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REVIEW ARTICLE

Infection and autoimmune disease

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Abstract Most infectious agents, such as viruses, bacteria and parasites, can trigger autoimmunity via different mechanisms. The development of an autoimmune disorder after infection tends to occur in genetically susceptible individuals. Some parameters, such as genetic predisposition, feature of the infectious agent and sometimes protective effect of the infections, have a significant role in this process. These parameters and various pathogens that could lead to enhancement or exacerbation of autoimmune disease were examined in this review. Recent studies were reviewed from a microbiological perspective.

Keywords Infection · Autoimmune disease

Introduction

Autoimmune disease is a group of disorders in which the primary cause is the inflammatory reaction caused by the body's own immune system attacking tissues.

Autoimmune diseases are the third most common category of disease in the United States after cancer and heart disease; they affect approximately 5–8 % of the population or 14–22 million persons [1]. Epidemiologic studies on the autoimmune disease indicated that prevalence of the diseases on the world showed regional differences. Autoimmune diseases can affect every site in the body, including the endocrine system, connective tissue, gastrointestinal tract, heart, skin and kidneys. At least 15 diseases are known to be the direct result of an autoimmune response, while circumstantial evidence implicates >80 conditions with autoimmunity [2].

Comprehending the autoimmune diseases is obstructed by the fact that some level of autoimmunity, in the form of naturally occurring autoantibodies and self-reactive T and B cells, is present in all normal persons [3]. An autoimmune response occurs in most persons, but clinically relevant autoimmune disease develops only in susceptible persons. Can "molecular mimicry," be the reason? Can infections trigger autoimmune disease? How can infections induce autoimmune disease?

Autoimmune diseases sometimes occur shortly after suffering from infectious diseases. To explain the connection between infection and autoimmunity, both antigen-specific and antigen-nonspecific mechanisms have been suggested [4]. For instance, a number of infectious agents have been proposed as possible triggering factors in systemic sclerosis. Four pathogenic hypotheses have been proposed: molecular mimicry, endothelial cell damage, super-antigens, and microchimerism [5].

Molecular mimicry

Molecular mimicry is among the most popular theories about how virus may induce autoimmunity [6]. Structural molecular mimicry occurs when a viral peptide has an amino acid sequence similar or identical to an amino acid sequence of a self peptide, resulting in cross-reactive T cell and B cell responses. A potentially autoreactive T cell, possessing T cell receptors that recognize both a foreign (viral) peptide and a self-peptide, is activated by a virus-derived peptide. Thus, in addition to mediating an antiviral response, the T cell is also capable of mediating self-

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directed responses [7]. The antigen-presenting cells (macrophages, dendritic cells, microglia) as well as the capability of the mimic peptide, being processed from the native pathogen protein, are two key factors that play important role in the molecular mimicry mechanism during the induction of autoimmunity. In addition, the nature of the innate immune response to the pathogen that determines the immunopathologic potential of the induced cross-reactive T cells, the site of the primary infection in the host and the ability of the pathogen to persist, and the potential requirement for multiple infections with the same or different pathogens, are all considered as contributing factors determining the mechanism of molecular mimicry [8].

There has been a long-standing association between infectious organisms and human autoimmunity. Two major theories have been proposed to account for the correlation between infection and autoimmune disease. The antigen-specific theory is explained by the concept of molecular mimicry in which microbial antigens and self-antigens share structural similarities. The antigen-nonspecific theory assigns a primary role to "bystander activation", in which the immune system can be activated by either the abnormal release of endogenous proteins as a consequence of microbe-induced cell death, or by antigen-presenting cells activated by the microbial stimulus to more effectively present self-antigen. It is also possible that direct engagement of toll-like receptors (TLRs) by inappropriately released or modified self-determinants may be sufficient to trigger an autoimmune response in the absence of infection [9]. TLRs are a major class of germ-line encoded receptors that activate the immune system in response to a variety of pathogen-associated molecular patterns (PAMPs). PAMPs contain conserved molecular motifs that are generally found in microorganisms, but not in their eukaryotic hosts. TLRs have a broad, heterogeneous tissue expression pattern, and their ligands can mediate effects on a various cell types. The TLR can bind a range of microbial components from bacteria, fungi, and viruses. In addition to mediating protective immunity against pathogens, TLR stimulation may potentially contribute to autoimmune responses. Exogenous, microbial nucleic acids can exacerbate SLE pathology presumably through TLR stimulation. TLRs distinguishing between nucleic acids of microbial and mammalian origin are imperfect so that endogenous, non-microbial nucleic acids can also potentially act as TLR ligands under certain conditions. As TLRs recognize nucleic acids and modulate B cell effector functions, it might be predicted that they would have a role in the activation of autoimmune B cells in SLE. The potential involvement of TLRs is not limited to the direct activation of B cells. Growing evidence suggests that TLR recognition of nucleic acids in SLE immune complexes could also contribute to activation of the innate immune system [10, 11].

Endothelial cell damage

In most adult organisms, endothelial cells are quiescent with turnover rates estimated to be in the order of years, with the exception of the reproductive cycle in fertile females and in wound healing or tissue regeneration [12]. However, endothelial cell proliferation and new vessel formation are characteristics of several diseases such as cancer and macular degeneration, while, on the other hand, endothelial cell death is also a typical feature of diseases such as atherosclerosis, allograft vasculopathy, heart failure, diabetic retinopathy and systemic sclerosis (SSc) [13]. In addition, there is ample evidence that endothelial dysfunction occurs in rheumatoid arthritis (RA) [14]. Intracellular adhesion molecule, E-selectin and L-selectin are upregulated in rheumatoid arthritis and correlate with inflammatory markers [15]. Not only do RA patients express adhesion molecules in synovium, which enables leukocytes to migrate there and cause inflammation, circulating concentrations of several cell adhesion molecules are increased, a sign of endothelial activation [16]. In SSc pathogenesis, chronic inflammation plays a role in endothelial cell aging and damage. It is likely that prolonged endothelial cell perturbation and activation may lead to dysfunction and irreversible loss of integrity, with cell detachment and persistent tissue injury endothelial cell damage with apoptosis resulting in the loss of capillaries is considered as one of the earliest changes in the pathogenesis of SSc [17]. Other mechanism is oxidative stress. Oxidative stress is associated with endothelial cell aging, due to a progressive reduction of the endogenous free radical scavengers over time. Chronic exposure of endothelial cells to radical oxygen species induces morphological changes and impairment of cell–cell adhesion. Oxidative stress also increases vascular endothelial permeability, which is coupled with alterations in endothelial cell signal transduction [13].

Superantigens

Superantigens are proteins produced by a variety of microorganisms, especially bacteria or mycoplasma, 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 [18].

Bacterial superantigens bind to MHC molecules outside of their peptide binding grooves and interact predominantly with only the Vβ domains of TCRs, resulting in the

stimulation of up to 20 percent of the entire T cell population. In this way, SAGs initiate a systemic release of inflammatory cytokines that results in various immune-mediated diseases. Bacterial superantigens have also been implicated in the pathogenesis of arthritis, asthma and inflammatory bowel syndrome [19].

Microchimerism

A longer term effect of pregnancy is the persistence of fetal cells in women after a pregnancy and of maternal cells in her offspring, known as microchimerism. These cells can be hematopoietic or can differentiate into somatic cells in multiple organs and are found in both healthy individuals and those with autoimmune diseases. How these cells are tolerated by the immune system is poorly understood, but it is possible that if these cells are targeted as foreign cells they could be implicated in the pathogenesis of autoimmune diseases [20].

In an article, microchimerism in peripheral blood mononuclear cells has been shown to be more frequent in women with scleroderma than healthy controls [21]. Another study has also shown that microchimerism with male DNA is also found in women who have never given birth to a son and suggests other sources of DNA, not only a history of a male birth, must be used in research studies [22]. Overall results indicate that fetal microchimerism is a common phenomenon including in healthy women, but that microchimerism levels are increased in women with systemic sclerosis [23].

A role for fetal microchimerism in systemic lupus erythematosus has also been controversial [24], although several studies suggest that lupus nephritis in particular is associated with an increased concentration of fetal microchimerism in circulation and in renal tissue [25, 26].

Within maternal tissues, the fetal microchimeric progenitor immature T cells, also known as CD4 cells, are capable of self-renewal, proliferation, differentiation and activation. Activation of progenitor cells can result in the production of paracrine and autocrine inflammatory cytokines and chemokines that are involved in autoimmune diseases [27]. Animal experimentation and collection of human data will be necessary to understand the relationship between fetal microchimerism and specific autoimmune diseases in women.

Can infections because of autoimmune diseases?

Infections and autoimmune diseases have multifaceted and multidirectional relationships [28].

Recently, it has been considered 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 [29]. Viruses and bacteria are the infectious agents that have been long associated with autoimmune diseases. Some of these agents and diseases will be discussed.

Cytomegalovirus

Cytomegalovirus (CMV) infects 70–100 % of adults in populations worldwide [29]. The development of systemic lupus erythematosus (SLE) may be triggered by a CMV infection. Existing SLE may undergo an exacerbation following a CMV infection [30]. Serological signs of active CMV infection have been detected in SLE patients [31]. In addition, the infection is associated with increased disease activity [32]. The virus has been detected in patients with RA, Sjögren's syndrome, dermatopolymyositis, psoriasis, Wegener's granulomatosis, ulcerative colitis and Crohn's disease [29].

Epstein–Barr virus

Another agent searched for pathogenesis of autoimmune diseases is Epstein–Barr virus (EBV). EBV is a human DNA virus that infects B cells and causes their polyclonal activation and produces polyclonal antibodies. Polyclonal B cell activation may be an early step in the pathogenesis of SLE. Serologic association, cross-reactivity of select EBV specific antibodies with SLE autoantigens, SLE-like autoimmunity after immunization with EBV peptides, increased viral load in SLE patients and SLE-specific alterations in EBV humoral and cellular immunity include EBV in the development of SLE [33, 34]. Esen et al. [35] reported significantly higher early antigen (EA/D) IgG immune response in SLE patients. The authors informed that the serologic profile of patients in the study may indicate reactivation of EBV infection in SLE patients which may be due to immune dysregulation induced by the disease itself, the effect of immunosuppressive therapy or the result of molecular mimicry mechanisms. In another study by Zandman-Goddard et al. [36], anti-EA IgG antibodies were found to be higher in lupus patients with cutaneous and joint manifestations and increased anti-Ro antibody titers.

Parvovirus B19

Lunardi et al. [37] have recently determined a peptide that shares homology with the capsid protein VP1 of Parvovirus and with human cytokeratin. Supporting the molecular mimicry hypothesis in the pathogenesis of autoimmune diseases, this peptide also shares similarity with globulin

transcription factor 1, which plays a significant role in megakaryopoiesis and in erythropoiesis. Endothelial cell damage may also be related to Parvovirus infections. A direct correlation between the extent of degenerative endothelial cell alterations and the degree of B19 RNA expression suggested a causal role of B19 in the propagation of the endothelial cell dysfunction [38].

In addition, chronic Parvovirus B19 infection can induce antiviral antibodies that also react specifically with collagen type II, single-stranded DNA and cardiolipin (29).

Zakrzewska et al. [39] studied Parvovirus B19 in SSc patients and showed some differences in the rate of persistence of B19 V DNA, in the simultaneous persistence of two genotypes and in the pattern of viral expression among SSc patients and controls.

Hepatitis C Virus

Ramos-Casals et al. [40] have investigated the clinical and immunologic characteristics of a large series of patients with systemic autoimmune diseases associated with chronic hepatitis C virus (HCV) infection. In the study group, Sjögren's syndrome (SS), RA and SLE were associated with chronic HCV infection.

In another study [41], it has been emphasized the strong associations of autoimmune thyroid disease with the HCV infection and interferon-α (IFNα) therapy. In addition, it was likely that HCV and IFN act in synergism to trigger autoimmune thyroid disease in patients. The association between HCV infection and thyroid autoimmunity and type 2 diabetes mellitus has been reported, and a common pathogenetic pathway of HCV-related extrahepatic diseases with these autoimmune endocrine manifestations has been suggested [42]. Chronic antigenic stimulation by HCV is considered a key mechanism sustaining the proliferation of rheumatoid factor-secreting B cell clones. It has been hypothesized that it may play a role as an early, chronic stimulus for autoreactive B cells in HCV-infected patients [43].

Hepatitis B Virus

Hepatitis B virus is associated with liver disease, but is also related to extrahepatic manifestations, such as prodromal serum sickness in acute hepatitis, membranous glomerulonephritis, membranoproliferative glomerulonephritis, cutaneous vasculitis, infantile popular acrodermatitis, essential mixed cryoglobulinaemia and polyarteritis nodosa (PAN), all forms of immune complex diseases. Furthermore, HBV infection is associated with other inflammatory syndromes in diseases such as rheumatoid arthritis, polymyalgia rheumatica and polymyositis [44, 45].

Several mechanisms have been linked to HBV as the inducer of some autoimmune phenomena. The mechanisms include: molecular mimicry between HBV antigens and self proteins, the generation of immune complexes between HBV antigens and antibodies and apoptosis/tissue damage resulting in the exposure of intracellular antigens [45, 46].

Influenza

Sivadon-Tardy et al. [47] reported that influenza virus can also induce Guillain–Barre′ syndrome, but the majority of infections were due to virus A (H3N2). However, Chaari et al. [48] have informed a case of Guillain–Barre′ syndrome (GBS) related to pandemic influenza A (H1N1) infection. In another article, it was informed that an analysis was conducted of 10,486 acute flaccid paralysis cases diagnosed as Guillain–Barre′ syndrome from 2000 through 2008 in children aged <15 years in Latin American and the Caribbean countries and territories. The acute flaccid paralysis surveillance system have represented a useful means of monitoring GBS during the pandemic [49].

Campylobacter

Drenthen et al. [50] discussed retrospective analysis of preceding infections in relation to serial electrophysiology and clinical data from 123 GBS patients. Accordingly, 17 (14 %) of 123 patients had *C. jejuni*-related GBS. C. *jejuni* patients had lower motor and higher sensory action potentials compared with viral-related cases. In another study, Usuki et al. [51] have established a rat model of peripheral nerve dysfunction induced by antiganglioside antibodies via sensitization by the lipooligosaccharide of *C. jejuni*. They have shown further that it is possible to utilize an anti-idiotype antibody design, on the basis of molecular mimicry, to ameliorate the neurological dysfunction in this animal model.

Streptococcus pyogenes

Guilherme and Kalil [52], using a proteomics approach, identified myocardium and valvular autoantigens that were recognized by heart-infiltrating and peripheral T cells from rheumatic fever/chronic rheumatic heart disease (RF/RHD) patients. Their results showed that there were several expanded T cell populations with an oligoclonal profile in the heart tissue of chronic and acute RHD patients. The researchers emphasized that molecular mimicry is defined as a sharing of epitopes between antigens of the host and the infectious agent, which in the case of RF/RHD is *S. pyogenes*.

In patients with Sydenham chorea antibody, cross-reactivity between *S. pyogenes* membrane and neuronal cytoplasm has been reported [29].

Staphylococcus aureus

Mulvey et al. [53] examined the association between individuals with multiple sclerosis (MS) and colonization with *S. aureus* harboring superantigens. In the research, nasal swabs were collected from non-MS subjects and patients with MS who had not experienced a relapse in the past 6 months (MS stable group) and who had suffered a relapse within 30 days of study recruitment (MS exacerbation group). They informed that among individuals colonized with *S. aureus*, the prevalence of staphylococcal superantigen gene (sea) was significantly greater in the MS exacerbation versus non-MS study group. This issue has been discussed in variety of articles frequently [54, 55].

Genetics, autoimmunity and infection

Genetics play an important role in autoimmunity and influence the response of an individual to environmental factors such as infections. The interaction among genetics, infection and autoimmunity was studied in a series of animal experiments by investigators. Neu et al. [56] demonstrated that infection with coxsackievirus induced autoimmune myocarditis in genetically susceptible BALB/c mice, dependent on major histocompatibility complex (MHC) and non-MHC genes. In humans, the presence of human leukocyte antigen (HLA) DR11 phenotype was linked to mixed cryoglobulinemia (MC) in patients with chronic HCV infection. In contrast, HLA-DR7 seemed to protect HCV-infected patients from mixed cryoglobulinemia [57]. Kudat et al. [58] informed that some HLA class II DR and DQ alleles such as HLA-DRB1*07 were found to be associated with the risk of developing post-Streptococcus acute rheumatic fever (RF). Furthermore, the HLA-DRB1*13, DRB5* and DRB3* were protective against the development of rheumatic valve damage. HLA-DR2 is associated with MS [59] and SLE [60], and HLA-B27 with ankylosing spondylitis (AS) [61]. Meanwhile, the frequency of HLA-B27 allelotypes in Crohn's disease (CD) patients without associated arthritis is usually the same as in the normal population, but it is increased to up to 60 % in those with involvement of the spinal joints [62]. In rheumatoid arthritis (RA), class II MHC gene, HLA-DR4, is the most strongly linked genetic marker to this disease. The frequency of this allelotype has been found to be around 70 % in RA patients, but it is detected in less than 30 % of the general population [63].

Vulnerability to infections can be influenced by genetic profiles. For instance, black ethnic groups are more prone to infection with mycobacterium tuberculosis and meningococcemia than are Caucasians [64].

Since the mid 1980 s, many studies have emphasized a role of *Proteus mirabilis* in the etiopathogenesis of RA [65]. For instance, Ebringer et al. [66] informed that rabbits injected with HLA-DR4-positive lymphocytes were found to produce antibodies which will only bind to *P. mirabilis* but not 18 other microorganisms. In another study, tissue-typing sera from pregnant women having anti-HLA-DR4 specificity were found to bind more significantly to *P. mirabilis* than to *E. coli* [67]. IgG antibodies from patients with RA were found to have cytotoxic activities against HLA-DR4 cells as shown by increased hemolysis for the sheep red blood cells coated with HLA-DRβ1*0404 peptides when compared to sera from AS and healthy control subjects [68]. These findings support the notions that there is a significant role for *Proteus* microorganisms in the initiation and perpetuation of RA.

The results of various studies have indicated microbiological evidence for a link between *Klebsiella* microorganisms and AS. Anti-sera from immunized rabbits with *Klebsiella* were found to bind equally to HLA-B27-positive lymphocytes whether obtained from AS patients or healthy controls but not to lymphocytes taken from HLA-B27-negative individuals [69]. Mäki-Ikola et al. [70] informed that *Klebsiella* antibodies were significantly elevated in the serum compared to the synovial fluid of AS patients. The result indicates that these antibodies are produced in extra-articular regions such as the enteric mucosal lymphatic system before gaining entry into the joints.

As can be inferred from the studies, genetic susceptibility might explain why only a subgroup of individuals will develop autoimmunity after infections. The relationship between immune dysregulation and autoimmune disease that can be triggered by an infectious agent has been demonstrated in animal models such as New Zealand black/white (NZB/W) mice and non-obese diabetic (NOD) mice. NZB/W mice are genetically prone to develop an SLE-like disease, exhibited by autoimmune hemolytic anemia, nephritis and high resistance to induction of tolerance [64].

Is there any protective feature of infections in autoimmune diseases?

The effects of certain parasitic and bacterial infections are to moderate the immune response; an excessive response can have a pathological outcome [71]. Some studies using animal models have led to the suggestion that human autoimmune or allergic diseases might be alleviated by the use of microbial products. There are some data that would support such an observation [72]. For example, it was demonstrated that infection with Schistosoma mansoni [73] or Coxsackieviruses [74] can prevent diabetes in NOD mice. This protective effect is result of a strong Th2- and regulatory T cell response [73]. Krause et al. [75] also

demonstrated epidemiological support for the protective role of infections. They found significantly fewer antibodies against *H. pylori*, CMV, EBV and Toxoplasma in sera of Type 1 diabetes (T1D) patients compared with their first-degree family members or healthy controls. Ram et al. [76] found a lower prevalence of anti-hepatitis B antibodies among patients with MS and SLE.

According to the "Hygiene Hypothesis", Strachan [77] assumed that the increase in ADs observed in Western countries was partly caused by a decline in infectious diseases and improved hygiene. In some cases, infections can actually protect individuals from autoimmune and allergic diseases. It was suggested that reduced exposure to infectious agents in infancy might predispose to hay fever. "Hygiene Hypothesis" applies to most autoimmune diseases, especially multiple sclerosis [78] and T1D [79].

Conclusion

There is an obvious fact that relationships between infections and many autoimmune diseases are complicated. Infections may trigger autoimmunity, and many different infectious agents seem to be potentially involved in the induction of different autoimmune diseases. The etiopathogenetic mechanism which plays a major role in the causation and the development of some autoimmune diseases involves interplay between the genetic and environmental factors. However, microorganisms form an important part of causal connection in the most immune-mediated rheumatic diseases.

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