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The IL-23/IL-17 Axis in Spondyloarthritis

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Abstract

Purpose of review—To inform readers of recent advances in our understanding of the development and function of Th17 T cells and emerging data suggesting that the IL-23/IL-17 axis may be involved in the pathogenesis of spondyloarthritis.

Recent findings—The discovery of CD4⁺ Th17 T cells and the IL-23/IL-17 axis has challenged existing paradigms and the role of Th1 T cells in many autoimmune diseases. The development and cytokine profile of Th17 T cells differs in mice and humans. In humans IL-23 synergizes with IL-6 and IL-1 to promote Th17 development. In mice TGF- β and IL-6 are critical, while IL-23 is more important at later stages promoting IL-17 production. In mice CD4⁺ cells producing IFN- γ appear to be distinct from IL-17-producing cells, while in humans cells secreting both cytokines have been observed. Growing evidence from animal models, cytokine analyses of patient fluids, and whole-genome association studies suggest that the IL-23/IL-17 axis plays an important role in spondyloarthritis pathogenesis. Possible links between an HLA-B27-induced unfolded protein response and activation of the IL-23/IL-17 axis have been observed in animal models and may contribute to the development of the spondyloarthritis phenotype.

Summary—Activation of the IL-23/IL-17 axis in spondyloarthritis has important therapeutic implications.

Keywords

Cytokines; T cells; inflammation; spondyloarthritis; ankylosing spondylitis

Spondyloarthritis (SpAs) are a heterogeneous group of disorders with clinical features that can include axial and peripheral arthritis, inflammatory bowel disease, uveitis, and psoriasis. Many of these disorders are strongly associated with the MHC class I allele, HLA-B27, particularly ankylosing spondylitis (AS). Animal models of HLA-B27 associated disease share features with the SpAs, yet there are important phenotypic differences. Evidence that these disorders are autoimmune in origin with autoreactivity mediated by the adaptive immune system is scant, and thus we refer to them as immune-mediated inflammatory diseases. The composition of inflammatory lesions varies, but activated macrophages, B cells, and T cells are consistently present. The nature and phenotype of these T cells remain to be defined. New information from synovial fluid cytokine analyses, animal models, and whole genome association studies provide a compelling argument for further analysis of the IL-23/IL-17 axis in the SpAs.

CD4+ T cells: Th17 adds to the complexity of Th1/Th2

Interleukin 17 (IL-17) is a proinflammatory cytokine that plays an important role in host defense against extracellular bacteria, protozoa, and fungi [1[•]–4]. It has also become recognized as a key mediator of chronic inflammation in animal models of immune-mediated inflammatory diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), inflammatory bowel disease (IBD), [5,6] and psoriasis [5–9^{••}], and there is growing evidence that IL-17 is important in the human disease counterparts. While IL-17 secretion by CD4+ T cells has been recognized for more than a decade [10,11], only recently has it become apparent that in mice CD4+ T cells producing IL-17 are a distinct lineage ('Th17') [12–14^{••}], of equal importance to Th1 and Th2 subsets first defined over 20 years ago.

Prior to the discovery of Th17, it was thought that antigenic stimulation of naïve CD4+ T cells resulted in differentiation into either Th1 cells capable of producing large quantities of IFN- γ , which is critical for clearing intracellular pathogens, or Th2 cells producing IL-4, IL-5 and IL-13 to clear extracellular organisms and elicit robust humoral immunity. Th1 and Th2 development is driven by IL-12 and IL-4, respectively. For Th1, IFN- γ from an initial innate immune response (e.g. activated NK cells) also has an impact early on as it activates the T-bet transcription factor through STAT1, thus turning on Th1-specific genes that enhance responsiveness to IL-12. Similarly, IL-4 promotes Th2 development through STAT4 and GATA-3 activation [15]. Development and activation of the Th17 lineage has many parallels with Th1/Th2, except that other cytokines are critical. There are also important differences between Th17 regulatory networks in rodents and humans. In mice TGF- β and IL-6 play key roles in directing naïve CD4+ T cells to become Th17-committed [16,17], with IL-1 and TNF- α also promoting this process [18]. TGF- β and IL-6 positively regulate retinoic acid orphan receptors (ROR γ t and ROR α) in naïve T cells, resulting in upregulation of the IL-23 receptor (IL-23R) [19,20], thus enabling cells to respond to IL-23. IL-23 is a member of the IL-12 family and is comprised of IL-12p40 and IL-23p19 in contrast to the IL-12p35/IL-12p40 heterodimer that forms the bioactive IL-12 (IL-12p70). IL-23 acts on Th17-committed cells promoting expansion and stimulating robust and prolonged IL-17 upregulation [7,21,22[•]].

TGF- β and IL-6 also upregulate ROR γ t expression in naïve human CD4+ T cells. However, in contrast to mice, they do not induce differentiation toward Th17, at least *in vitro* [23[•]]. IL-1 and IL-23 appear to be more important for Th17 development in humans, with reports that these cytokines have synergistic effects. In addition, IL-1 can synergize with IL-6 causing sustained ROR γ t expression and promoting Th17 development [23[•]]. IL-23 is also a potent inducer of IL-17 in human CD4+ T cells. One of the key differences between humans and mice is that TGF- β appears to negatively regulate Th17 cells in humans, whereas in mice it has a positive effect. This seems surprising given its positive effect on ROR γ t expression, and more will need to be done to better understand the role of TGF- β on Th17 development in humans.

There are also important counter-regulatory circuits that control Th17, and influence the balance between Th17 and regulatory T cells (Treg). For example, the signature cytokines of Th1 and Th2, IFN- γ and IL-4, respectively, inhibit IL-17 production [12,13,24,25]. This may account for the more pronounced collagen-induced arthritis seen in IFN- γ -deficient mice, which is associated with increased IL-17 production [26[•]]. IL-2, which positively regulates both Th1 and Th2, inhibits Th17 cell differentiation by downregulating ROR γ t [27]. In addition, IL-27 (also an IL-12 family member) suppresses the development of IL-17-producing T cells at least in part by promoting IL-10 production from Treg cells [28–32]. Interestingly, the vitamin A metabolite retinoic acid, can inhibit the induction of pro-inflammatory Th17 cells by IL-6 [33[•]], and induce FoxP3 expression and promote Treg

differentiation [34*]. These findings may explain some of the anti-inflammatory effects of retinoic acid and suggest it may be important for regulating the balance between immunity and autoimmunity.

Th17 Cytokines

There is a large family of IL-17 molecules in addition to IL-17A and IL-17F produced by Th17 CD4⁺ T cells [14**]. There is also evidence that CD8 and $\gamma\delta$ T cells, NK cells, and neutrophils can produce other IL-17 family cytokines. CD4⁺ T cells that produce IL-17 can also be important sources of other cytokines including TNF- α and IL-6 [5,35], and IL-22 [9**,36]. IL-22 and IL-17 cooperatively enhance the induction of antimicrobial peptides [36], and IL-22 has been shown to mediate epidermal hyperplasia and dermal inflammation in psoriasis [9**,37*]. In contrast to mice, human CD4⁺ Th17 T cells can produce IFN- γ as well as IL-17 [38*]. These memory T cells can express chemokine receptors CCR6 and CXCR3, while memory T cells that express CCR6 and CCR4 appear to produce only IL-17 [1*,39*]. Interestingly, the different IL-17 producing CD4⁺ T cell populations have been correlated with certain pathogens: *M. tuberculosis* responsive T cells were CCR6/CCR4 positive whereas CCR6/CXCR3 T cells responded to *C. albicans*. Chemokine receptors or other differences might determine the homing of the IL-17 producing T cell populations.

IL-17 family members have important and diverse effects on several cell types including monocytes/macrophages, osteoblasts, fibroblasts, and endothelial and epithelial cells. They induce cytokines and chemokines (e.g. IL-6 and IL-8/CXCL8, CXCL1 and CXCL10), TNF- α , IL-1 β , colony stimulating factors (G-CSF and GM-CSF), and several matrix metalloproteases, as well as recruiting neutrophils to sites of inflammation [14**]. Although there is redundancy as a consequence of the multiple IL-17 family members, and in particular IL-17A and IL-17F from CD4⁺ T cells, IL-17A is particularly important as *il17a*-deficient mice exhibit a suppression of certain inflammatory phenotypes including collagen-induced arthritis (CIA) [40].

The IL-23/IL-17 Axis in Inflammation

Major advances in the discovery of Th17 T cells and the importance of the IL-23/IL-17 axis in inflammation were made using mouse models of autoimmunity that were previously thought to be mediated by uncontrolled Th1 responses. Experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, and CIA, were both responsive to antibodies directed against IL-12p40 or genetic elimination of the gene encoding this cytokine subunit. However, targeting of the IL-12p35 gene was not protective (and in fact exacerbated arthritis), and thus it became apparent that there was redundancy in the IL-12 family of cytokines. Subsequent studies showed that these autoimmune diseases are ablated in mice deficient in IL-23p19 [35,41] the unique subunit of the active IL-23 cytokine [42], thus providing an explanation for the results described above.

In recent years Th17 CD4⁺ T cells and their products have been recognized with increasing frequency in association with several human autoimmune or immune-mediated inflammatory diseases like MS, IBD, psoriasis and RA [43–45]. Like the mouse models, these diseases were thought to be Th1-mediated, with IFN- γ playing an important role. In MS patients IL-17 producing cells are overrepresented in cerebrospinal fluid compared to peripheral blood [46], and the cytokine is overexpressed in the sera and colon of patients with IBD [44,47].

In RA patients both IL-17 and IL-23 have been found in sera, synovial fluids and synovial biopsies [45,48]. Interestingly, Sato et al. reported, that in the synovial tissue of RA patients mRNA expression of RANKL correlates with IL-23 expression, suggesting that the IL-23/

IL-17 axis is involved in bone destruction [49]. The authors showed that IL-17 promotes osteoclastogenesis-supporting cells like osteoblasts or stromal cells by inducing RANKL, which is also expressed on Th17 cells. RANKL is also induced by TNF- α and interacts with RANK on pre-osteoclasts (monocytes/macrophages) at sites of inflammation [14,50].

In the gut of patients with Crohn's disease (CD) more Th17 cells were found than in healthy people [39^{*}]. Interestingly, IL-23 induced the proliferation of Th17 cells derived from CD patients but not of healthy donors, despite the presence of the IL-23 receptor (IL23R). Whether *IL23R* gene polymorphisms were associated with sensitivity or resistance to IL-23 was not investigated. However, there is increasing evidence that IL23R polymorphisms play a key role in inflammatory diseases like Crohn's disease, psoriasis, and SpAs.

IL-23 Receptor (IL23R) and IL-12 (IL12B) Polymorphisms in Immune-Mediated Inflammatory Diseases

IL-12 and IL-23 are important immunoregulatory cytokines that bridge innate and adaptive immunity and also play critical roles in the pathogenesis of inflammation. IL-12/IL-23 generate signals through receptors that also share a common subunit (IL12R β 1). The IL-23 receptor is a heterodimer of IL12R β 1 and IL23R, whereas the IL-12 receptor contains IL12R β 1 in association with the unique subunit IL12R β 2. Several studies have examined whether polymorphisms in the IL-12/IL-23 family of cytokines and receptors influence susceptibility to immune-mediated inflammatory diseases. A single nucleotide polymorphism (SNP) in the IL23R gene (rs11209026) can protect from inflammatory bowel disease (IBD), both Crohn's [51–58^{*}] and ulcerative colitis [59]. The same polymorphism (rs11209026) as well as another SNP on IL23R (rs7530511) and rs3212227 on IL12B (the gene encoding IL-12p40) were also reported to be associated with psoriasis [60^{*},61].

Spondyloarthritis, the IL-23/IL-17 Axis, and HLA-B27

New prevalence figures suggest that spondyloarthritis (SpA) occurs in up to 1.3% of the population, with ankylosing spondylitis comprising close to half (0.52%) of the cases [62]. These figures suggest that SpA is at least as prevalent as RA, which occurs in 0.5–1% of the population. These figures underscore the relative importance of this group of diseases, and the need to find additional predisposing genes that will inform us on pathogenic mechanisms and new targets for therapy.

Two recent studies support a role for IL-17 in SpA pathogenesis in humans. Serum IL-17 was elevated in a study of 28 AS patients with established, active disease compared to healthy controls [63^{*}]. It was also notable that bone alkaline phosphatase (a marker of bone formation) was decreased, while tartrate-resistant alkaline phosphatase (a marker of bone resorption) was elevated, although these differences were small. In a second study, synovial fluid levels of IL-17 were increased in patients with reactive arthritis or undifferentiated SpA compared to RA and osteoarthritis (OA) patients [64^{*}]. IFN- γ , IL-6, and TGF- β followed the same pattern, while IL-12p40 was increased compared to OA, but not much higher than in RA where it was also elevated. Since measurements of IL-12p40 can reflect both IL-12 and IL-23, it is not clear how to interpret these results. It will be important to measure IL-12p70 (IL-12p35/IL-12p40) and IL-23 in biological fluids (serum and synovial fluid) from patients with SpA in future studies. IL-17 was also reported to be increased in enthesitis-related arthritis (ERA), a form of undifferentiated SpA in children [65].

Possible roles for IFN- γ in SpA pathogenesis are worth further consideration. Several years ago it was shown that PBMC-derived T cells from AS patients had a lower capacity to express IFN- γ than healthy controls [66]. Interestingly, this difference was also found in

HLA-B27+ healthy controls as well as HLA-B27+ patients. In another study synovial fluid levels of IFN- γ were lower in HLA-B27+ patients with Chlamydia-induced reactive arthritis compared to HLA-B27- patients [67]. More recently, macrophages derived from the peripheral blood of AS patients were found to have a defect in IFN- γ expression [68]. These data raise the possibility that while IFN- γ expression can be found in patients with SpA, it may not be overexpressed to the extent that it is in other immune-mediated inflammatory diseases. Lower expression of IFN- γ during infection with organisms that trigger reactive arthritis may contribute to increased survival of these organisms, which could promote reactive arthritis [69].

The ability of IFN- γ to antagonize Th17 development raises another possibility, namely that this cytokine might be playing a protective role in SpA. Reduced IFN- γ production in the course of an immune response in individuals who are prone to SpA might be permissive for increased Th17 development. IFN- γ might also be a double-edged sword. It is an important stimulus for upregulation of MHC class I expression, and in HLA-B27 transgenic animals that develop SpA-like disease, HLA-B27 upregulation results in activation of the unfolded protein response (UPR) [70]. The UPR triggers enhanced production of certain cytokines in response to bacterial products that stimulate Toll-like and other pattern recognition receptors [71]. One of these cytokines is IFN- β [71]; and additional preliminary data suggest that IL-23 may be overexpressed in this situation as well [72]. This is of interest because of the important role for IL-23 in stimulating Th17 T cells and IL-17 production. Therefore it is of considerable interest that HLA-B27 transgenic rats that develop SpA-like disease exhibit striking activation of their IL-23/IL-17 axis in the inflamed colon [72].

Two recent studies have demonstrated that SNPs in the IL23R gene are also associated with ankylosing spondylitis [73,74]. Interestingly, the IL23R variant SNP (rs11209026) that results in an Arg381Gln substitution is protective for ankylosing spondylitis, similar to IBD and psoriasis. In the whole genome association study [73] IL23R was not associated with autoimmune thyroid disease or MS.

Conclusions

Th17 T cells and their cytokines have been implicated in a number of immune-mediated inflammatory diseases. Although the data are limited at this point, early indications are that the IL-23/IL-17 axis may be activated in AS and other SpAs (Fig. 1). Further investigation of IFN- γ dysregulation and its effects on Th17 development in SpA pathogenesis is also warranted.

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Abbreviations

AS	ankylosing spondylitis
CD	Crohn's disease
CIA	collagen induced arthritis
EAE	experimental autoimmune encephalomyelitis
ERA	enthesitis-related arthritis
IBD	inflammatory bowel disease

IL	interleukin
JIA	juvenile idiopathic arthritis
MS	multiple sclerosis
OA	osteoarthritis
RA	rheumatoid arthritis
SpA	spondyloarthritis

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Figure 1.

Proposed mechanism linking HLA-B27 misfolding to activation of the IL-23/IL-17 axis in spondyloarthritis. Cytokines that upregulate class I (HLA-B27) expression may trigger UPR activation under conditions where HLA-B27 misfolding reaches a critical threshold. This in turn would polarize cells such as macrophages to produce more IL-23 relative to IL-12. In susceptible individuals with permissive (non-protective) IL-23 receptor genotypes (Θ) this may promote Th17 activation over Th1, thus promoting IL-17 production and inflammation. Other UPR-modulated cytokines such as IFN- β (not shown) could create a positive feedback loop exacerbating HLA-B27 upregulation, misfolding, and UPR activation.

(Modified from Colbert RA et al., HLA-B27 Misfolding and Spondyloarthropathies. In: Lopez-Larrea, C. ed. Molecular Mechanisms of Spondyloarthropathies. Austin, TX. Landes Bioscience/Eurekah 2008:(*in press*).)