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Update on Ankylosing Spondylitis: Current Concepts in Pathogenesis

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Abstract Ankylosing spondylitis is an insidiously progressive and debilitating form of arthritis involving the axial skeleton. The long delay in diagnosis and insufficient response to currently available therapeutics both advocate for a greater understanding of disease pathogenesis. Genome-wide association studies of this highly genetic disease have implicated specific immune pathways, including the interleukin (IL)-17/IL-23 pathway, control of nuclear factor kappa B (NF-κB) activation, amino acid trimming for major histocompatibility complex (MHC) antigen presentation, and other genes controlling CD8 and CD4 T cell subsets. The relevance of these pathways has borne out in animal and human subject studies, in particular, the response to novel therapeutic agents. Genetics and the findings of autoantibodies in ankylosing spondylitis revisit the question of autoimmune vs. autoinflammatory etiology. As environmental partners to genetics, recent attention has focused on the roles of microbiota and biomechanical stress in initiating and perpetuating inflammation. Herein, we review these current developments in the investigation of ankylosing spondylitis pathogenesis.

Keywords Ankylosing spondylitis · Spondyloarthritis · Pathogenesis · Genetics · Interleukin-23 · Interleukin-17 · ERAP1 · Autoimmunity · Autoinflammatory disease · TNF-α · Microbiome · Mechanical stress · SKG model · Ustekinumab · Secukinumab

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Introduction

Ankylosing spondylitis is a debilitating spinal arthritic condition beginning before age 40, with male predominance, and a prevalence of roughly 0.5 % in the USA [1]. Extra-axial manifestations include acute uveitis, peripheral arthritis, enthesitis (inflammation of where tendons insert on bones), psoriasis, aortic root, and gut inflammation [2]. Unlike its rheumatologic cousin rheumatoid arthritis, ankylosing spondylitis (AS) involves both inflammatory erosive osteopenia and unusual bony overgrowth. In the spine, bridging syndesmophyte formation between vertebrae ultimately results in the iconic "bamboo spine." From the patient perspective, years of pain and the rigid stooped posture incur significant disability and economic cost [3]. Due to the insidiously progressive nature of AS, delay between onset of symptoms and diagnosis is up to 8–10 years [4]. Ironically, the most effective current medications, the class of biologic agents blocking TNF-α, are best given early in disease when inflammatory burden is greatest. Not all AS patients respond to TNF blockers: In large multicenter phase III trials, ASAS20 (≥20 % improvement in three of four assessment domains) response rates are on the order of 60 % [5, 6]. Furthermore, the ability of TNF blockers to prevent ankyloses remains controversial, although recent more long-term studies are encouraging [6]. Considering the diagnostic delay and insufficient therapeutic options, a greater understanding of pathogenesis is required. The last few years have witnessed exciting developments in this regard along with related new therapies. Themes around which the exposition of these developments will be woven include genetics, the concept of autoimmunity vs. autoinflammatory disease, environmental triggers, and new therapeutics.

Genetics of Ankylosing Spondylitis

Generally speaking, autoimmune diseases develop from a complex interplay of genetic risk and environmental triggers. Among rheumatologic conditions, AS is one of the most genetic diseases. High monozygotic twin concordance (63 %) and familial aggregation studies indicate a heritability of over 90 % [7]. Presence of the major histocompatibility complex (MHC) class I allele human leukocyte antigen B27 (HLA-B27) accounts for the lion's share of genetic risk, occurring in 6 % of the US population but more than 90 % of patients with AS. The prevalence of AS in different populations around the world generally correlates with the prevalence of HLA-B27 [8]. More than 40 years after the discovery of this MHC linkage, it is still unclear how HLA-B27 predisposes to disease. Multiple theories have been interrogated, including the presentation of arthritogenic peptides, cell surface HLA-B27 dimer recognition by NK receptors, and the unique propensity of HLA-B27 to misfold during its biosynthesis and trigger pro-inflammatory endoplasmic reticulum (ER) stress. These theories and supporting data have been reviewed elsewhere [9, 10]. A more recent study comparing AS and non-AS-associated HLA-B27 subtypes transfected into HeLa cells suggests that disease-associated alleles have increased intracellular aggregates of misfolded MHC protein in the absence of an overt ER stress response [11]. The functional impact of these aggregates is unclear. Even though HLA-B27 plays an undisputedly critical role in disease pathogenesis, recent estimates suggest that it only accounts for 20–25 % of the total heritability and 40 % of the genetic risk. Fewer than 5 % of HLA-B27 carriers in the general population develop disease [7, 12••]. So where is the rest of the genetic susceptibility coming from?

Genome-wide association studies (GWASs) have identified common single nucleotide polymorphisms (SNPs) in non-HLA-B genes highly significant for association with AS. Interestingly, some of the most significant non-MHC SNPs encode variants with a *loss* of function that confers protection against developing disease (e.g., *IL23R* R381Q and *ERAP1* rs30187) [13, 14•]. A noteworthy study in 2013 from the International Genetics of Ankylosing Spondylitis Consortium (IGAS) studying 10,619 AS subjects and 15,145 controls of European, East Asian, and Latin American ancestry brought the number of AS-associated gene loci up to 31 [12••]. Intriguingly, many of these genes congregate along distinct immunomodulatory pathways (Table 1). Thus, GWAS have been instrumental in identifying immune pathways deserving of further inquiry. In particular, multiple genes shape the development and activity of a recently identified population of T helper cells known as *Th17*, so called for their production of interleukin (IL)-17 [15]. Th17 cells play a role in maintaining gut integrity and fighting bacterial and fungal infections but have also been implicated in multiple experimental models of autoimmunity including multiple sclerosis and arthritis. Th17 cells develop from naïve T cells under conditions where both TGF-β and pro-inflammatory cytokines such as IL-6 and IL-1β induce the expression of the IL-23 receptor (IL-23R). However, in order to become pathogenic, Th17 cells require IL-23, which may be produced by innate immune cells such as macrophages and dendritic cells [16]. GWAS-identified genes influencing the IL-17/IL-23 pathway include cytokines and cytokine receptors (*IL23R*, *IL12B*, *IL6R*, *IL1R1*, *IL1R2*, *IL27*), signaling molecules immediately downstream of the IL-23R (*JAK2* and *STAT3* in studies of Han Chinese, *TYK2*), and gene products transducing signals from infectious stimuli (e.g., *CARD9*) [17]. Other genetic loci have been identified that influence the activity of the pro-inflammatory transcription factor nuclear factor kappa-light-chain-ehancer of activated B cells (NF-κB) (which would also affect IL-17 and IL-23) and the production of other inflammatory mediators (*PTGER4*, *TNRSF1A*, *UBE2E3*). In addition to these cytokine modulatory pathways, a subset of genetic loci encode aminopeptidases that trim amino acid peptides for class I MHC presentation (*ERAP1*, *ERAP2-LNPEP*, *NPEPPS*). Indeed, one of the strongest single disease risk loci, apart from HLA-B27 itself, is *ERAP1*, but only in HLA-B27-positive individuals [14•]. Interestingly, the other aminopeptidases such as ERAP2 remain significant at the genome-wide level in HLA-B27-negative individuals. ERAP1 will be discussed in greater depth below. The relevance of G protein-coupled receptor proteins (*GPR25*, *GPR65*, *GPR35*) to AS pathogenesis is not clear, though GPR65 regulates matrix metalloproteinase 3 [18]. Finally, multiple genes were identified whose products would be predicted to coordinately shape T cell development, activity, and abundance, including *RUNX3*, *IL7R*, *EOMES*, and *ZMIZ1* (regulating CD8 T cells) and *ICOSLG*, *SH2B3*, and *BACH2* (CD4 T cells).

Each of the non-HLA-B27 gene SNPs individually confers a tiny amount of risk, with odds ratios ≤1.65 [12••]. Additively, all these genetic loci together still account for less than 5 % of the heritability, raising the question of missing heritability. Several theories have been put forth: GWASs are geared to identify common polymorphisms (allele frequency >0.5 %) but would miss rarer genetic variants. Different combinations of risk factors can produce similar phenotypic outcomes, leading to genetic heterogeneity [19]. There may be unclear epistatic interactions between genetic loci, as illustrated by ERAP1 and HLA-B27 [14•]. Multiple GWAS-identified genes influencing the IL-17/IL-23 pathway would either be directly or indirectly predicted to interact (Table 1). For example, several of the genes involved in regulating CD8 T cell number form a dependent cascade, whereby IL-7R induces RUNX3, which upregulates eomesodermin (EOMES). EOMES blocks IL-17 production, so a defect in any preceding step would be predicted to increase IL-17 production (reviewed in [20]). The transcription factor T-bet (*TBX21*)

Table 1 GWAS-identified gene loci and related immune pathways associated with AS

Immune pathway	Gene locus	Proteins encoded by loci
IL-17/IL-23 cytokines and receptors	*IL23R*, *IL12B*, *IL6R*, *IL1R1*, *IL1R2*, *IL27*	Interleukin-23 receptor, interleukin-12p40 (common subunit for IL-23 and IL-12), interleukin-6 receptor, interleukin-1 receptors 1 and 2, interleukin-27 (IL-12 family of interleukins)
IL-23R signaling molecules	*TYK2*, *STAT3**, *JAK2**	Tyrosine kinase 2, signal transducer and activator of transcription 3, Janus kinase 2
NF-κB activation and cytokine production	*PTGER4*, *LTBR-TNRSF1A*, *UBE2E3*	Prostaglandin E receptor 4 (EP4), lymphotoxin-β receptor, TNF receptor 1, ubiquitin-conjugating enzyme E2E 3 (inhibits NF-κB)
Pattern recognition receptor (PRR) related	*CARD9*	Caspase recruitment domain containing protein 9 (downstream of the PRR receptor dectin-1)
Aminopeptidases and other linked immunomodulators	*ERAP1*, *ERAP2-LNPEP*, *NPEPPS-TBKBP1-TBX21*	Endoplasmic reticulum aminopeptidases 1 and 2, leucyl/cystinyl aminopeptidase, puromycin-sensitive aminopeptidase, tank-binding kinase-binding protein 1 (TNF and PRR signaling), T-box transcription factor 21 (T-bet, regulates Th1 and NK cells)
Unknown function in AS, though GPR65 regulates matrix metalloproteinase 3	*GPR25*, *GPR65*, *GPR35*	G protein-coupled receptors
CD8 T cell	*RUNX3*, *IL7R*, *EOMES*, *ZMIZ1*	Runt-related transcription factor 3, interleukin-7 receptor (T cell survival), eomesodermin, zinc-finger MIZ domain containing protein 1 (member of STAT inhibitor family, regulates transcription factors)
CD4 T cell	*SH2B3*, *BACH2*, *ICOSLG*	SH2B adaptor protein 3 (T cell receptor signaling), BTB, and CNC homology 1 (transcription factor regulating Th differentiation), inducible T cell co-stimulator ligand (CD278)

Associations with AS are described in [12••], except for genes (indicated with an asterisk) described in AS GWASs of Han Chinese [17]. Comments on proteins are in parentheses

plays a role in multiple adaptive and innate immune cell types and specifically regulates Th1 lineage commitment, thus indirectly counter regulating Th17 [21]. One study has identified a combinatorial effect of having multiple SNPs in *IL12B* and *IL23R* on Th1 vs. Th17 gene expression in restimulated peripheral blood T cells [22•]. However, much remains to be learned about how interactions between genetic variations in these immune pathways contribute to susceptibility and phenotypic expression.

The genetic overlap and differences in GWAS-identified SNPs in AS and potentially related conditions have been evaluated. A number of GWAS-identified loci, particularly along the IL-17/IL-23 pathway, have been identified in GWAS for inflammatory bowel disease (IBD): 11 loci have been associated with ulcerative colitis and 12 with Crohn's disease [12••]. This overlap is not surprising, as 7–10 % of AS patients develop overt IBD, and another 50–60 % of patients have subclinical gut inflammation [23]. Patients with AS have an increased proportion of circulating blood IL-23R+IL-17 producing γδ T cells [24]. Most γδ T cells reside in the gut, thus providing a potential link between gut and joint diseases [25, 26]. However, some genetic associations remain unique to IBD (e.g., *NOD2* and *ATF16L1*) and others unique to AS (e.g., *HLA-B* and *ERAP1*) [27]. Histologic studies of patient specimens reinforce some of the unique features found in AS subclinical gut disease: Although both Crohn's disease and AS specimens have increased IL-23 expression, IL-17 (and IL-1β and IL-6) was not upregulated in AS [28]. Rather, AS specimens manifest an increase in another IL-23-regulated cytokine IL-22, which may be protective in AS [29, 30]. The IL-22 appears to be made by activated gut resident CD44+ natural killer cells. Subclinical gut inflammation is also marked by a predominance of CD163+ and *M2* wound repair macrophages [31]. The overlap of genetic loci with psoriatic arthritis also confirms the relationships of AS and psoriatic arthritis, where 40 % of psoriatic arthritis patients develop axial disease and 10 % of AS patients ultimately develop psoriasis [2, 32]. Several of the genes in common between AS and psoriasis include *ERAP1*, *IL23R*, and *IL12B* [33]. Interestingly, some of the SNP associations for AS are in the opposite direction (alternate allele) compared to classic autoimmune diseases such as multiple sclerosis (*LTBR-TNFRSF1A*, *NPEPPS-TBKBP1-TBX21*, *ZMIZ1*) and type I diabetes mellitus (*SH2B3*, *IL27*) [12••].

Autoimmune vs. Autoinflammatory Disease

Hallmarks of autoimmune disease include readily detected autoantibodies that are specific for self-antigens as well as autoreactive T cells. In contrast, autoinflammatory conditions typically stem from mutations in single immunomodulatory genes, whereby inflammatory disease develops from excess cytokine production in the absence of overt autoimmunity

(e.g., cryopyrin-associated diseases of excess IL-1β) [34]. AS belongs to the group of diseases historically known as *seronegative* spondylarthritides (SpAs), related to the lack of circulating rheumatoid factor. SpA includes psoriatic arthritis, reactive arthritis, inflammatory bowel disease-associated arthritis, acute anterior uveitis, undifferentiated spondyloarthritis, and juvenile spondyloarthritis. In an autoimmune model, HLA-B27 would be predicted to generate autoreactive CD8 T cells through its nominal role of antigen presentation; however, the search for CD8-restricted arthritogenic peptides has been unrevealing. The spondyloarthritis HLA-B27-overexpressing rat model develops disease in the absence of CD8 T cells [35]. Simply overexpressing TNF-α in mice (the TNF ΔARE mice lacking a regulatory AU-rich region) is sufficient to generate enthesitis, aggressive polyarthritis, and IBD [36, 37•]. This mouse model does not depend upon B or T cells for disease expression [37•]. Mice overexpressing membrane-bound forms of TNF reportedly develop spinal arthritis and new bone formation ([38] and abstract reviewed in [39]). Finally, clinical response to the T cell targeting agent abatacept has been disappointingly negligible [40]. Together, these features have suggested that AS is more of a polygenic autoinflammatory disease. However, some recent developments have "stirred the pot," revisiting the issue of autoimmune vs. autoinflammatory disease.

This past year, two groups have reported on circulating antibodies in AS and SpA: Patients with axial SpA have a greater prevalence of antibodies specific for the invariant chain peptide (CLIP/CD74) involved in MHC class II antigen loading, with 85 % of axial SpA patients positive for anti-CD74 vs. 8 % of non-SpA controls [41•]. The pathogenic potential of these antibodies is unknown. Of perhaps more obvious disease relevance is the finding of anti-noggin and anti-sclerostin-containing immune complexes in AS patients [42•]. Bony overgrowth occurs through currently unclear mechanisms in AS, though Wnt signaling is likely to be involved. Wnt proteins stimulate osteoblasts (and thus osteogenesis, reviewed in [43]). Proteins such as dickkopf and sclerostin antagonize Wnt signaling; thus, lower levels or functionality of these proteins, as detected in AS, would be predicted to enhance osteogenesis [44–46]. Noggin antagonizes bone morphogenic protein, and induced overexpression inhibits ankylosing enthesitis in a mouse model [47]. The role of these immune complexes in disease pathogenesis is not presently clear. B cells and antibody production may also play more of a role in specific subsets of patients or at different points in the disease process (e.g., TNF blocker-naïve patients), particularly in light of the select individual responses to the B cell-depleting antibody therapy rituximab [48]. Thus, the characterization of SpA as a seronegative disease may reflect prior ignorance of antibody targets.

The preponderance of GWAS genes revolving around antigen presentation and T cell regulation is also very suggestive. Aminopeptidases trim potential antigenic peptides to the eight to ten amino acid lengths that optimally fit in the peptide binding groove of MHC class I molecules. The different peptidases vary in specificity and thus complement each other to generate the peptide repertoire [49]. In fact, ERAP1 and ERAP2 may function as a heterodimer [50]. Even as the aminopeptidases potentially generate specific antigens, they also have the potential to destroy antigens [51, 52]. Not surprisingly, ERAP1 polymorphisms have a profound effect on the peptidome presented by HLA-B27 [52, 53]. HLA-B27 positivity confers a survival advantage for infection with certain viruses, notably HIV and hepatitis C (reviewed in [8]). ERAP1 polymorphisms may influence the capacity of HLA-B27 to present both viral and pathogenic peptides. A recent study in an MHC transgenic ERAP−/− mouse model showed that ERAP was essential for generating specific influenza responses to HLA-B27, but not HLA-B7-restricted peptides [54]. ERAP1 variants associated with AS potentially affect protein domain interactions, transitions between open and closed states, and peptide binding to the catalytic site [55]. Interestingly, protective variants generally have decreased aminopeptidase activity, resulting in less efficient peptide trimming, and decreased HLA-B27 molecular stability [14•, 19, 53, 55]. This data is consistent with older studies documenting increased HLA-B27 cell surface expression in AS patients compared to HLA-B27-positive controls [56]. The effect of ERAP1 polymorphisms on HLA-B27 misfolding and ER stress is unknown. At this point, it is unclear whether ERAP and the other aminopeptidases alter disease risk through the generation of specific arthritogenic peptides, thymic selection of the T cell repertoire, alteration of surface homodimers (which might stimulate IL-17-producing KIR3DL2-positive cells), or alteration of intracellular oligomerization and misfolding.

Weighing in on the autoinflammatory side, a landmark murine study in 2012 by Sherlock et al. showed that induced systemic overexpression of IL-23 in mice via injection of genetic mini-circles was sufficient to induce enthesitis, osteoproliferation, and aortic root inflammation [57••]. Using an IL-23R-GFP reporter, the investigators found unusual IL-23R-bearing cells in both entheses and aortic roots that were CD3+, but negative for both CD4 and CD8, suggestive of an innate lymphoid subset. Further, the enthesitis and subsequent arthritis depended upon both IL-17 and IL-22. Injection of IL-22 mini-circles (but not IL-17) reproduced the enthesitis and osteoproliferation. Pro-inflammatory cytokines such as TNF-α and IL-6 were detected in arthritic lesions, suggesting that some previously implicated inflammatory mediators may be downstream of IL-23.

Increasing evidence has been accruing to support the relevance of this mouse study to human SpA. In particular, increased production of IL-17 and IL-23 has been detected both in the peripheral blood, the gut, and skeletal tissue

biopsies from AS patients (recently reviewed in [39, 58, 59]). Multiple cell types may be involved in the excess IL-17 production, including Th17, γδ T cells, NK receptor-bearing KIR3DL2+ T cells, and even innate immune cells such as neutrophils and mast cells [24, 60–63]. AS spinal facet joints have increased numbers of IL-23-producing macrophages as compared to osteoarthritis [64]. In subclinical gut inflammation in AS, infiltrating monocytic cells appear to be responsible for the increased IL-23 production [28]. This last group of investigators has also detected HLA-B27 heavy chain misfolding and upregulation of autophagy in the gut, an intracellular process implicated to a greater degree in frank inflammatory bowel disease [65]. Together, these studies support an emerging picture of aberrant IL-17/IL-23 immune activation in AS patients

How do we put together the evidence for autoimmunity and sufficiency of cytokine dysregulation? Interestingly, one experimental model of SpA combines autoimmunity, IL-23 dysregulation, as well as an environmental trigger. Ranjeny Thomas's group has established a mouse model on the SKG background, which has a deficiency in the ZAP70 T cell receptor signaling molecule. This deficiency alters thymic education and deletion of potentially autoreactive T cells, predisposing the mice to autoimmunity [66]. Upon injection with a specific environmental stimulus curdlan (β-glucan present in fungus cell walls), these mice develop enthesitis, sacroiliitis, uveitis, and ileitis [67]. The inflammation ultimately depends upon production of IL-23 [68]. However, blockade of the two downstream cytokines in this model have disparate effects: Blocking IL-17 reduces joint and gut inflammation. However, blocking IL-22 reduces arthritis but exacerbates ileitis, consistent with a protective role for IL-22 in the decreasing gut inflammation. This model casts a new light on the finding of IL-22 in subclinical human gut inflammation and has therapeutic implications as well. By extrapolation of this model, do patients with skewed T cell response thresholds develop excess IL-23/IL-17 activity with appropriate environmental triggers? Alternatively, could the aberrant T cell responses be a secondary phenomenon following excessive innate immune activation? It will be interesting to see how this tension between autoimmunity and primary cytokine dysregulation plays out with further investigation.

Environmental Triggers: Microbiota and Mechanical Stress

Even with the unusual high heritability of AS, the twin concordance rate is not 100 %. For either autoimmune or autoinflammatory models, the microbial environment plays a critical role in triggering disease. Microbial triggers may be infectious or endogenous. In recent years, there has been a widening appreciation for the role of the trillion microbial passengers cohabitating the human body in the pathogenesis of complex inflammatory diseases. The interaction between immune system and gut flows both ways: The immune system shapes the constituents and quantity of microbiota, and the microbiome sets immune tone (reviewed vis-à-vis AS in [27, 69]). This bidirectional interaction complicates the assignment of causality. The development of overt IBD in a subset of AS patients, and striking high prevalence of subclinical gut inflammation testifies to the critical interplay between gut and joint inflammation [23, 70]. AS patients and their first-degree relatives have increased gut permeability, thus perhaps allowing greater systemic exposure to gut microbes [71]. In the HLA-B27 transgenic rat model, a germ-free environment prevented disease, but disease occurred upon transfer of the common gut bacteria bacteroides [72]. Recently, in the SKG-curdlan model, a germ-free environment ameliorated arthritis. Further, ileitis was attenuated by wild-type (non-SKG) microbiota transfer and deficiency of the lipopolysaccharide receptor TLR4 [73•]. Although the possibilities are intriguing, the study of microbiome in both animal models and AS patients is in its infancy. Hopefully, greater understanding of the normal microbiome, and how (and why) it is deranged in AS, will provide greater insight into disease pathogenesis.

In addition to the microbial barrage humans are subjected to, both internal and external mechanical stress may also shape and promote inflammation. AS distinguishes itself from rheumatoid arthritis by the prominent involvement of the entheses and the pattern of joint involvement. Since aberrant immune responses could involve any tissue, why this predilection for axial skeleton and large weight-bearing joints in AS? The identification of entheseal resident IL-23R+T cells provides one explanation [57••]. Another recent study has implicated weight-bearing or biomechanical stress itself [37•]. The enthesis is a unique site, juxtaposing synovium, tendon, and bone and transducing immense mechanical forces. In a mouse TNF overexpression model (the TNF ΔARE mice), investigators suspended the hind limbs of the mice. Decreasing the weight on these limbs significantly decreased the development of enthesitis and subsequent arthritis and osteoproliferation in this model [37•]. The authors postulated that triggering of mechanoreceptors such as integrins could be signaling via the MAP kinase extracellular signal-regulated kinase (ERK) to stimulate production of inflammatory mediators such as TNF. However, other studies offer an additional potential contributor: Mechanical stress induces the release of prostaglandin which signals via the EP4 receptor and ERK to inhibit sclerostin, thus disinhibiting osteoblast stimulation [74, 75]. GWASs have implicated *PTGER4* (encoding the prostaglandin receptor), a key lynchpin in this cascade [14•]. Other studies, as mentioned above, have associated sclerostin [42•, 46]. More work is needed to flesh out how pathways integrating mechanical stress, inflammation, and osteoproliferation contribute to AS.

Proof of Concept and New Therapeutic Approaches

Finding evidence for increased production of a cytokine or implication of a cytokine receptor locus has not always translated well into therapeutic efficacy. This is particularly true for tocilizumab, which blocks IL-6, despite a rationale for clinical trials [76–78]. Therefore, the recent developments surrounding agents targeting the IL-23/IL-17 pathway have generated excitement by providing proof of concept. Ustekinumab is a monoclonal antibody specific for the common IL-12/IL-23 subunit IL-12p40 that has proven effective in psoriasis [79•]. In the 28-week prospective open label TOPAS study (Ustekinumab for the Treatment Of Patients with active Ankylosing Spondylitis), an ASAS20 was achieved by 75 % of 20 study subjects, a figure comparable to results with TNF blockade [80]. More recently, the monoclonal antibody secukinumab (targeting IL-17A) has also shown at least short-term efficacy in AS [81•]. In a randomized double-blind placebo-controlled trial, 59 % of 23 secukinumab-treated patients achieved an ASAS20 vs. 24 % on placebo (six patients) at week 6 after two infusions (time 0 and 3 weeks). These initial promising results for both agents certainly justify larger trials. In particular, it is important to determine if these new agents provide therapeutic options for those who have failed TNF blockers. Long-term effects of IL-12/IL-23 and IL-17 blockade in AS specifically are unknown. Finally, it is possible that specific patients may have either more TNF or IL-23/IL-17-driven disease, so better stratification of individual patients a priori based on their underlying pathogenesis may provide greater therapeutic optimization.

Conclusions

Sparked by genetics, over the past few years, a number of very interesting and promising developments have occurred in the study of AS pathogenesis:

1. Large-scale GWASs have identified a variety of immune pathways that deserve further study, including the relatively recently described IL-17/IL-23 pathway, factors modulating NF-κB activation, antigen presentation, and T cell phenotype.
2. Based on aminopeptidase studies and the finding of autoantibodies in AS patients, interest in the role of adaptive immunity has resurfaced.
3. As a counterbalance, striking studies in murine models have pointed to the sufficiency of cytokine dysregulation (particularly TNF-α and IL-23) in generating SpA clinical phenocopies. Ultimately, how adaptive and innate immunity interacts to establish the observed state of cytokine dysregulation remains to be clarified.
4. Environmental triggers complement genetics in causing disease. Recent attention has highlighted the potential role of the microbiome and biomechanical stressors.
5. As a proof of concept, initial studies examining the blockade of IL-17/IL-23 cytokines in AS have revealed an exciting therapeutic potential. Greater knowledge of AS pathogenesis will help inform the future development of therapeutics and optimize the application of current therapeutics.

One of the major future challenges in AS pathogenesis is to follow up the initial clues offered by GWASs. We need to learn more about the biology of the genetically implicated pathways, through the investigation of model systems and human subjects. More particularly, more insight is needed into how the genetically modulated pathways function, interact, and regulate the responses to infectious and mechanical stressors in AS.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Smith has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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