peptides originated from certain bacterial proteins and cross-reactivity with peptides found in joints and entheses, through induction of an immune-mediated cross-reactivity, mediated by CD8<sup>+</sup> T-cells (7). Besides HLA-B27, other major histocompatibility complex (MHC) genes have been directly related to AS (i.e. HLA-B60, HLA-B61, HLA-B39) as well as non-MHC ones [endoplasmic reticulum aminopeptidase-1 and -2 (ERAP-1, ERAP-2), leucyl/cysteiny aminopeptidase (LNPEP), IL-23 pathway genes, CD8<sup>+</sup> T-cell associated genes] (8-11).

This review includes a summary of the most recent data on AS pathogenesis from recent years, and their possible therapeutic impact.

## 2. Immunopathogenesis of ankylosing spondylitis

RA, psoriasis and PsA, as well as AS, are considered to be pathological processes regulated by the T helper type 1 (Th1) subpopulation, and interferon- $\gamma$  (IFN- $\gamma$ ) and IL-2 were reported to be the leading mediators in the generation of the inflammatory cascade; recently, emerging data have underlined the role of the T helper type 17 (Th17-cells) subset and IL-17 in the pathological mechanisms leading to chronic arthritis such as PsA, AS, and even RA (12). The concept that states that AS is an IL-17 dependent disease has been clarified by genetic and immunological research (8-12).

**IL-17.** The Th17 cells, a subset of CD4<sup>+</sup> T-cells, described for the first time in 2005, exert immunity against extracellular bacterial and fungal infections, as the major physiological effect. Differentiation of Th17 cells is regulated by a combination of cytokines, such as IL-1 $\beta$ , IL-6, transforming growth factor- $\beta$  (TGF- $\beta$ ) and especially IL-23. Th17 cells release several cytokines, represented by IL-17A, IL-17F, IL-22, IFN- $\gamma$ , or granulocyte-macrophage colony-stimulating factor (GM-CSF) (12,13). In AS, elevated levels of IL-17 have been found in serum, joint and synovial fluid. It has been recognized as a major pawn in disease pathogenesis, and the remarkable results obtained on animal models of SpA, sustained its therapeutic targeting. Consequently, it has been a continuous effort to identify whether IL-17 is the starting point or target of other cells (14,15).

It has been reported that IL-17A producing cells, are frequently observed in AS patients. The decoy of epithelial cells, macrophages, neutrophils, or the release of IL-1 $\beta$ , TNF- $\alpha$ , or other cytokines, supports its pathogenic involvement (16).

Despite its proinflammatory effect, IL-17A and IL-17F alone are not very powerful inflammatory cytokines; in fact, their potent inflammatory action is mostly related to the function of recruiting immune cells, and to the synergistic effect along with other pro-inflammatory cytokines such as TNF, IL-1 $\beta$ , IFN- $\gamma$ , GM-CSF and IL-22 (17).

There is increasing evidence that IL-17A blockade can be effective in patients with active SpA and knowledge regarding the mechanisms of IL-17/IL-23 pathway has increased with genetic, experimental models and functional data suggesting that it plays a crucial role in SpA (18).

Secukinumab, a fully human monoclonal antibody against IL-17A, is the first non-TNF- $\alpha$  inhibitor agent approved for AS, which opens up a therapeutic step of other cytokine targets beyond TNF (18). The benefits of secukinumab are generally seen regardless of whether patients were naive or not to TNF inhibitor therapy, and were persistent up to 5 years treatment; secukinumab was also associated with visible improvement of mobility and physical function, quality of life and work productivity in some of the trials (19).

Ixekizumab, a second emergent IL-17A blocker, has helped focus research towards IL-23/IL-17 axis in enthesal disease and the manner of IL-17A inhibition may be linked to innate and adaptive immune cells that are capable of IL-17A elaboration in these target tissues (19-21).

Ustekinumab, a human monoclonal antibody targeting the IL-12/23 p40 subunit, is effective in treating active psoriasis, CD and PsA, generating inhibition of radiographic progression, and improving axial symptoms in a subgroup of PsA patients with physician-reported spondylitis (22).

Clinical trials performed so far using new biologic compounds, targeting the IL-23/IL-17 axis, suggest important features that differentiate SpA and psoriasis from inflammatory bowel disease (IBD) and RA; these differences are obvious in therapeutic response and therefore require attention and further availability of new effective drugs that target different cytokines and inflammatory pathways. The observations made so far are creating new opportunities for the physician to impact disease activity and progression, for the benefit of these patients (13).

**IL-23.** The pathogenic role of IL-23, a heterodimeric cytokine, with some subunits, including IL-12B (IL-12p40), shared with IL-12 and IL-23A (IL-23p19) (23), was first supported by identifying IL-23R as involved in susceptibility to the disease. IL-23 might also be secreted by intestinal epithelium and produced by dendritic cells and macrophages (24). It has a major role in regulating, activating, and multiplying Th17 cells that express IL-17 and in inducing IL-22. The link between IL-23 and IL-17 has been proven on murine models, studying the differentiation of T-cells in Th17 cells (24,25). The presence of IL-6 induces Th17 cell differentiation via TGF- $\beta$ , while its absence induces differentiation of regulatory T-cells. The production of IL-17 was potentiated by IL-23 addition, but exclusively after their activation (26). Later experimental studies demonstrated the differentiation of non-pathogenic Th17 cells, under the action of IL-6 and TGF- $\beta$ , in case of IL-23 absence (27).

Furthermore, for mast cells, NK cells,  $\gamma$ - $\delta$  T-cells subpopulation ( $\gamma$ - $\delta$  T-cells; a population of CD3<sup>+</sup> T-cells) or innate lymphoid cells, IL-23 represents the main controller of IL-17 and IL-22 expression. Recent studies concluded that patients with AS or axial SpA present a significantly higher number of  $\gamma$ - $\delta$  T-cells that express IL-23R and produce IL-17 (27,28). Moreover, stimulation of  $\gamma$ - $\delta$  T-cells with IL-23 induced a 6-fold increase for IL-17, expanded to 9-fold, after anti-CD3/CD28 addition (29).

A report, published in 2019 by Venken *et al* (30), described a new innate-like T-cells subset, ROR $\gamma$ t+TbetloPLZF-invariant NK T-cells (iNKT), that respond fast to IL-23 stimulation. The contribution of this cytokine to disease pathogeny is directly dependent on the presence of IL-23 producing cells.

Regarding therapeutic approach, it has been suggested that IL-23 exerts a role only in initiating pathological process, both for AS or axial SpA, and not in perpetuating the damage in established disease. Administering IL-23 inhibitors did not provide satisfactory results, compared with IL-17. Studies with ustekinumab or risankizumab, that included subjects naïve to TNF inhibitors, did not show promising results (31,32); moreover, ustekinumab was administered in patients with previous anti-TNF treatment or non-radiographic SpA, also without result (31).

Currently there are no data available on radiologic progression. Enteseal inflammation, a characteristic of SpA group, is potentiated by IL-23 using a population of CD3<sup>+</sup> CD4<sup>+</sup> CD8<sup>+</sup> enteseal lymphocytes. Although in axial SpA ustekinumab showed no promising results, it is noteworthy that in patients with PsA it showed superior results, compared with placebo, in treatment of enthesitis (33,34).

The lack of therapeutic response, compared with anti-IL-17 therapies, shows and underlines the importance of similarities and differences between IL-17 and IL-23, especially concerning cell differentiation, inflammation, bone destruction and formation (4). Related to cell differentiation, the first events are represented by IL-17 producing cell activation, via IL-1 and IL-6, subsequent to inflammation, followed by an increase of Th17 and  $\gamma\delta$  T-cells; the presence of IL-23 can promote maturation into pathogenic Th17 cells (26,35).

### 3. Effects of IL-23 and IL-17 on the bone

Similar to other rheumatic inflammatory conditions, SA is associated with an early process of systemic bone loss, both trabecular and cortical, consecutive osteopenia, osteoporosis, and high fracture risk. The focal new bone formation is a process that starts in well-established sites and it is related to future enteseal involvement (1,6).

A wide view of structural damage in AS requires understanding how the cytokines released in an immune-mediated inflammatory disease act and regulate the bone loss or formation. The complete understanding of IL-23 action on osteoclasts and osteoclastogenesis is poorly understood, but it is clear that it promotes osteoclasts differentiation by inducing IL-17A production (36-38). It has been suggested that the process is induced in human cells by IL-23, in the absence of osteoblasts or the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) (36).

IL-23 promoting action on osteoclastogenesis is related to IL-23 stimulation inducing RANK expression on osteoclasts precursor and activation of DNAX protein 12 (DAP12) (38-42). There are also reports on sustained inhibitory effect on osteoclasts. Several *in vitro* and *in vivo* studies reported that IL-23 promotes GM-CSF production (inhibitor of osteoclast differentiation), limiting the resorption (39); osteoclast differentiation and bone resorption, enabled by IL-17 and RANKL expressed by Th17-cells, show that the effect on the bone can be a catabolic one. IL-23 has no effect on differentiation or proliferation of osteoblasts (43-46).

Evidence involving the effects of IL-17A on osteoblast differentiation and function are still not clear; it is suggested that IL-17A exerts a protective role for bone loss, indicating their positive effect on osteoblasts differentiation from

mesenchymal stem cells (47-49). Inhibiting the cytokine with antibodies or soluble receptors determines a decrease of IL-6 and the carboxy-terminal collagen crosslinks (CTX) production and diminishes bone damage, an effect potentiated when associating TNF and IL-1 (44).

It is important to keep in mind that in inflammatory conditions, characterized by interaction and activation of mesenchymal cell-derived osteoblasts and osteoclasts, IL-17 and TNF produce a negative regulation of osteoblasts and bone damage, whereas in the absence of osteoblast-osteoclast interaction, determines new bone formation (50-54). The link between the two types of cells is the RANK-RANKL interaction (36,55). Under the action of IL-17 and TNF, RANKL expression on mesenchymal cells increases, along with the RANK effect on osteoblasts (6,48). Evidence shows that both IL-17 and IL-23 induce an imbalance in bone homeostasis, by a direct or indirect effect on osteoclasts, clinically visible as a systemic bone loss, contributing to bone erosions. The process of bone formation, in the cortical bone, common to AS and PsA, is enabled by the two cytokines via a local inflammatory environment that promotes bone response. Their action on bone is an open subject for future research to benefit therapeutic management (3,6).

### 4. Conclusions

Improved knowledge of AS pathogenesis has shown results progressively and studies are being performed in order to advance our current understanding of the disease. Current and future personalized therapeutic options certainly benefit from new data, in order to prevent future complications and improve quality of life.

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BAC, LIC, FAV, CDP, SCF, ŞCD, DAC, AAT, RES, IS, MVB, ISP, AMU, LB and ALB contributed equally to the acquisition, analysis and systematization of the data, and the writing and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

### Ethics approval and consent to participate

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## Competing interests

The authors declare that they have no competing interests.

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