

Infections and autoimmunity: the multifaceted relationship

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ABSTRACT

Multiple factors are thought to contribute to the development of immune response to self, including differences in genotypes, hormonal milieu, and environmental factors. This review focuses on the pivotal role of infection in the induction of autoimmune disorders. Although the development of autoimmune phenomena linked to infections is a common finding, the onset of autoimmune diseases is a rare event, arising from a combination of genetic susceptibility and environmental factors. There are several mechanisms through which pathogens can initiate or perpetuate autoimmunity. Some of them are antigen-specific, including molecular mimicry, expression of modified, cryptic, or new antigenic determinants, and superantigens. Others are nonspecific and collectively known as "bystander activation." They include enhanced processing and presentation of self-antigens, immune cell activation, cytokine release, and cell apoptosis/necrosis. Infections may also trigger organ-specific autoimmune diseases, but studies carried out until now have provided conflicting and inconclusive results regarding the role of viral and bacterial agents. Infections and autoimmune diseases have multifaceted and multidirectional relationships. It has been suggested recently that infections cannot only induce or precipitate autoimmune diseases, but they may also protect from autoimmunity or even abrogate an ongoing autoimmune process depending on the interaction between microorganisms and host. Therefore, we should look at microorganisms, not only as causes of infections but also as potential agents able

to modulate the immune system. On the other hand, numerous evidences have emerged regarding the higher susceptibility of autoimmune patients to infections, possibly as a result of immunosuppressive therapy and treatment with biologic agents. *J. Leukoc. Biol.* **87**: 000–000; 2010.

Introduction

The autoimmune diseases are a diverse group of conditions characterized by abnormal immune reactivity in association with autoreactive B and T cell responses. There are more than 80 different autoimmune diseases [1] that affect hundreds of millions of people around the world. These systemic or organ-specific conditions are the third leading cause of morbidity and mortality in the industrial world after cancer and heart disease [2]. Multiple factors are thought to contribute to the development of immune response to self, including differences in genotypes, hormonal milieu, and environmental factors [3–6]. The role of environmental factors is clearly apparent when considering the low disease concordance rate between monozygotic twins for major autoimmune diseases. Of all environmental factors with a potential to trigger autoimmunity, the most important seems to be viruses, bacteria, and other infectious pathogens. The pivotal role of infection in the induction of these disorders has been supported by several evidences, such as disease seasonal onset, disease occurrence after some infections, and the isolation of viral genomic DNA/RNA from affected tissues of patients once the disease gets started [7–9]. Infections and autoimmune diseases have multifaceted and multidirectional relationships [10]. It has been suggested recently that infections cannot only induce or precipitate autoimmune diseases, but they may also protect from autoimmunity or even abrogate an ongoing autoimmune process depending on the interaction between microorganisms and host. Therefore, we should look at microorganisms, not only as causes of infections but also as

Abbreviations: AS=ankylosing spondylitis, Bb=*Borrelia burgdorferi*, DAMP=damage-associated molecular pattern, DC=dendritic cell, DMARD=disease-modifying antirheumatic drug, GlcNAc=N-acetylglucosamine, HBV=hepatitis B virus, HCMV=human CMV, HCV=hepatitis C virus, HERV=human endogenous retrovirus, HHV-6B=human herpes virus 6B, iNKT=invariant NK T cells, MC=mixed cryoglobulinemia, MTX=methotrexate, NOD=nucleotide-binding oligomerization domain, Ospa=outer surface protein A, PAMP=pathogen-associated molecular pattern, pDC=plasmacytoid DC, PRR=pattern recognition receptor, pulA/D=pullulanase A/D, RA=rheumatoid arthritis, RLR=retinoic acid-inducible gene-like receptor, SLE=systemic lupus erythematosus, Treg=T regulatory cell

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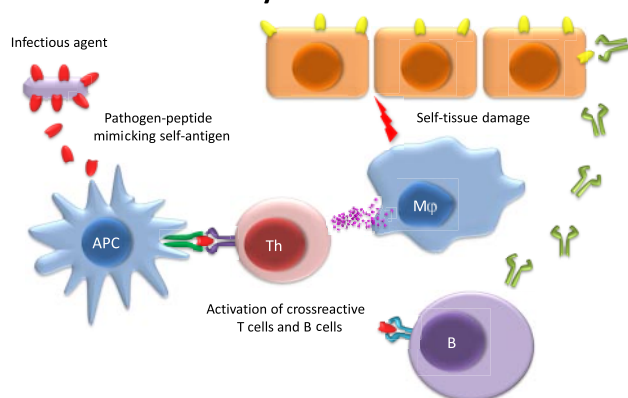
potential agents able to modulate the immune system [11–14]. On the other hand, numerous evidences have emerged regarding the higher susceptibility of autoimmune patients to infections, possibly as a result of immunosuppressive therapy and treatment with biologic agents.

INDUCTION AND PERPETUATION OF AUTOIMMUNITY BY INFECTIOUS AGENTS

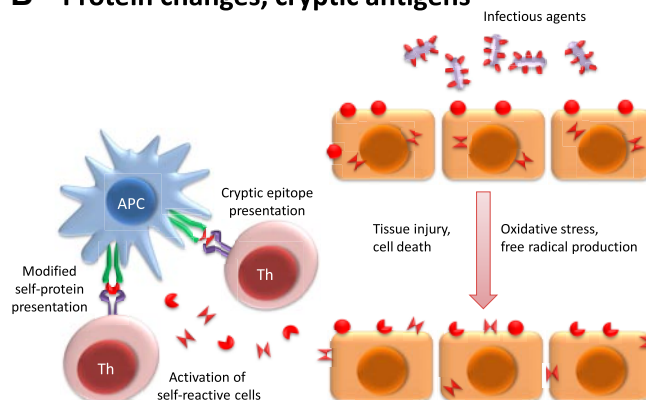
The human immune system is highly complex, having evolved to fight a broad spectrum of pathogens. The host

response to infections encompasses a huge number of immunological mechanisms that can eventually lead to autoimmunity. Although the development of autoimmune phenomena linked to infections is a common finding, the onset of autoimmune diseases is a rare event, arising from a combination of genetic susceptibility and environmental factors [7–10, 15–20] (**Fig. 1**). There are several mechanisms through which pathogens can initiate or perpetuate autoimmunity. Some of them are antigen-specific, including molecular mimicry, expression of modified, cryptic, or new antigenic determinants, and superantigens. Others are nonspe-

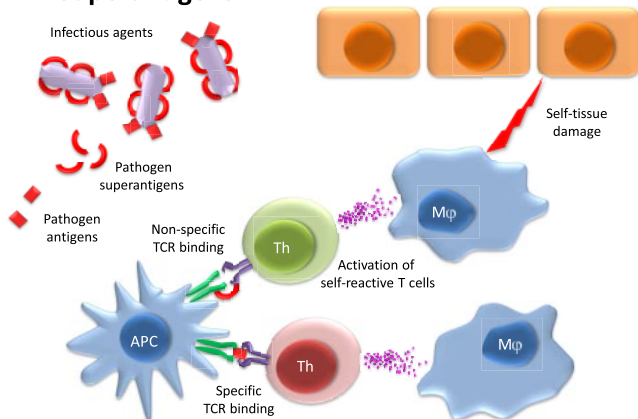
A Molecular mimicry



B Protein changes, cryptic antigens



C Superantigens



D Bystander activation

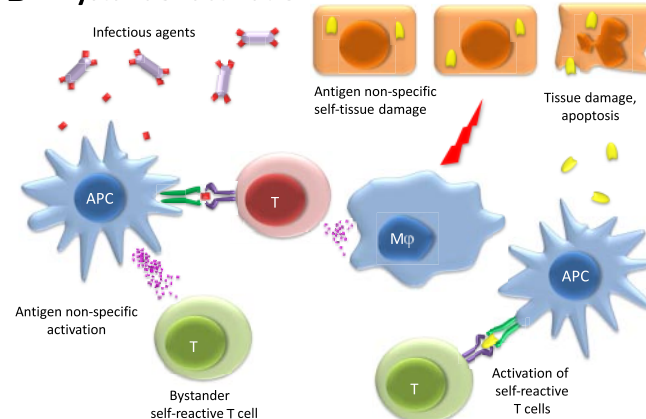


Figure 1. Host response and autoimmunity: mechanisms that can eventually lead to autoimmunity in a susceptible individual. (A) Molecular mimicry: Pathogens bear elements that are similar enough in amino acid sequence or structure to self-antigen. The immune response can eventually turn toward the self-peptide as a result of cross-reactivity, leading to the activation of naïve, autoreactive T cells specific to the corresponding self-molecule. Mφ, Macrophage. (B) Protein changes, cryptic antigens: Following tissue injury, cell death, oxidative stress, free radical production, and reparative changes, as happens in several infections, proteins that are usually recognized as self can become nonself and induce an autoimmune response. In addition, proteins that are normally sequestered and shielded from immune recognition can be exposed to the immune system and become immunogenic. Therefore, cryptic antigens become accessible to self-reacting T lymphocytes that had escaped central and peripheral tolerance, as they had not been presented appropriately to induce tolerance. (C) Superantigens: Superantigens are proteins produced by a variety of microorganisms, especially bacteria or mycoplasmae, or virus-infected cells that can bind TCR irrespective of its antigenic specificity, resulting in the activation of a large number of T lymphocytes of different antigenic specificity, thus behaving as a potent immune-stimulating molecule. (D) Bystander activation: The enhanced processing and presentation of self-antigens induce the expansion or spreading of immune response toward different self-antigens. This process, known as “epitope spreading,” has been widely involved in the pathogenesis of many systemic autoimmune diseases as well as in determining the different expression of such diseases.

cific and collectively known as “bystander activation.” They include enhanced processing and presentation of self-antigens, immune cell activation, cytokine release, and cell apoptosis/necrosis [21].

Molecular mimicry

In molecular mimicry, pathogens bear elements that are similar enough in amino acid sequence or structure to self-antigen. Immune response can eventually turn toward the self-peptide as a result of cross-reactivity, leading to the activation of naïve, autoreactive T cells specific to the corresponding self-molecule. Molecular mimicry can be responsible for initiating an autoimmune phenomenon in various diseases including rheumatic fever, SLE [11], and systemic sclerosis [12], but many other factors are necessary to develop autoimmunity.

Protein changes, cryptic antigens

Following tissue injury, cell death, oxidative stress, free radical production, and reparative changes, as happens in several infections, proteins that are usually recognized as self can become nonself and induce an autoimmune response [21]. This occurs as a consequence of protein changes as a result of altered expression, post-translational modifications, denaturation, misfolding, or mutations [22]. In addition, the inflammatory environment can induce differential processing of released self-epitopes by APCs. Proteins that are normally sequestered and shielded from immune recognition can be exposed to the immune system and become immunogenic. Therefore, cryptic antigens become accessible to self-reacting T lymphocytes that had escaped central and peripheral tolerance, as they had not been presented appropriately to induce tolerance.

Superantigens

Superantigens are proteins produced by a variety of microorganisms, especially bacteria or mycoplasmae, or virus-infected cells that can bind TCR, irrespective of its antigenic specificity, resulting in the activation of a large number of T lymphocytes of different antigenic specificity, thus behaving as a potent immune-stimulating molecule [21].

Bystander activation

As far as nonspecific mechanisms are concerned, one of the most important is bystander activation, which is defined as the activation of T cells through a mechanism that is independent of specific TCR stimulation. Bystander activation can lead to enhanced processing and presentation of self-antigens, which induces the expansion or spreading of immune response toward different self-antigens. This last process, known as epitope spreading, has been widely involved in the pathogenesis of many systemic autoimmune diseases as well as in determining the different expression of such diseases [23].

Apoptosis, necrosis, and clearance deficiency

Infections can induce cell death via the physiological process of apoptosis [24]. If the removal of dying cells fails as a

result of different reasons, including genotype, the apoptotic process may progress to secondary necrosis, leading to accumulation of nuclear material, which may lead to autoimmunity [25]. Deficiency in the clearance of apoptotic or necrotic cells has been shown in patients with SLE, where noningested nuclear material may provide survival signals for autoreactive B cells with the consequent production of antibodies against nuclear structures [26].

Innate immunity

Recently, the pivotal role of innate immunity in the induction of autoimmunity throughout the activation of the adaptive immune system or the initiation of the immune inflammatory process has been highlighted [10, 27, 28]. The innate immune system is an evolutionarily conserved system that provides the first line of protection against invading microbial pathogens. Phagocytes, such as macrophages and DCs, sense microbial signature and endogenous molecules through PRRs and initiate signaling leading to the production of proinflammatory cytokines.

The TLR family detects PAMPs on the cell surface or on the lumen of intracellular vesicles such as endosomes or lysosomes. Cytosolic PRRs, specifically sensing intracellular PAMPs, include RLRs and NOD-like receptors. Activation of PRRs results in secretion of cytokines and chemokines, including types I and II IFN, TNF, IL-1, IL-6, and IL-12, and thus, mediates inflammatory responses to infection and enhances responses of the adaptive immune system. Moreover, their overproduction is often associated with autoimmune or autoinflammatory diseases [29]. It has been shown that viruses are able to activate intracellular PRRs via intracellular signaling pathway, particularly MyD88, inducing the expression of type I IFN genes and genes regulated by type I IFNs. This process, termed “IFN signature,” has been demonstrated in various systemic autoimmune diseases, including SLE, Sjögren’s syndrome, and polymyositis-dermatomyositis [30–32].

Type I IFN and IFN-related cytokines and chemokines can induce a favorable immune setting to develop autoimmunity. IFN signature seems to be one of the first steps in the pathogenesis of SLE and other autoimmune diseases [33]. IFN- α can contribute to the pathogenesis of SLE through various mechanisms, including direct and indirect effects on APCs, T cells, and B cells. IFN- α is largely produced by immature DCs, now known as pDCs, which are stimulated by viruses to produce IFN- α , and this production up-regulates expression of TLR7 by B cells, promotes cell death, increasing the release of certain RNA and DNA autoantigens, and primes pDCs to respond more effectively to immunocomplexes [34]. Recent studies suggested that hypomethylated plasma DNA might be influential in the pathogenesis of SLE. Bacterial and viral DNA, which are hypomethylated, can induce various immune changes that are similar to those observed in SLE, including activation of TLR9 signaling, leading to the overexpression of type I IFN genes, polyclonal B cell activation, and production of autoantibodies such as anti-DNA antibodies, production of IL-6, and resistance to apoptosis, which potentially allows the survival of

autoreactive cells [35]. Indeed, induction and/or aggravation of SLE are well known to occur after bacterial or viral infection.

It has to be mentioned also that some drugs, including procainamide and hydralazine, can induce SLE by inhibiting DNA methylation. Therefore, the inhibition of DNA methylation may represent a critical step in the induction of SLE. DNA is a central autoantigen in SLE. Bacterial DNA is a PAMP and can stimulate immune response via TLR9 after its translocation into the endosome. Endocytosis may be facilitated by DNA-binding molecules, including antimicrobial protein LL37 (a cathelicidin) or the nuclear protein high-mobility group box 1. Interestingly, these molecules can bind exogenous as well as endogenous DNA released from dead or dying cells [36]. Similarly, immune complexes can also promote proliferation of autoreactive B cells through dual recognition by the BCR and TLR9 [37].

Self-RNA also contributes to autoimmunity by activating TLR7. Small nuclear ribonucleoprotein complexed with autoantibody is taken up in pDCs and induces TLR7-triggered type I IFN and inflammatory responses [38]. This complex can also activate autoreactive B cells via dual recognition by the BCR and TLR7 [39]. Self-RNA is also recognized by RLRs. Viral RNA promote the activation of an endonuclease, RNaseL, which subsequently cleaves host cellular RNA to create small RNA species [40]. These RNA serve as the ligand for retinoic acid-inducible gene I and melanoma differentiation-associated protein 5; however, it is not clear whether this pathway contributes to autoimmune diseases.

In vivo, it has been shown that immune complexes containing nucleic acids, DNA or RNA, play a major role in the activation of the innate immunity in SLE, and it is interesting to note that the majority of antinuclear, antinucleolar, and anticytoplasmic autoantibodies observed in SLE and in other autoimmune rheumatic diseases are directed toward DNA and RNA molecules, isolated or complexed with proteins. Cooperative interactions of innate and adaptive immunity are required for elimination of infective pathogens with the highest efficiency. DCs are equipped with a variety of PRRs and are known to be the most potent activator and modulator of the adaptive immune system [41]. These cells reside in most tissues in the body, and a multitude of subsets has been identified in human peripheral tissues, secondary lymphoid organs, and peripheral blood [42]. Activated DCs induce different effector functions in T cells, primarily depending on the type of TLR ligand and DC subset. Long-term activation of innate immunity can break peripheral tolerance to self-antigens and result in the induction of autoimmune disease, even in resistant hosts [43]. Immune responses against pathogens require fine regulation to avoid excessive inflammation and maintain tolerance. There is accumulating evidence that interactions between DCs and Tregs play a crucial role in the balance between immune response and tolerance [44].

Noteworthy, even endogenous stimuli, including remnant materials derived from apoptotic or necrotic cells, named DAMPs, can activate TLRs with a consequent stimulation of immune cells [45, 46]. Whether and how the host is able to

discriminate between DAMPs and PAMPs are not clear. Recently, at least one mechanism by which tissue injury and infection are distinguished, although they both use the evolutionarily conserved TLRs, has been identified. CD24-deficient mice exhibit increased susceptibility to DAMPs but not PAMPs. CD24 is a small glycosylphosphoinositol-anchored protein that is able to provide costimulatory signals to T cells and has been implicated in the development of autoimmune disease [47–51]. Chen et al. [52] demonstrated that CD24 associates with DAMPs and through interaction with sialic acid-binding Ig-like lectin-10, negatively regulates their stimulatory activity and inhibits NF- κ B activation. These data suggest that CD24-Siglec-10 negatively regulates the immune response to proteins released by damaged cells but not to the ligand of microbial origin.

Inflammatory pathways and autoimmunity

Chronic autoimmune diseases are characterized by unresolved inflammation [53, 54]. There is accumulating evidence that prolonged inflammatory response as a result of infections could play a pivotal role in the initiation, progression, and perpetuation of these diseases [55]. Inflammation is mediated by proinflammatory cytokines, which are also responsible for limiting the diffusion of microbial agents in the host. However, in individuals with immune-regulatory dysfunctions, a heightened inflammatory response, can contribute to the pathogenesis of autoimmune diseases.

An interesting example is the Spin mutation induced in mice by random germ-line mutagenesis [56]. This mutation was found to be a hypomorphic allele of protein tyrosine phosphatase nonreceptor type 6 encoding the protein tyrosine phosphatase Src homology-2-containing tyrosine phosphatase 1. Spin mice develop autoimmune and inflammatory disease characterized by antichromatin antibodies, spontaneous inflammation of the footpads, and inflammatory lesions in the lungs, salivary glands, and bone marrow. The inflammatory phenotype requires MyD88, IL-1R-associated kinase 4, and the IL-1R but not type I or type II IFNs or TNF. It is noteworthy that the disease must be initiated by microbes, and in the absence of microbes, inflammation and autoimmunity never result [56].

MODULATION OF THE HOST IMMUNE RESPONSE BY INFECTIOUS AGENTS

Infections cannot only trigger autoimmune diseases but can also modify or suppress their clinical expression. iNKT cells are a unique subset of T lymphocytes that have been implicated in the control of various types of immune responses, including activation of responses against pathogens and repression of responses that lead to autoimmune diseases. Interestingly, infections affect iNKT cell responses quantitatively and qualitatively. It has been shown that *Listeria monocytogenes* or *Mycobacteria* infections lead to a prolonged loss of iNKT cells in the spleen. Moreover, remaining infection-primed iNKT cells are functionally hyporesponsive to anti-

genic challenge for at least 1 month [57]. Chronic diseases, such as RA and inflammatory bowel diseases, are characterized by a robust immune response, resulting in unresolved inflammation that is chronically sustained by the release of proinflammatory cytokines. Recently, a subset of IL-17-producing cells (Th17 cells), which develop and function in a distinct way from Th1 or Th2 cells, has been identified [58]. Th17 cells have been shown to play a crucial role in inflammation and autoimmune diseases [59].

Recent evidence suggests that fungi, commensals or ubiquitous, may help microbes to accommodate within immune homeostasis and its dysregulation. A cross-regulation between protective Th1 and nonprotective Th17 cells has been demonstrated in experimental models of mucosal candidiasis or pulmonary aspergillosis. TLR4 appeared to play a major role in controlling the balance between protective and nonprotective immune responses to fungi through its ability to promote and inhibit Th17 development [60]. If the ability of fungi to subvert the inflammatory program through the activation of the IL-23/IL-17 axis may eventually lead to immune dysregulation, their ability to activate Tregs may represent a mechanism, whereby dysregulated immunity is prevented. Many epidemiological studies and experimental systems support the protective role of infections from autoimmune and allergic diseases [61]. Several evidences suggest that early exposure to particular environmental factors directs the body's immune system along a particular path and that this offers long-term protection from the development of autoimmunity. This concept, termed the "hygiene hypothesis," was suggested 20 years ago by Strachan [62], who assumed that the increase in autoimmune diseases observed in Western countries was caused partly by a decline in infectious diseases and improved hygiene.

Inflammation caused by several pathogens, and in particular, by parasites, can shift the Th1–Th2 balance toward a more immunosuppressive state, where Tregs might be induced. Furthermore, infection at another location might keep autoaggressive cells from reaching the site of autoimmune destruction. Christen et al. [63] elucidated the protective effect of lymphocytic choriomeningitis virus infection on the onset and recurrence of type 1 diabetes in NOD mice. The extensive expression of CXCL10 in the pancreatic draining lymph nodes results in the accumulation of autoaggressive T cells outside of the islets. Moreover, many islet-specific CD8 lymphocytes undergo apoptosis in the pancreatic draining lymph nodes, suggesting that sites of strong inflammation might act as a filter for autoaggressive T cells.

Direct experimental evidences show that parasites can exert bystander immunosuppression of autoreactive T cells. It has been demonstrated recently that infection of mice with *Fasciola hepatica* exerts bystander suppression of immune response to autoantigens and attenuates the clinical signs of experimental autoimmune encephalomyelitis [64]. Interestingly, the suppression of Th1 and Th17 responses is TGF- β -mediated but is maintained in IL10^{-/-} mice. Similarly, following inoculation of NOD mice with the helminth parasite *Heligmosomoides polygirus*,

pancreatic insulinitis is markedly inhibited through CD25- and IL-10-independent mechanisms [65].

INFECTIOUS AGENTS INVOLVED IN AUTOIMMUNITY

Viruses and bacteria are the infectious agents that have been long associated with autoimmune diseases.

HCMV

HCMV infects 70–100% of adults in populations worldwide. In immunocompetent subjects, primary HCMV infection is usually asymptomatic; however, after a primary infection, the virus persists, establishing life-long latency. In immunocompromised patients, HCMV is one of the most common opportunistic pathogens. The virus targets several types of immune cells and subverts host immune functions to its own advantage. Beside immunosuppression, HCMV-infected patients often develop autoimmune phenomena. Non-organ-specific autoantibodies, such as antiendothelial cell autoantibodies, anti-smooth muscle cell autoantibodies, and anti-nucleus autoantibodies, have been found in transplant recipients with HCMV infection [66, 67]. Furthermore, hyper- γ -globulinemia, cryoglobulinemia, and autoantibody production are features of HCMV-induced mononucleosis and postperfusion syndrome [68, 69]. The virus has been detected in patients with RA, Sjögren's syndrome, dermatomyositis, psoriasis, Wegener's granulomatosis, ulcerative colitis, and Crohn's disease. Of note, active, low-grade viral infection in these patients was evident only in inflamed tissues specimens. HCMV DNA, specific antigens, and infectious viral particles have been detected in synovial tissue and fluid from the joints of 10–50% of patients with RA [70–73].

Serological signs of active HCMV infection have been detected in SLE patients [74], and the infection is associated with increased disease activity [75]. mAb against topoisomerase I, which are specific for systemic sclerosis, recognize a pentapeptide of the autoantigen, sharing homology with the HCMV-derived UL70 protein. Furthermore, it has been demonstrated that anti-UL94 peptide antibodies induce apoptosis of endothelial cells upon engagement of the novel antigen-2–integrin complex and activate dermal fibroblasts, linking anti-HCMV antibodies to the pathogenesis of systemic sclerosis [76].

Parvovirus B19

Supporting the molecular mimicry hypothesis in the pathogenesis of autoimmune diseases, Lunardi et al. [77] have recently identified a peptide that shares homology with the capsid protein VP1 of Parvovirus and with human cytokeratin. Interestingly, this peptide also shares similarity with globulin transcription factor 1, which plays an essential role in megakaryopoiesis and in erythropoiesis. Chronic parvovirus B19 infection can induce antiviral antibodies that also react specifically with collagen type II, single-stranded DNA, and cardiolipin. A correlation has been described between

the clinical features and main autoantigen specificity. Igs from patients with arthritis react preferentially with collagen II, whereas Igs from patients with skin rashes react preferentially with keratin.

Endogenous retroviruses

HERVs constitute 8% of our genome [78]. Even if they are, for the most part, replication-deficient, they may still code for functional products. It is known that HERV-K18 contains three alleles (K18.1–3), which all display superantigenic properties, and that the risk of multiple sclerosis is three-fold higher among individuals homozygous for K18.3 when compared with K18.2 [79]. Infection with EBV may induce K18.3, which activates predominantly human TCR V β 13-bearing cells [80]. In addition to EBV infection, expression of HERV-K18 is induced by IFN- α [81]. Recently, Turanova et al. [82] reported that the expression of HERV-K18 is up-regulated rapidly in PBMCs infected with HHV-6B. This finding suggests that HHV-6B mediated this induction directly, rather than through IFN- α , and that the transactivation of the superantigen may also be induced in cells abortively infected, including APCs in the brain.

HCV

HCV infection is associated with several B cell-related disorders. Extrahepatic disease manifestations, autoimmune phenomena, and frank autoimmune diseases may complicate the clinical features of chronic HCV infection in almost half of chronic carriers [83–86]. The HCV is the etiologic agent in the large majority of MC syndrome, a systemic vasculitis prevalently mediated by immune complexes and characterized by non-neoplastic B cell lymphoproliferation. The association between HCV infection and thyroid autoimmunity and type 2 diabetes mellitus has been reported recently, and a common pathogenetic pathway of HCV-related extrahepatic diseases with these autoimmune endocrine manifestations has been suggested [84]. Moreover, antineuronal antibodies, including anti-GM1 ganglioside and antisulfatide, were observed in patients with peripheral neuropathy as a result of HCV-related MC, suggesting their potential role as a direct trigger of neurologic injury in this disorder [86]. Chronic antigenic stimulation by HCV is considered a key mechanism sustaining the proliferation of rheumatoid factor-secreting B cell clones. B-lymphocyte stimulator, is a critical survival factor for B cells, promoting their activation and maturation, and it has been hypothesized that it may play a role as an early, chronic stimulus for autoreactive B cells in HCV-infected patients [87].

HBV

Similarly to HCV, although to a lesser extent, HBV also seems to be able to infect not only hepatic but also lymphatic cells, leading to some hepatic and/or extrahepatic disorders of an autoimmune and/or lymphoproliferative nature. In the case of HBV chronic infection, membranous glomerulonephritis and systemic necrotizing vasculitis are the most documented manifestations; MC appears to be

HBV-related only in a minority of cases, and the association with lymphoma is still the subject of some debate [83]. Recent data about the possibility of HBV and HCV “occult” infections, negative for conventional viral markers, suggest interesting pathogenetic hypotheses to be ascertained in further studies.

Streptococcus pyogenes

Infection with *S. pyogenes* can lead to rheumatic fever. It has been demonstrated that antibodies to heart tissue cross-react with group A streptococcus because of molecular mimicry. It has also been shown that bacterial components can persist in host tissue for some years after infection, leading to prolonged immune activation and bystander damage to the organ [88]. The dominant autoantigen in rheumatic fever is cardiac myosin. Affinity-purified antimyosin antibodies from sera of patients with acute rheumatic fever have been shown to cross-react with the M protein (the major virulence factor of group A streptococci) [89] and the streptococcus carbohydrate epitope GlcNAc [90]. These antibodies have been proven to be cytotoxic for heart and fibroblast cell lines. Antibodies have also been found to cross-react to other heart proteins such as tropomyosin and laminin [91, 92]. The same autoantigens can be recognized by T cell clones from heart lesions and peripheral blood of rheumatic heart disease patients, which recognize the streptococcal M protein simultaneously. In patients with Sydenham chorea antibody, cross-reactivity between *S. pyogenes* membrane and neuronal cytoplasm has been reported. Furthermore, mAb from serum and cerebrospinal fluid of patients with Sydenham chorea have been shown to react with the immunodominant carbohydrate epitope on the *S. pyogenes* cell wall (GlcNAc) and with lysoganglioside GM1 on the surface of neurones [93], as well as with intracellular brain protein β -tubulin [94].

Bb

The tick-borne spirochete Bb can lead to Lyme disease. Bystander inflammatory response to the spirochete is responsible for early arthritis. Patients with joint inflammation have high titers of Bb-specific antibodies, and Bb DNA can be detected in the joint fluid by PCR [95, 96]. A subset of patients develops chronic arthritis subsequently, despite the lack of detectable Bb DNA in synovial fluid [97]. In these patients, arthritis is associated with HLA-DRB1*0401, *0101, and *0404 and characterized by cell and humoral responses to OspA of Bb (in particular, to the T cell epitope OspA165–173). Interestingly, LFA 1aL332–340 has been identified as homologous to OspA165–173 and able to bind HLA-DRB1*0401 [98]. Moreover, several other self-peptides have been identified, which could be even more important in the pathogenesis of the disease [99].

Klebsiella pneumoniae and other gram-negative bacteria

AS is a chronic inflammatory disease with a prevalence between 0.1% and 1.0%, which involves mainly the lumbar spine and sacroiliac joints. At least 30% of patients do de-

velop severe spinal restriction during the natural course of the disease. Specific antibodies against *K. pneumoniae* were detected in the synovial fluids of affected subjects. It is well established that HLA-B27 is associated with AS, however the majority of HLA-B27 carriers is free from disease. Several gram-negative microorganisms carry antigens that cross-react with HLA-B27. An amino acid sequence homology has been recognized between HLA-B27 and the nitrogenase reductase enzyme of the *K. pneumoniae*. There are also other *Klebsiella* sequences that cross-react with human molecules. Molecular mimicry is present between HLA-B27 and secretion protein (pul D) of the inducible, starch-debranching enzyme pul. Moreover, amino acid homology has been identified between *Klebsiella* starch-induced enzymes pul A and types I, III, and IV collagens [100]. Infections by a broad range of bacteria play a clear role in the pathogenesis of spondyloarthropathies associated with HLA-B27. Reactive arthritis occurs in HLA-B27-positive individuals following infections with *Salmonella*, *Shigella*, and *Yersinia* species or *Campylobacter jejuni*. Furthermore, there is evidence that *Chlamydia* and *Mycoplasma* species may play a role in the induction of reactive arthritis [101–103].

AUTOIMMUNITY AND SUSCEPTIBILITY TO INFECTIONS

The increased prevalence of infections during the course of systemic autoimmune diseases is another important aspect in the multifaceted relationship between infections and autoimmunity. It has been shown clearly that infections represent a common cause of morbidity and mortality in patients with systemic autoimmune diseases [104], although the reason for this has not yet been fully elucidated. The characteristic immune dysregulation of such diseases could, at least in part, account for the higher prevalence of infections; however, the conventional and/or biologic drugs, which are used currently in the treatment of systemic autoimmune diseases, also seem to be largely responsible [105].

Steroids

Glucocorticoids exert many complex quantitative and qualitative immunosuppressive effects, which induce cellular immunodeficiency and consequently, might increase host susceptibility to various viral, bacterial, and especially fungal and parasitic infections [106]. There is growing evidence that a number of the immunosuppressive and anti-inflammatory effects of glucocorticoids may be a result of the inhibition of NF- κ B and other transcription factors [107]. Glucocorticoids affect virtually every cell type involved in immune and inflammatory responses. The risk of infection increases with dose and duration of treatment and tends to remain low in patients exposed to low doses, even if the cumulative doses are high. Consequently, the use of the lowest possible glucocorticoid dose at night, i.e., during the turning-on phase of TNF secretion and even for the shortest possible time, should decrease dramatically the risk of infections in autoimmune patients.

Conventional DMARDs

The potential risk of infections related to conventional DMARDs is not yet clear completely [108]. Hydroxychloroquine and sulfasalazine are not associated with an increased risk for infection. Early clinical studies suggested that low-dose MTX in RA was associated with increased incidence of infection. However, it is now clear that patients with RA have a higher rate of infection when compared with a healthy control population. This risk appears to be increased, particularly in patients with increased disease severity and comorbidities. In large studies, infection rates are clearly increased with glucocorticoids, cyclophosphamide, or azathioprine, whereas MTX appears to be associated with minimal, if any, increased infection risk. Finally, MTX may increase infectious risk, but its positive effect on disease activity and immunological function results in a reduction of disease-related risk factors for infections [109]. Data about the increased prevalence of pneumonia or reactivation of silent infections in patients treated with MTX remain controversial. In controlled clinical trials, the safety of leflunomide has been demonstrated, although it was associated with some infections requiring hospitalization, such as pneumonia. DMARDs combination therapy appears generally safe and well-tolerated, but caution and appropriate monitoring for a potential increased infectious risk are required. Data about other DMARDs are scarce, and the main cause of therapy withdrawal is related to toxicity rather than infection [110].

Biologic agents

Over the last decade, new biologic agents have become available for the treatment of patients with inflammatory arthritis. In contrast to conventional DMARDs, these new drugs have a rapid onset of action and pronounced disease-reducing activity when administered as monotherapy or in combination with MTX. However, biologic agents are not free of toxicity, and concerns have been raised that they can increase the incidence of common and opportunistic infections.

TNF- α is a cytokine that plays a critical role in the regulation of inflammatory processes—idiopathic and infectious. In the case of infection, one of its key roles is to facilitate cell-to-cell communication in the control of invasive infection. As might be expected, TNF- α plays an important role in host defense. An increased evidence of reactivation of latent tuberculosis and some increased susceptibility to new tuberculosis should be considered a class characteristic of TNF-blocking agents. The risk of incident tuberculosis in patients latently infected with *Mycobacterium tuberculosis* increases substantially to four- or fivefold over baseline after initiation of anti-TNF- α therapy [111]. Thus, particular attention should be made using anti-TNF- α therapy in subjects with latent tuberculosis infection [112].

TNF- α may also play a role in clearing or controlling HBV, and case reports indicate that the combination of infliximab and MTX reactivates chronic HBV infection [113]. It is therefore crucial to screen all patients for hepatitis B before administering anti-TNF- α therapy by measuring hepatitis B surface antigen, hepatitis B surface antibody, and

hepatitis B core antibody, and patients with chronic hepatitis B should only use anti-TNF- α therapy together with an antiviral hepatitis B treatment. Some studies have found that serious infections occur more frequently in association with TNF-blocking agents than with other DMARDs. Atypical mycobacterial infection, aspergillosis, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystis jirovecii, pneumonia, cryptococcal infections, CMV, and other infections have occurred [114].

However, the data concerning infections in anti-TNF- α -treated RA patients are still controversial. A meta-analysis by Bongartz et al. [115] showed that the risk of serious infections was twice as high in patients treated with anti-TNF- α agents than in DMARD-treated controls. The British Society for Rheumatology Biologics Register [116] and the Swedish Arthritis Treatment Group reported a nonsignificant relative risk ratio for severe infections [117]. On the other hand, the German Biologics Registry found that the relative risk ratio for serious infection was ~ 2.1 [118]. Moreover, recent data from the same German cohort suggest that treatment with anti-TNF- α mAb may be associated with increased risk of Herpes zoster [119]. A numerical increase of infections has been also seen in patients receiving other biologic agents. Therefore, it has become increasingly clear that long-term registries continue to be needed to monitor this risk. Opportunistic infections are emerging as an important cause of death in patients with systemic autoimmune diseases in developed as well as developing countries. Progressive multifocal leukoencephalopathy is a rare and frequently fatal opportunistic infection that has been well reported in patients with rheumatic diseases [120]. The contributions of predisposing factors such as underlying disease and immunosuppressive drugs are not understood completely. Natalizumab, a biologic agent approved for multiple sclerosis and Crohn's disease, has the clearest pattern of small but definite risk for progressive multifocal leukoencephalopathy. Although the risk of Rituximab is difficult to assess given the multiple confounders, continued vigilance is justified [121]. Patients should be informed about this risk when initiating treatment with immunosuppressive therapies. Moreover, rheumatologists need to pursue the diagnosis of progressive multifocal leukoencephalopathy in all patients with unexplained neurological signs or symptoms and clinical and magnetic resonance imaging findings compatible with the diagnosis.

VACCINATIONS

Nowadays, great effort should be taken in preventing infections in patients with systemic autoimmune diseases [122, 123]. In this regard, vaccinations could be a useful approach, but concern about the safety and the immunogenicity of vaccines in these patients limits their use [124]. Most of the data against the use of vaccines come from the reported cases of previously healthy individuals who presented the onset of rheumatic diseases after immunization; nevertheless, a causal relationship has not been clearly established. Interestingly, influenza and pneumococcal vaccines have been found to be safe and generally, immunogenic in patients with systemic lupus erythematosus and RA. More-

over, influenza vaccination does not seem to alter the percentage of healthy adults with positive autoantibodies [125]. Transiently or persistently increased levels of autoantibodies or appearance of new autoantibodies were shown in up to 15% of healthy adults after the influenza vaccination, apparently without clinical significance.

The last issue that should be addressed is the treatment of patients with systemic autoimmune diseases and concomitant infections. A wide variety of rheumatic diseases has been documented in patients with HCV or HIV infection [126]. In these conditions, physicians are to refrain from using corticosteroids and/or immunosuppressants because of the risk of favoring the viral replication and progression of the underlying disease [127]. Interestingly, Cyclosporine A and anti-TNF- α agents seem to be safe, in terms of viral load and liver toxicity, in the treatment of HIV- or HCV-infected patients with systemic autoimmune diseases [128].

CONCLUDING REMARKS

There are clearly inextricable relationships between infections and many autoimmune diseases. Infections may trigger autoimmunity, and many different infectious agents seem to be potentially involved in the induction of different autoimmune diseases. On the other hand, experimental evidences have been accumulated that indicate that some pathogens, especially fungi, might modulate autoimmune processes, leading to a sort of protection from autoimmune diseases. Finally, clinicians should continue to be alerted about the potential infectious complications as a result of traditional and nontraditional treatments, especially the new biologic agents.

AUTHORSHIP

Paolo Sfriso organized and prepared the last draft of the manuscript. Anna Ghirardello carried out the literature search and arranged the first draft of the section "Induction and perpetuation of autoimmunity by infectious agents." Costantino Botsios carried out the literature search and arranged the first draft of the section "Autoimmunity and susceptibility to infections." Michele Tonon carried out the literature search and arranged the first draft of the section "Vaccinations." Margherita Zen carried out the literature search and arranged the first draft of the section "Modulation of the host immune response by infectious agents." Nicola Bassi carried out the literature search and arranged the first draft of the section "Infectious agents involved in autoimmunity." Franco Bassetto organized and helped to draft the manuscript. Andrea Doria organized and helped to draft the manuscript and is responsible for the last draft version. All authors read and approved the final manuscript.

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KEY WORDS:

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