Role of infectious agents in autoimmunity

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The primary purpose of the immune system is to protect the body against a plethora of microorganisms, which are readily recognized as foreign under normal circumstances. However, the immune system must also be able to distinguish the protein fragments of these microorganisms from those of its own self-antigens through mechanisms of immune tolerance. In addition to genetic susceptibility, crossing this precarious line between responses to foreign versus self antigens may lead to autoimmunity.

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]. This presentation provides an overview of the proposed pathomechanisms underlying such interesting associations, and the various organisms implicated in some autoimmune diseases.

Overview of pathomechanisms

There are a variety of pathomechanisms (Table 1) that elucidate the relationship between infection and autoimmunity. Whereas some concepts are applicable to most diseases, others are specific for certain types of inflammatory or autoimmune conditions. Furthermore, the role of genetics and other environmental factors cannot be overemphasized. It is likely that different pathomechanisms, either singly or in combination, in multistep processes, are in effect in the development of autoimmunity (Figure 1).

The complexity of the immune response to microbes has given rise to putative pathways that draw the link between innate immunity, adaptive immune responses and autoimmunity [6,7]. 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 (Th)1-cell development. The same cytokines can also upregulate costimulatory molecules on antigen-presenting cells and activate natural killer (NK) cells, NK T cells and γδ T cells, which interplay to promote downstream adaptive responses, specifically T-cell and/or B-cell-mediated autoimmunity [8,9].

Toll-like receptors (TLRs) are a recently identified family of innate receptors that recognize a set of microbial molecules known as pathogen-associated molecular patterns (PAMPs). Ligation and activation of receptors such as TLR4 on macrophages by viral or bacterial PAMPs leads to release of the proinflammatory cytokines TNF-α, IL-1β, -18 and -4. Although these cytokines protect the host against infection, they also overcome tolerance mechanisms resulting in chronic inflammation and autoimmune processes, including alterations in cell signaling pathways [9–11]. Studies have shown that TLR9 agonists aggravate immune complex glomerulonephritis and induce progression of renal disease in rodents [12].

Molecular mimicry is one of the most cited pathomechanisms underlying the associations between infectious agents, arthritis and autoimmunity [13]. This concept suggests that the body's immune response to an infectious agent eventually directs itself against the body's self-antigens owing to similarities in antigenic epitopes. For instance, immunologic cross-reactivity of a viral antigen with self can lead to the production of autoantibodies, which may also be anti-idiotypic in nature [14]. It is currently 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. Examples of SAgs are those derived from *Staphylococci*, *Streptococci*, *Mycoplasma* organisms, retroviruses, cytomegalovirus (CMV) and Epstein–Barr virus (EBV) [15]. These bind avidly

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Table 1. Some pathomechanisms that link infectious agents with autoimmunity.

Pathomechanisms	Examples of molecules and/or peptides
Cytokine pathways in innate immune response	IL-1, -6, -12, -18 and TNF
TLRs and ligands	TLR4, TLR9, LPS and PAMPs
Molecular mimicry	Most viral and bacterial antigens
Superantigens	*Staphylococci*, *Streptococci*, *Mycoplasma*, CMV, EBV and HERV

CMV: Cytomegalovirus; EBV: Epstein–Barr virus; HERV: Human endogenous retrovirus; IL: Interleukin; LPS: Lipopolysaccharide; PAMP: Pathogen-associated molecular patterns; TLR: Toll-like receptor; TNF: Tumor necrosis factor.

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 Bcell activation [16]. They may further influence the course of autoimmune disorders by inducing a relapse during clinical remission.

Retroviruses, including human endogenous retroviruses (HERVs), have been repeatedly suggested as etiological factors for autoimmune rheumatic diseases such as systemic lupus erythmatosus (SLE) [17]. Interestingly, HERVs are inherited in a stable Mendelian fashion and make up 0.1–0.6% of human DNA, thus contributing substantially to the architecture of the human genome by integration, particularly into sites of immune regulation. Expressed proteins of HERVs can also perpetuate the autoimmune disease process by acting as SAgs or as cross-reactive antigens inducing molecular mimicry [18,19].

Models derived from spondyloarthropathies & inflammatory arthritides

The intricate relationship between ankylosing spondylitis, infectious triggers, genetic factors and immune reactivity has formed the basis of most of the models that link all these factors into a unified concept [20–22]. For instance, recent studies suggest that, in addition to its function as an antigen-presenting molecule, human leukocyte antigen (HLA)-B27 causes disease by altering the susceptibility of host cells to bacterial invasion and survival, and that aberrant forms of HLA-B27 may be recognized by $CD4^+$ (instead of $CD8^+$) T cells and immunomodulatory killer cell immunoglobulins [23,24]. Recent studies on cytokine networks also show a predominance of Th2 cytokines in the synovium of reactive arthritis (ReA) patients, partially explaining why intracellular organisms, such as *Chlamydia*, are more likely to persist in ReA [25].

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 (BCG) and the 65 kDa heat shock protein (hsp) of *Mycobacterium leprae*, have been reported in the literature [26,27]. 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.

Lyme disease resulting from persistent infection with the tick-borne spirochete *Borrelia burgdorferi*, may present with arthritis in approximately 60% of Lyme patients [28]. Furthermore, *B. burgdorferi* has been implicated as a potential cause of ReA in the genetically susceptible HLA-B27-positive host [29]. Studies on treatment-resistant Lyme arthritis patients suggest a role for the adhesion molecule human lymphocyte function antigen 1α in the perpetuation of joint inflammation and autoimmunity, as well as the observation that *B. burgdorferi* can undergo antigenic variation leading to immune evasion and persistent infection [30,31].

Rheumatoid arthritis (RA) is a chronic inflammatory erosive polyarthritis of unknown etiology. Among possible infectious triggers, EBV has been the most frequently implicated agent. This is based on several observations where sera and synovial fluids of RA patients contained antibodies to a variety of EBV antigens [32,33]. More recent studies found EBV DNA in the synovial tissue of these patients, suggesting that synoviocytes (in addition to B lymphocytes) also provide targets for EBV infection [34–36]. Similarly, CMV [37,38], human retrovirus [39,40] and hepatitis viruses [41,42] have been reported and studied as possible infectious triggers, if not a mimic of RA and other rheumatic diseases.

Bacteria such as *Yersinia enterocolitica* [43], *Proteus mirabilis* [44] and *Mycoplasma pulmonis* [45] have also been implicated, indicating that RA may really be a form of ReA [46,47].

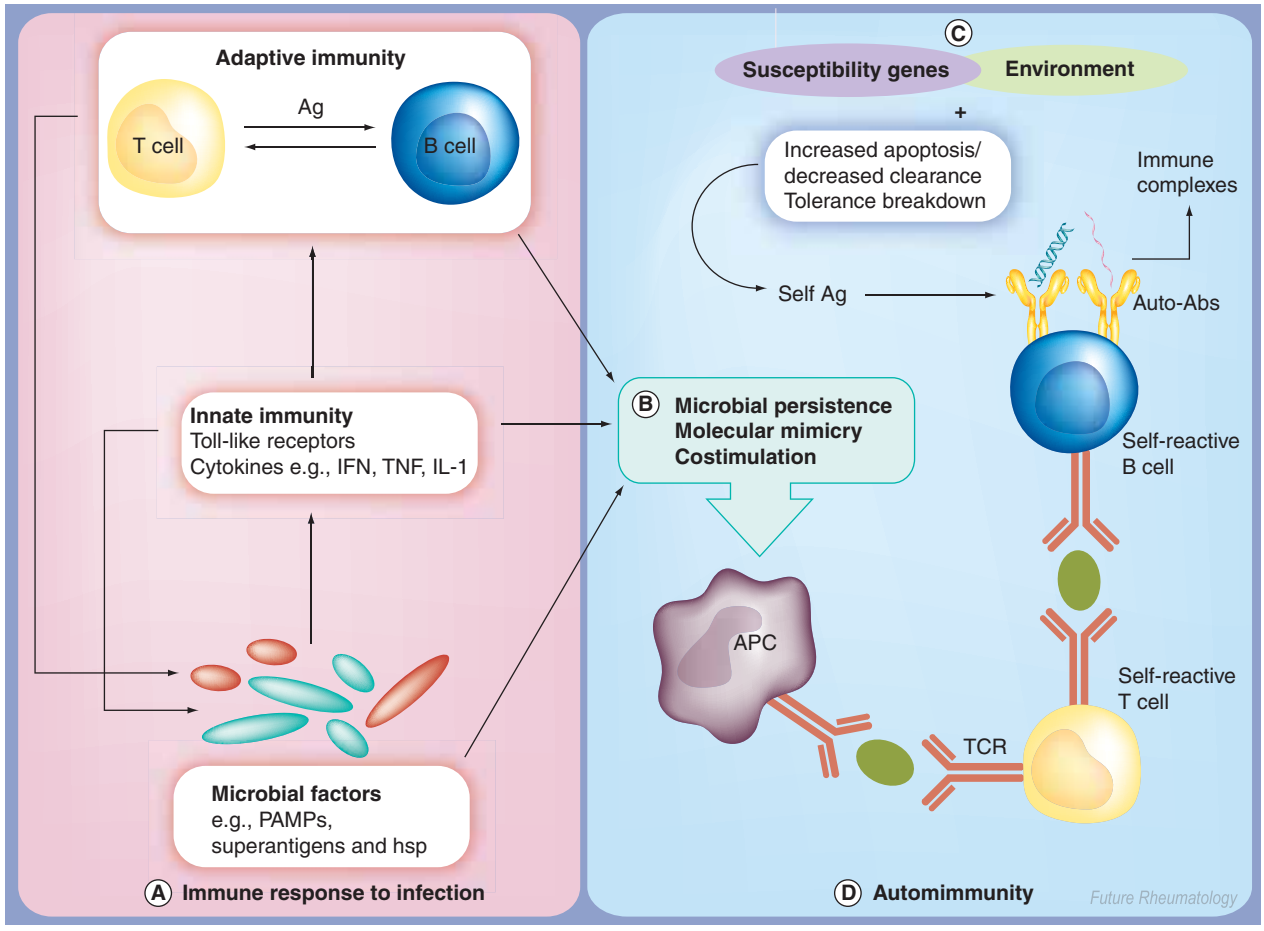
Molecular mimicry provides the most acceptable explanation for these associations, but interest has also been shown in those possessing homology sequences with the shared epitope found in host HLA-*DRB1*0401* and **0404* alleles. For instance, primary cytotoxic damage to hyaline cartilage and HLA-DR1/DR4-positive chondrocytes can be induced by antibodies to *Proteus mirabilis* following urinary tract infection. Leading to secondary cytotoxic and collateral damage by cytokines, with resultant chronic synovitis of RA [44].

Infectious agents & systemic autoimmune diseases

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 [48,49]. Viruses have been suggested as triggering factors for lupus [50,51], with EBV as one of the viruses most directly linked to the pathogenesis of SLE [52], whereas parvovirus B19 has been most cited as a mimic of SLE [53–56]. On the other hand, EBV infection during treatment for

Figure 1. Schematic model of the processes that link infection with autoimmunity.



Schematic model of the pathomechanisms that link the natural immune response to infectious agents to the development of autoimmunity. **(A)** The immune system is designed to control and eradicate infections through natural processes that include elements of both innate and adaptive immunity. **(B)** Owing to various mechanisms, including microbial persistence, molecular mimicry and excess costimulation, immune responses become aberrant and may lead to the development of autoimmunity in a susceptible host. **(C)** In addition to genetic predisposition, environmental factors such as ultraviolet rays and drugs, may lead to increased apoptosis and/or impaired clearance of apoptotic cells with a breakdown of tolerance. **(D)** Autoimmunity ensues with the stimulation of similar immune responses, this time directed to self-antigens/peptides.

Ab: Antibody; Ag: Antigen; APC: Antigen-presenting cell; hsp: Heat shock protein; IFN: Interferon; IL: Interleukin; PAMP: Pathogen-associated molecular pattern; TCR: T-cell receptor; TNF: Tumor necrosis factor.

SLE can induce a hematophagocytic syndrome, which can simulate a hematologic SLE flare [57]. Recently, transfusion-transmitted virus (TTV), a newly identified DNA virus of yet unknown pathogenicity, has been linked to SLE [58].

Although it has been stipulated that HIV infection and SLE may be mutually exclusive – perhaps due to HIV immunosuppression, which reduces the risk of developing SLE – several papers report the association of HIV infection and the presence of autoantibodies, including antinuclear antibodies, antineutrophil cytoplasmic antibodies, lupus anticoagulant and anticardiolipin antibodies [56,59–63], occasionally accompanied by lupus-like manifestations.

Evidence of high titer antibodies to retroviral proteins in SLE patients, particularly human T-cell lymphotropic virus-1 related endogenous sequence (HRES)-1, has led to the consideration of these viruses as candidate lupus viruses [19,51]. HRES-1 encodes a 28 kDa nuclear autoantigen, HRES-1/p28, antibodies to which have been detected in 21–30% of SLE patients. It has been proposed that molecular mimicry between HRES-1 and the small ribonucleoprotein (snRNP) complex epitopes may serve as a trigger for autoimmune responses to self-antigens, leading to more clinically active disease. [19,64–65]. Moreover, there is recent data to support the notion that cross-reactivity of HRES-1 epitopes with infectious viral antigens, including TTV and EBV, mediate epitope spreading to self-antigens, such as the 70 kDa U1snRNP, contributing to the formation of antinuclear autoantibodies in SLE [66].

Cytokine abnormalities abound in SLE, among which interferon (IFN)-α may play a pivotal role [67]. Furthermore, IFN-α correlates with disease activity and contributes to the development of antinuclear antibodies. Since human leucocytes 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 [68].

Lupus-like illness is also known to occur in individuals with inherited complement deficiencies, aside from having a greater risk of infections caused mainly by *Streptococcus pneumoniae* and *Neisseria* organisms [69]. Mannose-binding lectin (MBL) is a calcium-dependent serum lectin secreted by the liver as an acute-phase protein. Since MBL is structurally homologous to C1q, a low serum MBL, as demonstrated in certain gene polymorphisms [70], can cause defective activation of the complement system, leading to impaired complement-mediated clearance of immune complexes – suggesting that MBL deficiency not only increases infection risk, but might predispose to the development of SLE [71]. Interestingly, some genetic polymorphisms linked with low MBL levels have been demonstrated in certain SLE populations, including Chinese [72] and Filipinos [73].

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is characterized by the presence of pathogenic antibodies to phospholipid/β-2-glycoprotein I (β2GPI). Infectious agents such as HIV have been implicated in the production of these antibodies, with a few studies demonstrating that bacteria homologous with the β2GPI structure can generate pathogenic anti-β2GPI autoantibodies along with APS manifestations, including thrombocytopenia and fetal loss [74,75]. High levels of antibodies to CMV-derived peptide have also been found in antiphospholipid (aPL)-positive sera, suggesting that aPL antibodies may be generated by immunization with CMV products during incidental exposure to the virus via a molecular mimicry mechanism [76]. Among studied infections, anti-β2GPI antibodies were more prominently elevated in leprosy patients than in those with syphilis, malaria and HIV [77]. However, different cytokine profiles, specifically, elevated IL-6 and circulating tissue factor, in autoimmune APS may distinguish this from the profile of leprosy patients with aPL-positive sera but without APS [78].

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 [79].

Similar to its well-publicized role in the induction of atherosclerosis and coronary artery disease [80], *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 [81]. Other microbial pathogens implicated in the pathogenesis of GCA include parvovirus B19 and parainfluenza virus type 1 [82]. Furthermore, the 65 kD hsp of *Mycobacterium tuberculosis* has been implicated in the pathogenesis of Takayasu's arteritis, another large vessel vasculitis [83].

Hepatitis viruses, particularly hepatitis C virus (HCV), have been linked to the pathogenesis of various rheumatic syndromes ranging from

asymptomatic production of autoantibodies and cryoglobulins, to arthralgias to systemic vasculitis. Of these, mixed cryoglobulinemia syndrome (MCS) has perhaps been the most consistently cited as having an established association with chronic HCV infection [84–86]. This association seems to have expanded itself to studies on more complex relationships between HCV, MCS and other syndromes, such as Sjogren's and lymphoproliferative disorders [87]. Furthermore, the presence of genetic markers such as HLA-DR11 appears to be associated with increased risk for the development of type II MCS [88], suggesting that the *DRB1*11* allele might play a crucial role in presenting immunogenic HCV antigens, with resultant strong antiviral CD4 responses 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 [89], and it is likely that the HCV-related manifestations, such as MCS, vasculitis and proteinuria, play a significant contributory role.

The prompt recognition of hepatitis-related vasculitis, including MCS secondary to HCV, becomes particularly important, because of the potential for treatment. Combination therapy using IFN plus ribavirin has demonstrated substantial efficacy on main HCV vasculitis manifestations, associated with a good virologic response [90]. Similarly, lamivudine in combination with steroids and plasma exchange can lead to clinical improvement, seroconversion and reduced viral load in hepatitis-B associated polyarteritis nodosa [91].

Future perspective

The intricate interplay between host, microbe and environment has brought the concept of autoimmunity to greater heights. The rapid developments 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, such as distinguishing true infection from epiphenomena. There are several proposed strategies on establishing the causative etiology of these microorganisms, including early identification and tissue banks for predisposed individuals [92]. Such repositories may also yield more specific information on the role of genetics in the expression of autoimmunity triggered by infectious agents. The growing impression that perhaps all autoimmune diseases are truly infectious in nature should be provocative enough to encourage more studies in this field. This concept has expanded to implicate infection as a trigger for accelerated atherosclerosis – a feature found in many of these chronic autoimmune diseases [93,94]. The challenge for researchers and clinicians becomes even more appealing because it holds the promise for treatment and potentially effective prevention of chronic inflammatory and autoimmune conditions.

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Executive summary

Infectious agents in autoimmune diseases

- Infectious agents have been implicated in autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome and systemic vasculitis.

Pathomechanisms

- Molecular mimicry entails immunologic cross-reactivity of a microbial antigen with self.
- Cytokine pathways arising from the innate immune response lead to the development of autoreactive T and B cells.
- Ligation and activation of Toll-like receptors by microbial molecules with continued release of proinflammatory cytokines may result in altered cell-signaling pathways.
- Inherent microbial factors, for example, superantigens, and persistence factors, can overcome tolerance mechanisms.

Future perspective

- Improved techniques will provide early and accurate identification of infectious triggers.
- Improved understanding of the role of infection in autoimmunity will broaden therapeutic strategies in the prevention and management of autoimmune diseases.
- Infectious agents provide the missing link between autoimmunity and other processes, such as atherosclerosis.

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