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Autoinflammation and HLA-B27: More than an Antigen

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Abstract

Spondyloarthritides comprise a group of inflammatory conditions which have in common an association with the MHC class I molecule, HLA-B27. Given this association, these diseases are classically considered disorders of adaptive immunity. However, recent data are challenging this assumption and raising the possibility that innate immunity may play a more prominent role in pathogenesis than previously suspected. In this review, the concept of autoinflammation will be discussed and evidence will be presented from human and animal models to support a critical role for innate immunity in HLA-B27 associated disorders.

Keywords

HLA-B27; autoinflammation; innate; IL-1; spondyloarthritis

INTRODUCTION

AUTOINFLAMMATION

Autoinflammation is a term coined by Dan Kastner over 10 years ago when he described episodes of “seemingly unprovoked inflammation in the absence of auto-antibodies or auto-reactive T cells”[1]. Since this initial description, autoinflammatory mechanisms have been better elucidated and the impact of autoinflammation on common diseases, even those traditionally felt to be due to adaptive immunity, is increasingly appreciated[2].

The immune response can be broadly characterized into innate and adaptive responses. Adaptive responses involve antigen specific B and T cell activation resulting in auto-antibody and antigen-specific T cell responses. Following activation, a highly specific memory response is generated. As these mechanisms were becoming increasingly understood, Polly Matzinger described an alternate hypothesis, the “danger theory”, which theorized that the immune system developed to respond to danger rather than antigen-specifc self vs. non-self[3]. While this was largely criticized at the time, it has since become accepted as the initial description of the innate immune system[4].

The innate immune response is the first line of defense to an insult to an organism such as a break in skin or mucosal integrity or the introduction of a pathogen. This occurs before the adaptive immune response has time to amplify and contain the insult and is important in directing the adaptive immune response[5]. Innate immune cells respond to danger through

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recognition of specific motifs on danger signals by highly conserved pattern recognition receptors (PRRs). The molecular patterns from microorganisms are termed MAMPS (microbe-associated molecular patterns) and damage patterns are termed damage- or danger-associated molecular patterns (DAMPs)[6]. The expanding group of PRRs includes Toll-like receptors (TLRs), Nod-leucine-rich repeat-containing receptors (NLRs), C-type lectin receptors (CLRs), RIG-1-like receptors (RLRs), and AIM-2 like receptors. Much focus has been placed on understanding the signals which activate MAMPs and DAMPs with known MAMPs including LPS, flagellin, dsRNA, and unmethylated CpG motifs and known DAMPs including DNA, RNA, uric acid, ATP, and adenosine. The net result is the activation of innate immune cells including monocytes, macrophages, dendritic cells, natural killer cells, and neutrophils with a resultant inflammatory cascade. Figure 1.

The clearest examples of autoinflammation come from the study of monogenic autoinflammatory diseases[7]. These are genetic disorders resulting from disruption of key mediators of the innate immune response. They are characterized by excessive inflammation, periods of relapse and remission, the lack of an antigen-specific response, and frequently neutrophilic infiltration[8]. The hallmark of these diseases are the cryopyrin associated periodic syndromes (CAPS) which are due to autosomal dominant mutations in *NLRP3* (also known as NALP3 or cryopyrin) resulting in a constitutively active NLPR3 inflammasome causing the conversion of pro-IL1β to active IL-1β[9,10]. This results in excessive IL-1 signaling and a characteristic pattern of damage to affected organs[11]. Inflammation in CAPS and organ damage can be completely abrogated by IL-1 inhibitors[12,13] and a response to IL-1 blockade can be used as a therapeutic test of the presence of an IL-1 mediated autoinflammatory disorder.

Other monogenic autoinflammatory disorders demonstrate the consequences of excessive activation of other key components of the innate immune response. This growing list includes familial Mediterranean fever (FMF due to mutations in *MEFV* leading to overactive pyrin)[14,15], TNF-receptor associated periodic syndrome (TRAPS due to mutations in *TNFRSF1A* which encodes the TNF receptor and leads to its sequestration in the endoplasmic reticulum and excessive signaling through activation of MAPKs)[1], PAPA (Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) syndrome due to mutations in *PSTPIP1* leading to eventual activation of pyrin)[16], and deletion of the IL-1 receptor antagonist (DIRA due to deletion *IL1RN* which encodes the IL-1 receptor antagonist leading to unopposed IL-1 signaling)[17,18]. Of note, the majority of these disorders respond to IL-1 blockade even in the absence of a direct role for IL-1 activation. While these disorders result in constitutive activation of inflammatory pathways, patients have periods of relapse and remission suggesting that there are important activation triggers which are largely not well understood.

HLA-B27 ASSOCIATED DISORDERS

HLA-B27 associated disorders include HLA-B27 related uveitis and members of the spondyloarthritides which include reactive arthritis, psoriatic arthritis, and ankylosing spondylitis (AS). The spondyloarthritides are characterized by axial spine, peripheral joint, and enthesial inflammation in addition to extra-articular manifestations including uveitis,

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psoriasis, aortic root inflammation, and gut inflammation[19]. The association with HLA-B27 is as high as over 90% of patients in the United Kingdom with AS[20] although not all subtypes are associated with disease[21]. Other HLA-B27 associations include reactive arthritis (67%)[22], IBD-associated spondyloarthritis (72%)[23], psoriatic arthritis – both peripheral and axial (24–90%)[23], juvenile enthesitis-related arthritis (76%)[24], and acute anterior uveitis (52%)[25].

The major histocompatibility complex (MHC) is located on chromosome 6 and encodes the human leukocyte antigens (HLAs). These complexes are responsible for antigen presentation to the immune system with class I molecules presenting antigen primarily to CD8+ T cells. MHC molecules are formed in the endoplasmic reticulum and then travel to the cellular surface after proper assembly. The HLA-B27 structure includes a groove which binds arginine at the second position of bound peptide which may be important in directing the bound antigen to immune cells[26]. The proportion of individuals carrying HLA-B27 varies widely but is approximately 7–8% in Caucasians and as low as 2% in African Americans[27] although only a minority of carriers develop a HLA-B27 related disease.

HLA-B27 PATHOGENIC MECHANISMS : AUTOIMMUNE OR AUTOINFLAMMATORY?

Despite the clearly recognized association of HLA-B27 with spondyloarthritis, the mechanism by which disease occurs remains incompletely understood. The robust association with HLA-B27, an antigen presenting complex, is the strongest argument that adaptive immunity is important in these diseases. However, mounting evidence suggests that the role of HLA-B27 may not be so simple and that it may in fact activate innate immune mechanisms. Three main theories to explain how HLA-B27 causes disease have been proposed: the arthrogenic peptide, homodimerization, and endoplasmic reticulum (ER) misfolding theories.

HLA-B27 TRANSGENIC RAT MODEL

The HLA-B27 transgenic rat model has been critical in understanding the pathogenesis of HLA-B27 related diseases[28,29]. In this model, HLA-B27 is overexpressed together with varying amounts of human β2-microglobulin resulting in bowel inflammation, peripheral arthritis, and spondyloarthritis. Interesingly, additional overexpression of β2-microglobulin results in more severe arthritis and is necessary for the development of high frequency spondyoarthritis[29]. Through this model, the three primary theories for pathogenesis have been studied.

ARTHROGENIC PEPTIDE THEORY

One of the earliest theories on how HLA-B27 causes disease is the “arthrogenic peptide” hypothesis. Given the role of MHC I in antigen presentation, was proposed that HLA-B27 presents a specific peptide to the immune system which then results in CD8+ T cells activation[30]. However, the arthrogenic peptide theory has fallen out of favor when it was found that CD8+ T cells are not in fact necessary for the disease phenotype in the HLA-B27 transgenic rat model[31,32]. This suggests that other mechanisms may be more important in

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disease pathogenesis and that HLA-B27 does not likely exert its effect by antigen presentation alone.

An additional argument challenging the arthrogenic peptide theory has been that despite investigations, no specific peptide(s) targeted by autoreative T cells have been identified. Even autoantibodies have not been reproducibly found in various forms of spondyloarthritis. However, this has been challenged recently with reports of autoantibodies to class II-associated invariant chain peptide (CLIP) in 85% of patients with axial spondyloarthrtitis compared to 8% of controls [33] and higher amounts of immune complexes containing anti-noggin and antisclerostin antibodies in patients with ankylosing spondylitis when compared to controls[34]. The significance and reproducibility of both of these findings remains to be determined.

HOMODIMERIZATION THEORY

HLA-B27 molecules are unusual in that they can form homodimers on the surface of cells[35]. Based on this finding, an alternate theory was proposed that these homodimers are recognized by the immune system resulting in activation and inflammation. Innate immune receptors on both natural killer and T cells, KIRs and LILRs, respectively, recognize HLA class I monomers as well as some homodimers resulting in cytokine production[36]. Further supporting this theory is that KIR genetic polymorphisms have been associated with AS in some populations[37,38] although notably, this has not been found consistently [39]. While this theory supports a role for innate immunity in disease pathogenesis through recognition of homodimers by KIRs and/or LILRs, it is unlikely that this is the sole mechanism for pathogenesis as homodimerization is not unique to disease associated HLA-B27 variants or even to HLA-B27 itself[40].

ER MISFOLDING THEORY

An alternate theory was proposed after recognition that HLA-B27 misfolds in the endoplasmic reticulum (ER) causing some heavy chains to undergo ER-associated degradation[41]. In HLA-B27 transgenic rats, this occurs in bone marrow macrophages following cytokine stimulation, is independent of antigen presentation, and is associated with the degree of HLA-B27 upregulation[42,43]. The net effect is ER stress resulting in IL-23[43], IFN-β[44], and IL-1α.[45] production. Attempts to reproduce these experiments in humans have yielded mixed results. One study found upregulation of the UPR target gene Hspa5/BiP in synovial macrophages[46] and there are conflicting reports regarding the role of the UPR in peripheral blood mononuclear cells[47,48].

HUMAN GENETICS

Genome-wide association studies (GWAS) allow for the examination of thousands of polymorphisms in the human genome and their association with the presence of disease. These studies have provided for powerful, cost-effective, unbiased studies of the genetic predisposition to disease shedding light on the pathogenic mechanisms.

Several GWAS have been completed in ankylosing spondylitis, psoriatic arthritis, and anterior uveitis confirming the polygenic nature of these diseases[49–57]. Given that these are

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B27 related diseases, not unexpectedly the region consistently most closely associated with disease is that of the MHC locus. However, HLA-B27 is responsible for only a minority of the genetically attributable risk in twin studies of ankylosing spondylitis indicating that other genetic factors are essential[58]. Perhaps more surprising is that many of these other associated variants have importance in innate as well as adaptive immunity.

In support of a role of adaptive immunity, *ERAP1* is associated with AS[50] and is also associated with acute anterior uveitis[53]. ERAP1 is important in peptide trimming prior to MHC loading which suggests a role for antigen presentation. However, it is also possible that peptide processing by ERAP1 is important for proper folding of HLA-B27 and that ERAP1 variants impact protein misfolding independent of antigen presentation. Other adaptive immune genes implicated in psoriatic arthritis include *TRAF3IP2* encoding ACT1[54], important in the regulation of B cell signaling, and *PTPN22*, important in the regulation of T cell activation[59]. Shared to AS and psoriatic arthritis is the association with *RUNX3* important in CD8+ lymphocyte activation[60].

IL-23 has a role in both innate and adaptive immunity and several genes in the IL-23/IL-17 pathway have shown associations with HLA-B27 diseases including *IL-23R, IL-23A, IL-12B*, *TYK2*, and *STAT3*[50,52,61]. This fits well with the known role of IL-23 in the development of these diseases (to be discussed)

However, several other variants have a more prominent role in innate immunity. These include those important in NFκB signaling in psoriatic arthritis including *TNIP1*, *REL* and *TYK2*[62] and in ankylosing spondylitis including *TRADD*, *TKBP1*, *TYK2,* and *CARD9*[49–52]. CARD9 in ankylosing spondylitis is of particular interest given its known role in the innate immune response by mediating signals through Dectin-1, a pattern recognition protein. Similarly, in acute anterior uveitis, variants in a gene known to be important in innate immunity, *IL18R1*, are associated with disease[53].

IMPORTANCE OF THE MICROBIOME IN HLA-B27 DISEASES

The importance of the microbiome, the collection of bacteria on and within our bodies, is becoming increasingly appreciated in many complex diseases including those of HLA-B27 related disorders[63]. The interplay between the innate immune system and the microbiome may be an important in both initiation and propagation of inflammation. The microbiome is critical in educating the immune system and in a pathogenic state, may be responsible for immune activation at distant sites.

One of the strongest lines of evidence that the microbiome is important in disease pathogenesis comes again from the HLA-B27 rat model. When raised in germ free conditions, bowel and joint inflammation is much reduced indicating that bacterial colonization of the gut is necessary for the disease phenotype[64]. Re-introduction of normal flora, specifically Bacteroides, results in the return of inflammation[65].

The mechanisms by which bacteria are associated with B27-related diseases remain unclear but an active area of research. An attractive hypothesis is that HLA-B27 may shape the gut microbiome or alter the way that antigen is presented to an individual. In fact, 16S

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sequencing revealed differences between HLA-B27 rats when compared to control in cecal bacterial composition with an increase in Prevotella and a decrease in Rikenellaceae relative abundance in the transgenic animals compared to the wild type animals[66]. This is beginning to be studied in humans where differences in terminal ileum microbiota are seen in patients with ankylosing spondylitis when compared to controls[67].

These findings are not surprising as it is well established that microbes may play a role in the development of certain forms of human spondyloarthritis. The clearest example of this is reactive arthritis (formerly Reiter's syndrome), where peripheral arthritis and/or spondyloarthritis can occur following an infection, most typically Chlamydia or enteric infections[68]. Similarly, Yersenia and Salmonella bacterial products have been observed in reactive arthritis joints further supporting the role of bacteria in the development of disease[69,70]. Similar associations have been proposed in ankylosing spondylitis where colonization with Klebsiella was found more often in active AS when compared to controls[71] although these results have not been reproduced.

Moreover, sub-clinical gastrointestinal inflammation has been demonstrated in the absence of symptoms in 50% of patients with HLA-B27 related arthritis[72]. The presence of a "leaky gut" due to mucosal barrier breakdown may then result in the interaction of gut bacteria with innate immune cells serving as an inciter of the inflammatory cascade.

IL-17/IL-23

The importance of IL-17 and IL-23 in the development of several B27-related diseases is well proven and may provide a link between innate and adaptive immunity. IL-23 is produced primarily by macrophages and dendritic cells, both innate immune cells[73]. These cells are active at mucosal surfaces and are produced by the gut, an area known to be inflamed in spondyloarthritis and psoriatic arthritis[74]. In AS, macrophages produce increased levels of IL-23 compared to controls [75] and IL-23 is found in high levels in spinal facet joints[76] as well as the gut[77] of spondyloarthritis patients. IL-23 is also found in higher levels in lesional compared to non-lesional skin in psoriasis[78] and is associated with keratinocyte growth in mouse models of psoriasis[79]. IL-23 responsive cells are then activated, including innate cells such as IL-23R+ γδ T cells, which are found to be in higher levels in AS patients with active disease[80]. IL-23 then activates cells producing IL-17A and IL-17F which is supported by the higher proportion of circulating Th17 cells in patients with AS compared to controls[81]. This is also true of psoriasis and psoriatic arthritis where a higher number of Th17 cells are observed in lesional vs. non-lesional psoriatic skin[82] and higher numbers of IL-17 producing CD4+ effector memory cells in psoriatic arthritis synovium compared to osteoarthritis synovium[83]. Further clinical data suggest that blockade of these pathways is highly effective in these diseases (to be discussed).

INNATE IMMUNE-LIKE CELLS IN ENTHESES

While the importance of IL-23 in HLA-B27 diseases is established, how this results in disease pathology is less well understood. A major advance occurred when a novel IL-23 responsive cell type residing in the entheses and aortic root was described in a mouse model

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of spondyloarthritis [84]. A novel IL-23R+CD3+CD4−CD8− lymphocyte cell was described which was found to reside in the entheses and aortic root. These cells had innate immune characteristics in that IL-23 alone – without antigen recognition, other cytokines, or other inflammatory cells - was sufficient to induce inflammation and cytokine expression including IL-6, IL-17, IL-22, and CXCL1. Systemic expression of IL-23 resulted in an inflammatory infiltrate of macrophages and neutrophils focused in the entheses, periosteum, and aortic root with resultant new enthesial bone formation. This was not reduced by Th17 or CD4 depletion suggesting that adaptive immunity is not essential for the phenotype. Moreover, the clinical phenotype could be abrogated by IL-23 blockade. Based on these observations, it has been proposed that IL-23 may be produced at distant sites, such as the gut, and that this then results in enthesial and aortic root inflammation by activation of resident cells with innate features.

Recently, IL-23 responsive innate lymphocyte cells producing IL-17 and IL-22 were described in the gut, peripheral blood, synovial fluid, and bone marrow from patients with ankylosing spondylitis lending support to the idea that a similar phenomenon may be relevant in humans[85]. These cells have a different phenotype than those described in the mouse model however result in similar inflammatory cytokine production.

CLINICAL TRIALS

While animal and pre-clinical data suggest a role for inflammatory pathways in the development of disease, the ultimate proof of this principal lies in the response to therapeutic blockade. The role of adaptive immunity has been tested through studies of both rituximab (pre-B cell blockade)[86,87] and abatacept (co-stimulation blockade)[88]. Both of these pathways are important in adaptive immunity, yet blockade in spondyloarthritis yielded disappointing results.

Mounting evidence supports that IL-23 and IL-17 blockade is effective in many of the B27 related diseases supporting the critical role of this pathway in disease pathogenesis. The first studies of IL-17 and IL-23 blockade were in psoriasis where overwhelmingly positive results were achieved[89,90]. These drugs were then studied in psoriatic arthritis where similarly positive results were found although the results were less robust[91–93]. They have been studied more recently in ankylosing spondylitis where positive results are also emerging[94,95]. Of great interest will be whether they are capable of blocking new bone formation to a greater extent than the most proven therapies, TNF inhibitors. Interestingly, similar results were not found with IL-17 blockade in noninfectious uveitis where three randomized studies failed to show benefit in reducing uveitis recurrence[96].

A good response to IL-1 blockade is frequently used as clinical evidence for a prominent role of autoinflammation in disease pathogenesis[97]. A single study was performed with anakinra, the recombinant IL-1 receptor antagonist, in ankylosing spondylitis. In this open label study of a relatively small number of patients, only a minority of patients reached the primary endpoint of an ASAS20 response which is disappointing in comparison to the results of TNF inhibitors[98]. No changes were observed in objective measures of inflammation including acute phase reactants or MRI scores however the study was not

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sufficiently long to study the effects of IL-1 blockade on structural damage. The dose of anakinra was not escalated so it is not clear if patients would have responded to a higher dose which is often necessary in autoinflammatory disorders.

Less is known about the role of IL-1 blockade in uveitis. Animal studies show that mice lacking the IL-1 receptor antagonist develop a particularly severe uveitis in an intraocular LPS-induced mouse model [99]. A large multi-center study is underway to test if IL-1 blockade with a long acting IL-1β blocking monoclonal antibody, gevokizumab, is effective in non-infectious uveitis[100]. While patients are not strictly HLA-B27+, this may lend insight into the role of IL-1 within the eye as this may differ from the effects of other organs in HLA-B27 related diseases.

CONCLUSIONS

HLA-B27 related diseases share many features with classic autoinflammatory diseases and mounting data suggests that autoinflammation is a key component of disease pathogenesis. However, ample data also exist to support the role of the adaptive immune system. The division between the innate and adaptive immune system is artificial as it is neither works in isolation and cross-talk is well described. The relative contribution of innate and adaptive immune mechanisms is under active investigation and further understanding of the role of autoinflammation in these disorders may lead to novel therapeutic directions.

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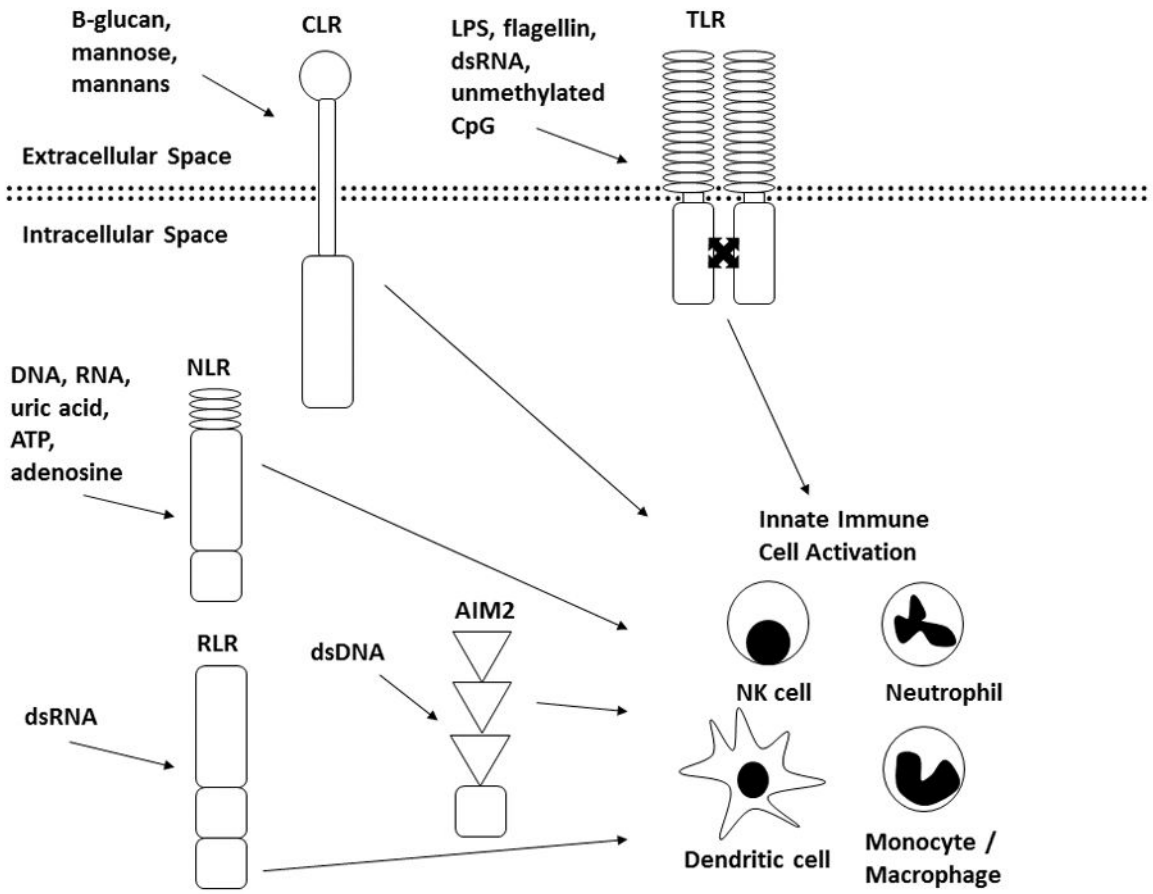

Figure 1. Activation of Innate Immunity

MAMPs and DAMPs activate CLRs, TLRs, NLRs, RLRs, and AIM-2 resulting in activation of innate immune cells including NK cells, neutrophils, monocytes/macrophages, and dendritic cells.

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Table 1

Shared Features of Autoinflammatory, HLA-B27 Associated, and Autoimmune Diseases

Feature	Autoinflammatory Diseases	HLA-B27 Associated Diseases	Autoimmune Diseases
Age of onset	Very young	Young	Varies
Sex	F = M	M > F	F > M
Fevers	Prominent feature	Rare	Rare
Disease course	Flares and remits	Flares and remits	Continuous and progressive
Ocular findings	Uveitis, conjunctivitis	Uveitis, conjunctivitis	Varied, scleritis, episcleritis, uveitis less common
Sacroiliitis	Present but not common	Prominent feature	Rare
Acute phase reactants	Greatly elevated	Typically normal	Elevated
Presence of autoantibodies	No	No	Yes
Histology	Neutrophils	Neutrophils and mixed inflammatory cells	Mixed inflammatory cells
Genetics	Typically monogenic mutations in innate pathways	Polygenic: MHC-I, ERAP1, IL-23/IL-17	Polygenic: MHC-II, PTPN22, CTLA4, TNFAIP3
Effective Treatments	Cytokine blockade, not B-cell blockade, not corticosteroids	Cytokine blockade, not B-cell blockade, not corticosteroids	Cytokine blockade, B-cell blockade, corticosteroids