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REVIEW ARTICLE

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Infectious agents in arthritis and autoimmunity

Abstract The distinctions between infection, chronic arthritis, and autoimmune diseases have steadily blurred over the past decades. The proposed pathomechanisms underlying these interesting associations include putative pathways from infection to innate and adaptive immunity, molecular mimicry, and certain microbial and host factors. This article further reviews the spectrum of microbial agents implicated in some rheumatic diseases and cites the potential clinical application of this expanding field of knowledge in the prevention and treatment of chronic inflammatory and autoimmune diseases.

Key words Arthritis · Autoimmunity · Infection

Introduction

The associations between infectious agents, arthritis, and autoimmune diseases have fueled volumes of hard scientific data, hypothetical assumptions, and exciting speculations among scientists and clinicians.[1–4] The contributory role of microbes in the induction and reactivation of chronic inflammatory and autoimmune conditions has been substantiated even in experimental systems.[5,6] This article provides an overview of the organisms implicated in chronic joint inflammation and autoimmune diseases and the proposed pathomechanisms underlying these interesting associations.

Pathomechanisms

There are a variety of pathomechanisms that elucidate the relationship between infection and autoimmunity. Although some concepts are applicable to most diseases, others are specific for certain types of inflammatory or autoimmune conditions. Furthermore, the role of genetics cannot be overemphasized. It is likely that different pathomechanisms, either singly or in combination, are in effect in many autoimmune diseases.

The complexity of the immune response to microbes has given rise to putative pathways that draw the link between innate immunity and autoimmunity.[7,8] For instance, pathogens trigger the release of innate cytokines such as interleukins (IL) 1, 6, 12, and 18, tumor necrosis factor (TNF), and nitric oxide, which confer self-protection but may also direct autoreactive T helper 1 (Th1) cell development. The same cytokines can also upregulate costimulatory molecules on antigen-presenting cells and activate natural killer (NK) cells, NKT cells and γδT cells that interact to promote downstream adaptive responses, i.e., T-cell and/or B-cell-mediated autoimmunity.[8,9]

Molecular mimicry is one of the most cited pathomechanisms underlying the associations between infectious agents, arthritis, and autoimmunity.[10,11] This concept suggests that the body's immune response to an infectious agent eventually directs itself against the body's self-antigens because of similarities in antigenic epitopes. For instance, immunological cross-reactivity of a viral antigen with self can lead to the production of autoantibodies, which may also be antiidiotypic in nature.[12,13] It is yet unclear whether the stimulation of the immune response is induced by the pathogen itself, or that the pathogen alters the immune system's ability to respond to self through breakdown of tolerance.

Microbial factors play a role in the induction of autoimmune disease, as illustrated by superantigens (SAgs), so called because they are capable of activating large numbers of T cells regardless of antigen specificity of the T cell.[14,15] These antigens bind avidly to major histocompatibility complex (MHC) class II molecules at a site distinct from the conventional antigen-binding cleft, allowing for a more productive interaction and the activation of antigen-presenting cells and normally tolerant self-reactive T lymphocytes, with consequent B-cell activation.[16] They may further

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influence the course of autoimmune disorders by inducing a relapse during clinical remission.[15,17] Examples of superantigens are those derived from staphylococci, streptococci, mycoplasma organisms, retroviruses, cytomegalovirus, and Epstein–Barr virus.

Other factors thought to contribute to the arthropathies and autoimmune syndromes following an infection include the "arthrogenicity" of certain microorganisms and the role of costimulatory molecules, heat shock proteins (HSPs), and MHC molecules.[2–5] These factors are further discussed in the specific rheumatic diseases.

Infectious Agents and Rheumatic Diseases

Spondyloarthropathies

Spondyloarthropathies (SpA) are a heterogeneous group of HLA-B27-associated diseases that include reactive arthritis (ReA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), enteropathic arthritis, and undifferentiated arthritis.

Reactive arthritis (ReA), historically known as Reiter's syndrome, is defined as a form of arthritis usually following enteric or genitourinary infections caused by a number of bacterial pathogens such as *Chlamydia*, *Salmonella*, *Yersinia*, *Campylobacter*, and others.[18,19] In contrast to intact although noncultivable chlamydial organisms found in the joints of gender-associated ReA, only bacterial DNA identified by polymerase chain reaction (PCR) has been so far reported in the joints of enteric-related ReA.[19,20]

Early evidence for an infectious trigger in AS was based on the observation that levels of anti-*Klebsiella pneumoniae* antibodies were higher in patients with AS than in controls.[21] The intricate relationship between the characteristic enthesopathy of AS, infectious triggers, genetic and biomechanical factors, and immunoreactivity has formed the basis of most models that elucidate the pathogenesis of the spondyloarthropathies.[22–24]

Psoriatic arthritis (PsA) is distinctly identified by its association with psoriatic skin lesions although sharing similar characteristics with the other spondyloarthropathies including rheumatoid factor seronegativity and predominant sacroiliitis or axial involvement. Environmental factors including stress and infection[25,26] have been considered in the etiology of PsA, with pathogenic mechanisms similar to that described for ankylosing spondylitis and other spondyloarthropathies.[23]

In addition to a defined association of enteric pathogens with classical ReA, recent studies confirm that 30%–40% of patients with inflammatory bowel disease (IBD) present musculoskeletal manifestations compatible with SpA.[27–30] On the other hand, subclinical gut inflammation may be present in 50% of SpA patients.[31]

Despite extensive diagnostic tests, about 50% of patients with mono- and oligoarthritis do not fit into a specific rheumatological diagnosis.[32,33] Certain clinical features of these patients with undifferentiated arthritis such as frequency of HLA-B27 and predominance of lower-extremity involvement suggest that they may have a "forme fruste" of ReA.[34,35] Furthermore, molecular techniques using optimized PCR protocols have continued to document the presence of bacterial products such as those of *Chlamydia*, *Borrelia*, and *Yersinia* in patients with undifferentiated arthritis.[36] Interestingly, panbacterial screening assays have identified a diverse array of chromosomal DNA from a variety of other organisms including *Moraxella*, *Klebsiella*, *Pseudomonas*, and *Stenotrophomonas*.[37] This latter study further showed (1) a high prevalence of polymicrobial agents in the synovial tissue rather than the fluid and (2) no correlation with any specific rheumatological diagnosis.

Most organisms associated with SpA are intracellular bacteria that cause primary mucosal infection. It is suggested that HLA-B27 further causes disease by altering the susceptibility of host cells to bacterial invasion and survival.[38] Aberrant forms of HLA-B27 have recently been elucidated that may be recognized by CD4+ (instead of CD8+) T cells and immunomodulatory killer cell immunoglobulins (Ig).[39,40] Recent studies on cytokine networks show a predominance of T helper 2 (Th2) cytokines in the synovium of ReA patients, partially explaining why intracellular organisms such as *Chlamydia* are more likely to persist in ReA.[36,41]

Spondyloarthropathies in HIV infection

The spondyloarthropathies are among the more commonly reported rheumatic diseases in patients infected with human immunodeficiency virus (HIV).[42–44] Although clinically indistinct from that seen in non-HIV individuals, there may be a direct role of HIV in the articular manifestations as evidenced by the presence of tubuloreticular retroviral inclusion structures in the synovial fluid of some patients.[45] In contrast, retroviral infection has not been clearly shown to play a role in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA).[46] Furthermore, antiretroviral agents do not appear to alter either the frequency or expression of rheumatic manifestations in HIV-infected individuals.[47]

Other forms of "reactive arthritis"

Poststreptococcal arthritis, although sharing the same antigenic trigger of rheumatic fever (RF), i.e., Group A streptococci, is nonetheless considered distinct from RF with its clinical features of arthritis usually poorly responsive to aspirin, significantly less incidence of carditis, more frequent tenosynovitis, and slightly different HLA-DR alleles.[48]

Poncet's disease is classically described as a form of nonseptic polyarthritis associated with disseminated tuberculosis. Similarly, several forms of arthritis induced by mycobacterial components such as bacillus Calmette-Guerin[49–53] and the 65-kDa heat shock protein (HSP) of *Mycobacterium leprae*[54] have been reported in the literature. Indeed, the clinical manifestations of arthritis with urinary symptoms and ocular inflammation plus a strong

genetic HLA-B27 background following BCG exposure incriminate mycobacteria as a possible pathogenic trigger in ReA.[53,55]

Lyme disease resulting from persistent infection with the tickborne spirochete *Borrelia burgdorferi* (Bb) may present with arthritis in about 60%.[56] It remains unclear whether some of these patients actually have a form of ReA, in the light of findings of Bb DNA in the synovial fluid of patients with undifferentiated mono- or oligoarthritis but negative Lyme serology.[57] Furthermore, Bb has been implicated as a potential cause of ReA in the genetically susceptible HLA-B27-positive host.[58] Studies on treatment-resistant Lyme arthritis (TRLA) patients suggest a role for the adhesion molecule human lymphocyte function antigen 1 (hLFA1α) in the perpetuation of joint inflammation and autoimmunity.[59] Another mechanism for post-Lyme arthritis may be the observation that Bb can undergo antigenic variation leading to immune evasion and persistent infection.[60]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory erosive polyarthritis of unknown etiology. Among possible infectious triggers, Epstein–Barr virus (EBV) has been the most frequently cited agent implicated in the pathogenesis of RA; this is based on several observations where sera and synovial fluids of RA patients contained antibodies to a variety of EBV antigens.[61–65] More recent studies found EBV DNA in synovial tissue of these patients, suggesting that synoviocytes (in addition to B lymphocytes) also provide targets for EBV infection.[66–68] Similarly, cytomegalovirus (CMV),[69–72] human retrovirus,[44,73] and hepatitis viruses[74] have been reported and studied as a possible infectious trigger, if not a mimic, of RA and other rheumatic diseases.

Bacteria such as *Clostridium perfringens*,[75] *Yersinia enterocolitica*,[76] *Proteus mirabilis*,[77] *Escherichia coli*,[78] and *Mycoplasma pulmonis*[79] have also been implicated, leading to speculations that RA may really be a form of "reactive arthritis."[80,81]

Although molecular mimicry provides the most acceptable explanation for these associations, particular interest has been shown in those that possess homology sequences with the shared epitope found in host HLA-DRB1*0401 and *0404 alleles.[78,82] For instance, primary cytotoxic damage to hyaline cartilage and HLA-DR1/DR4-positive chondrocytes can be induced by antibodies to *Proteus mirabilis* following urinary tract infection; this leads to secondary cytotoxic and collateral damage by cytokines with the resultant chronic synovitis of RA.[77,82]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the universal presence of autoantibodies and a wide range of clinical manifestations. Speculations on the role of infections in the etiology of SLE have largely emerged from the production of various autoantibodies during the course of many types of infections.[83,84] Epstein-Barr virus (EBV) has been one of the most directly linked to the pathogenesis of SLE,[85] whereas parvovirus B19 has been additionally most cited as a "mimic" of SLE.[86–90] Several papers further report the association of HIV infection and the presence of autoantibodies including antinuclear antibodies, antineutrophil cytoplasmic antibodies, lupus anticoagulant, and anticardiolipin antibodies,[91–95] occasionally accompanied by "lupus-like" manifestations. On the other hand, evidence of high-titer antibodies to retroviral proteins in SLE patients[96] has led to the consideration of these viruses as "candidate lupus viruses."

Cytokine abnormalities abound in SLE, along which interferon-α (IFN-α) may play a pivotal role.[97] Furthermore, IFN-α correlates with disease activity and contributes to the development of antinuclear antibodies.[98] Because human leukocytes produce IFN-α when exposed to a wide variety of infectious agents, it is possible that the initial appearance and sustained production of autoantibody-producing cells can be precipitated, and thereafter maintained, by infection-induced IFNs.[97]

Systemic vasculitis

Viral infections have been implicated in the pathogenesis of certain systemic vasculitides. For instance, in addition to self-limited arthritis syndromes, chronic hepatitis B antigenemia may be associated with polyarteritis nodosa (PAN).[99]

Similar to its well-publicized role in the induction of atherosclerosis and coronary artery disease,[100,101] *Chlamydia pneumoniae* has been found in temporal artery specimens from patients with giant cell arteritis (GCA), a vasculitis predominantly affecting medium- and large-sized vessels.[102] An extensive review on this subject mentions other microbial pathogens implicated in the pathogenesis of GCA, including parvovirus B19 and parainfluenza virus type 1, as well as reports of GCA following influenza vaccination.[103,104] Furthermore, the 65-kDa HSP of *Mycobacterium tuberculosis* has been implicated in the pathogenesis of Takayasu's arteritis, another large vessel vasculitis.[105]

Hepatitis viruses, particularly hepatitis C virus (HCV), have been linked to the pathogenesis of various rheumatic syndromes ranging from arthralgias to systemic vasculitis.[106] Of these, mixed cryoglobulinemia syndrome (MCS) has perhaps been the most consistently cited as having an established association with chronic HCV infection.[107] This association seems to have been expanded by studies on more complex relationships between HCV, MCS, and other syndromes such as Sjogren's and lymphoproliferative disorders.[108–111] Furthermore, the presence of genetic markers such as HLA-DR11 appears associated with increased risk for the development of type II MCS,[112] suggesting that the DRB1*11 allele might play a crucial role in presenting immunogenic HCV antigens, with resultant strong antiviral CD4 response, and causing widespread immune complex release and cryoglobulinemia-induced vascular injury.

The increased morbidity and mortality rates of patients coinfected with HIV and HCV cannot be entirely explained by a more fulminant HIV disease.[113] It is likely that the extrahepatic and autoimmune involvement in HCV such as MCS, vasculitis, and proteinuria play a significant contributory role.

The prompt recognition of HCV-related vasculitis including MCS becomes particularly important because of the potential for treatment. Combination therapy using interferon-α plus ribavirin has demonstrated substantial efficacy on main HCV vasculitis manifestations, associated with a good virologic response.[114]

Conclusion

The intricate interplay between host, microbe, and environment has brought the concept of autoimmunity to greater heights. The rapid development in laboratory technology is expected to provide more accurate identification of microbes and their products and precisely define the relationship between these ubiquitous agents and autoimmune disease. There are several proposed strategies on establishing the causative etiology of these microorganisms, including early identification and tissue banks for predisposed individuals.[115] The growing impression that perhaps all "autoimmune" diseases are truly infectious in nature should be provocative enough to encourage more studies in this field. Indeed, the ensuing challenge for researchers and clinicians becomes even more appealing because it holds promise of treatment and prevention of many chronic inflammatory and autoimmune conditions.

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