Review Article

Infectious diseases and autoimmunity

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Abstract

Introduction: Autoimmunity occurs when the immune system recognizes and attacks host tissue. In addition to genetic factors, environmental triggers (in particular viruses, bacteria and other infectious pathogens) are thought to play a major role in the development of autoimmune diseases.

Methodology: We searched PubMed, Cochrane, and Scopus without time limits for relevant articles.

Results: In this review, we (i) describe the ways in which an infectious agent can initiate or exacerbate autoimmunity; (ii) discuss the evidence linking certain infectious agents to autoimmune diseases in humans; and (iii) describe the animal models used to study the link between infection and autoimmunity.

Conclusions: Besides genetic predisposition to autoimmunity, viral and bacterial infections are known to be involved in the initiation and promotion of autoimmune diseases. These studies suggest that pathogens can trigger autoimmunity through molecular mimicry and their adjuvant effects during initiation of disease, and can promote autoimmune responses through bystander activation or epitope spreading via inflammation and/or superantigens.

Key words: viral infection; bacterial infection; autoreactive lymphocyte; molecular mimicry; bystander activation; epitope spreading; autoimmune disease

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Introduction

The immune system must distinguish self from harmful non-self to repel invaders and to preserve the integrity of the host without inducing autoimmunity. Any deficit in this function can result in susceptibility to infections, malignancies [1-3] or over-reactivity to harmless antigens, leading to immunopathology and autoimmunity. The etiology of autoimmune diseases has been difficult to elucidate. Several factors are thought to contribute to the development of immune response to self, including genetics and environment [4-6]

Several common autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis, are genetically linked to distinct human major histocompatibility complex (MHC) class II molecules and other immune modulators. Furthermore, autoimmunity often clusters families, indicating the potential for a broad-spectrum genetic defect in immunological tolerance mechanisms. However, the genetic factors leading to the development of immune responses against specific antigens in a tissue and/or organ-specific manner remain largely unknown. Among the environmental factors, infections have been implicated in the onset and/or promotion of autoimmunity [7].

This article reviews the evidence regarding the association of pathogens with autoimmune diseases. We searched PubMed, Cochrane, and Scopus without time limits. The following search terms were employed in various combinations: "bacterium", "parasite", "virus", "infection" and "autoimmunity".

There are more than eighty identified autoimmune diseases [8]. Multiple arms of the immune system may be involved in autoimmune pathology. Antigens are taken up by antigen presenting cells (APC) such as dendritic cells (DC) and processed into peptides which are loaded onto MHC molecules for presentation to T cells via clonotypic T cell receptors (TCR). Cytolytic T cells (Tc, activated by MHC class I on APC) can directly lyse a target, while T helper cells (Th, activated by MHC class II) release cytokines that can have direct effects or can activate macrophages, monocytes and B cells. B cells themselves have surface receptors that can bind surface antigens. Upon receiving signals from Th cells, B cells secrete

antibodies specific for the antigens. Antibody may bind its specific target alone or may bind to and activate macrophages simultaneously via the Fc receptor.

Multiple mechanisms have been described to explain how pathogens might induce activation and critical expansion of autoreactive T cells and start autoimmune disease [9-14]. A microbial antigen can include an epitope that is structurally similar to an autoantigen epitope, providing the basic element of the mechanism referred to as molecular mimicry [13-18]. Another mechanism would imply that the inflammatory setting and the paracrine secretion of T cell growth factors induce the expansion of activated autoreactive T cells, whose small number was previously insufficient to drive an autoimmune disease. Such a mechanism is referred to as bystander activation [19]. Pathogen-induced tissue inflammation may result in local activation of APC and enhanced processing/presentation of self-antigens that causes T cell priming, followed by T cell activation and expansion of additional specificities (epitope spreading) [20,21]. Activation of resting autoreactive T cells may be achieved by viral and bacterial superantigens that bind a variety of MHC class II molecules and activate large numbers of T cells, irrespective of their specificity [22].

In this review, we outline the mechanisms by which pathogens could trigger autoimmune diseases and the evidence available for the involvement of specific pathogens in the initiation or exacerbation of representative autoimmune diseases.

Pathogen responses and autoimmunity

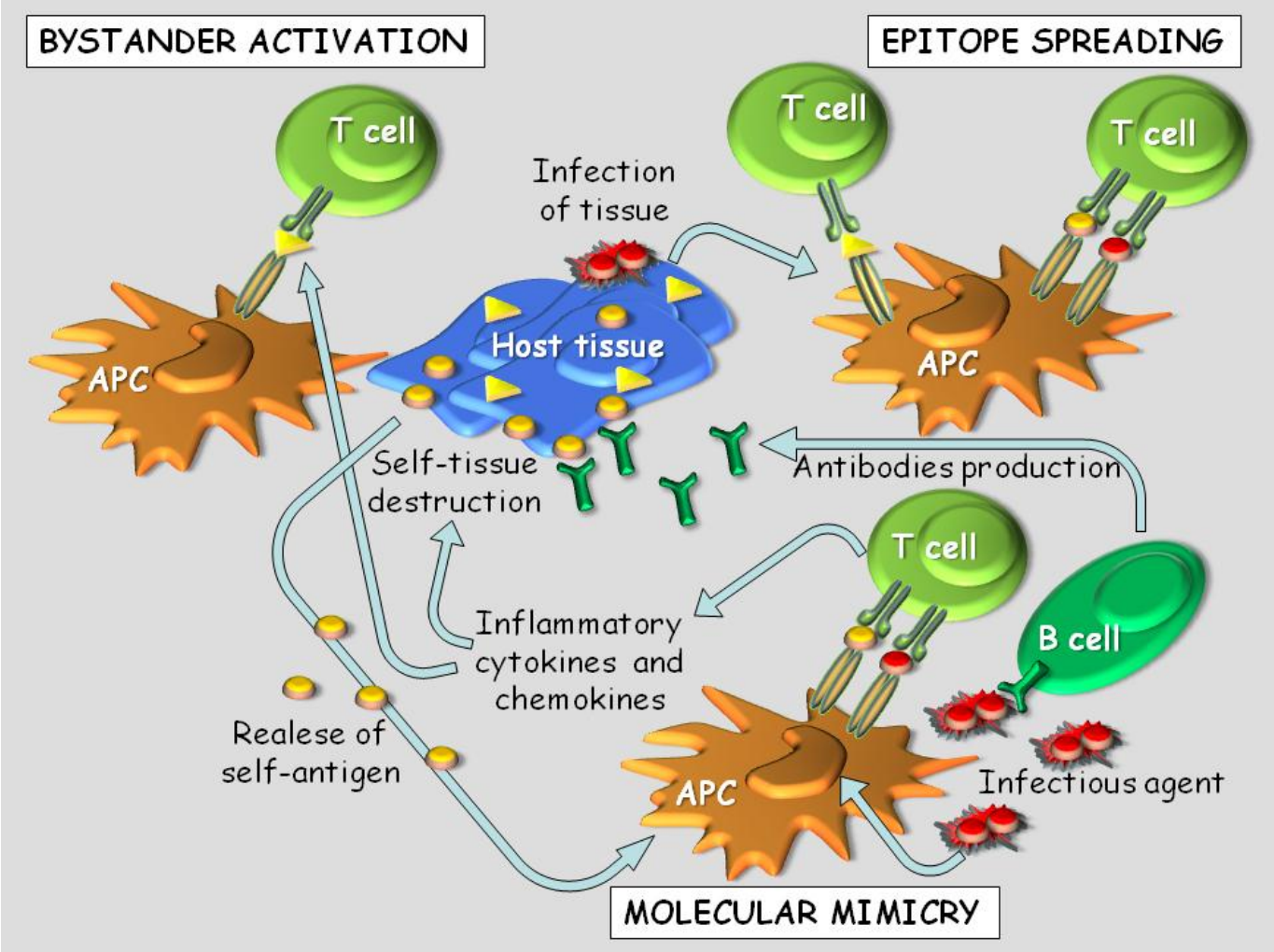
The ability of the host to defend against invading pathogens is to a large extent mediated by a group of germline-encoded receptors known as pattern-recognition receptors (PRR). These molecules include Toll-like receptors (TLR), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLR), (RIG-I)-like helicases and a subset of C-type lectin receptors, which together recognize a large number of molecular patterns present in bacteria, viruses and fungi [23]. The signalling pathways that are triggered by engagement of these molecules lead to cellular activation, which increases the antigen-presenting capacity of and the expression of co-stimulatory molecules by APC, as well as their production of type I interferons, pro-inflammatory cytokines and chemokines, which initiate and direct the immune response against the invading pathogen. Microbial antigens as well as PRR-triggered inflammatory molecules drive the clonal expansion of pathogen-specific T and B cells. By triggering PRRs, stimulating early responses by the innate immune system and increasing the function of APC, pathogens act as adjuvants for the immune response, while at the same time providing an antigen source to drive T-cell and B-cell activation. In this highly inflammatory environment, it is easy to envision how an aberrant destructive immune response can be triggered and/or escalated if autoreactive cells are present. There are several postulated mechanisms by which pathogenic infections can trigger autoimmune disease (Figure 1).

Molecular mimicry

Antigen recognition by the TCR allows T-cell activation by different peptides bound to one or even several MHC molecules [24]. The pathogen may carry elements that are similar enough in amino acid sequence or structure to self-antigen, so T cells that are activated in response to the pathogen are also cross-reactive to self and lead to direct damage and further activation of other arms of the immune system. Similarly, antibodies reflecting B-cell receptor specificity were found to recognize both microbial and self-antigens [25]. This hypothesis is known as molecular mimicry [10,26]. It is now generally accepted that a single T cell can respond to various distinct peptides, and that different peptide/MHC complexes can lead to cross-reactivity by the same TCR as long as the complexes have similar charge distribution and overall shape [27-29]. This flexibility of TCR recognition is thought to be central to many immunological processes including thymic selection and the ability to recognize nearly all pathogen-derived peptides. A side effect of this is the induction of autoimmunity by microbial antigens [7].

Animal models in which molecular mimicry can trigger autoimmune disease are abundant. These include: Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease (TMEV-IDD), a model of human multiple sclerosis in which intracerebral TMEV infection of mice leads to an autoimmune demyelinating disorder 30-40 days after infection [21]; herpes simplex virus (HSV)-associated stromal keratitis, in which HSV infection leads to blindness secondary to corneal-antigen-specific T-cell responses in both humans and mice [30-33]; cytotoxic reactions caused by antibodies against Streptococcus pyogenes antigens, which may be one mechanism to explain the origin of autoimmune heart disease in rheumatoid myocarditis [34]; infection of prediabetic mice with a virus expressing an H-2Kb-restricted

Figure 1. Mechanism by which pathogens may cause autoimmunity. a) Molecular mimicry describes the activation of crossreactive T cells that recognize both the pathogen-derived epitopes and the self-derived epitopes. Pathogen-derived epitops are taken up by APC and presented to T cells. Activation of T cells results in the direct lysis of self-tissue or release of cytokines and chemokines that activate macrophages, which mediate self-tissue damage, and provide help to pathogen-specific B cells. The subsequent release of self-tissue antigens and their uptake by APC perpetuates the autoimmune disease. b) Bystander activation is the nonspecific activation of self-reactive T cells. Activation of pathogen-specific T cells leads to inflammation that damages self-tissue in an antigen non-specific manner, and triggers activation of self-reactive T cells. c) Epitope spreading involves a persistent pathogen infection that causes damage to self-tissue. This results in the release of self-peptides, which are engulfed by APC and presented to self-reactive T cells. Continual damage and release of self-peptides results in the spread of the self-reactive immune response to multiple self-epitopes.



mimic ligand to a self-epitope present on beta cells, which accelerates the development of autoimmune diabetes [35]; autoimmune demyelinating disease associated with Semliki Forest virus (SFV) [36]; autoimmune myocarditis associated with coxsackie virus infection [37]; and murine cytomegalovirus [38]. T cells with low affinity for a self-antigen and that have escaped thymus negative selection, as would be the case for many self-antigen-specific responses, can become activated by infection with a microrganism containing an identical antigen, which provides appropriate innate immune signals, resulting in overt autoimmune disease.

In keeping with the observation that specific T cells that have been primed by pathogens and cross-react with self-antigens can cause autoimmunity in animal models, patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis have been found to have higher frequencies activated self-reactive lymphocytes [39-42]. In multiple sclerosis, receptor analysis of T and B cells in central nervous system (CNS) tissue and in the cerebrospinal fluid (CSF) showed clonal expansions in both populations, indicating that there is clonal reactivity to a restricted number of disease-relevant antigens [43-45]. In

addition, longitudinal studies provided evidence for long-term persistence of individual myelin-specific T-cell clones tracked over several years in the blood of patients with multiple sclerosis [46-48], indicating a strong, persisting memory response and/or ongoing autoantigen exposure at least for a subset of myelin-reactive T cells in multiple sclerosis. These memory responses may reflect, at least in part, persisting clonal expansions of polyspecific T cells recognizing both self and virus antigens. For example, high viral loads that occur during symptomatic primary EBV infection, resulting in infectious mononucleosis, are associated with an increased risk of developing multiple sclerosis [49-51], and could prime these polyspecific T-cell responses. Accordingly, patients with multiple sclerosis have predominant clonal expansions of T cells specific for the EBV-encoded nuclear antigen 1 (EBNA1), which is the most consistently recognized EBV-derived CD4+ T-cell antigen in healthy virus carriers, and EBNA1-specific T cells recognize myelin antigens more frequently than other autoantigens that are not associated with multiple sclerosis [52].

Autoimmune chronic gastritis (AIG) is an organ-specific inflammatory disease, characterized by lymphocytic infiltrates in the gastric mucosa and by destruction of parietal cells, resulting in mucosal atrophy, hypochloridria, and eventually pernicious anemia. [53]. In most AIG patients, serum anti-parietal cell autoantibodies (PCAs) are detectable. The autoantigen recognized is the gastric H+K+ adenosine triphosphatase (ATPase), the proton pump, localized in the parietal cell canaliculi [54,55]. H+K+ ATPase is also the target of autoreactive T cells that infiltrate the gastric mucosa of AIG patients [56]. Autoimmune gastritis and Helicobacter pylori-associated gastric atrophy develop through similar mechanisms involving the proton pump H+K+ ATPase as autoantigen. Helicobacter pylori-infected patients with gastric autoimmunity harbor in vivo activated gastric Th1 CD4 cells that recognize both H+K+ ATPase and Helicobacter pylori antigens [57,58]. So, in genetically susceptible individuals, Helicobacter pylori infection can activate cross-reactive gastric T cells leading to gastric autoimmunity via molecular mimicry.

Bystander activation of autoreactive cells and epitope spreading

Bystander activation describes an indirect or non-specific activation of autoimmune cells caused by the inflammatory environment present during infection. APCs that have become activated within the inflammatory milieu of a pathogenic infection can stimulate the activation and proliferation of autoreactive T or B cells. In this case, APC present self-antigen, obtained subsequent to tissue destruction and/or the uptake of local dying cells, to autoreactive cells [59,60]. In addition to autoimmune responses that are initially primed by APC and stimulated by bystander activation, additional autoantigen-specific T or B cells can be primed through epitope spreading [20], a situation in which an immune response that is initiated by various stimuli, including microbial infection, trauma, transplanted tissue or autoimmunity, spreads to include responses directed against a different portion of the same protein (intramolecular spreading) or a different protein (intermolecular spreading). Activating a broader set of T cells through epitope spreading is helpful in an anti-pathogen or anti-tumour immune response, because the pathogen or tumour cannot easily escape immune control with a single mutation in an immunogenic epitope. However, autoimmune disease potentially arises when spreading cross-reacts with self-proteins, leading to the destruction of self-tissue.

Epitope spreading in animal models proceeds in an orderly and hierarchical manner, such that more immunodominant epitopes elicit responses first, followed by less dominant responses. This type of spreading has been shown in experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis [61,62], as well as in the non-obese diabetic (NOD) mouse model of type 1 diabetes [63]. These examples document epitope spreading within autoantigens and to additional autoantigens.

Mycobacterium leprae is known to preferably reside in Schwann cells. Antibodies to neuronal glycolipids such as galactocerebroside [64,65], ceramide [64] and asialo GM1 of myelin may be associated with nerve damage in leprosy patients. Anti-ceramide IgM antibody titre was significantly higher in multibacillary leprosy patients in comparison to both controls and paucibacillary leprosy patients [66].

An even broader form of bystander activation is achieved by cross-linking MHC class II molecules on APC with TCR comprising a certain Vβ domain by superantigens. T-cell populations that are stimulated in this manner could potentially contain a subset of T cells specific for a self-antigen [67]. There are multiple examples in which superantigens are involved in diseases such as EAE, arthritis and inflammatory bowel disease, making superantigens another mechanism by which bystander activation can initiate,

or at the least exacerbate, autoimmunity in mouse models [68-70].

Although molecular mimicry might initially prime autoreactive T cells, these responses could be amplified by superantigen-mediated expansion and by activation of autoantigen-specific T cells that express a given Vβ chain that is targeted by microbial superantigens.

Others mechanisms

Infections can affect the immune response in many ways, and mechanisms such as molecular mimicry and bystander activation are certainly not the only ways in which pathogens might trigger or accelerate autoimmune disease. Infection may lead to autoimmunity through the processing and presentation of cryptic antigens. In contrast to dominant antigenic determinants, subdominant cryptic antigens are normally invisible to the immune system. The inflammatory environment that arises after infection can induce increased protease production and differential processing of released self-epitopes by APC [71].

A recent study showed that in a spontaneous animal model of systemic lupus erythematosus, lipid raft aggregation on T cells, induced by Cholera toxin B from Vibrio cholerae, enhanced T-cell signalling and exacerbated systemic lupus erythematosus activity [72].

Persistent infection of microglia with TMEV has been shown to cause upregulation of MHC and costimulatory molecules and enhance the ability of these cells to function as effective APC [73]. This shows that viral infections could also directly maintain autoreactive effector cells or autoantigen-presenting cells.

The fact that the various mechanisms for infection-induced autoimmunity discussed here are interrelated and non-mutually exclusive make them both more complicated and more plausible as potential causes for human autoimmune disease. For example, molecular mimicry and adjuvant effects of pathogens might work early on during the development of autoimmune responses, whereas bystander activation end epitope spreading through the inflammatory environment of infections and/or superantigens might exacerbate autoimmune responses later on [13,26,31,74].

Induction of overt autoimmune disease

Although several causal relationships between pathogen infection and autoimmunity have been identified in animal models and correlations have been drawn in human autoimmune diseases, pathogen-derived triggers of autoimmunity have been difficult to identify because evidence of autoimmunity is likely to become clinically apparent only after a considerable period of subclinical autoimmune responses.

Autoreactive adaptive immune cells are unavoidably present in the periphery in humans and animals. These cells can exist because their cognate self-antigen was not expressed in the thymus and the antigen will therefore only become apparent to the immune system after tissue destruction as a result of infection or trauma. Alternatively, whereas many autoreactive T cells are deleted in the thymus during development, some T cells that make their way to the periphery might be highly specific for a microbial antigen, but also have lesser affinity for a self-antigen. The presence of autoreactive cells in the periphery, however, does not necessarily predispose for clinical autoimmune disease.

It is clear that, in many cases, an infection is necessary for the development of overt disease, even when abundant autoreactive T cells are present. The potential for the development of overt disease is clearly dependent on the presence of autoreactive T cells. However, whether overt disease actually occurs can depend on various other coincident events, including the number of autoreactive T cells present, the avidity and affinity of these cells (determined by co-receptor expression and binding to MHC/peptide complexes, respectively), and the presence of innate inflammatory signals required for activation and differentiation of those T cells to a pathogenic phenotype. Despite the requirement for all these elements, it is clear that they do not need to happen at the same time or in the same place to elicit autoimmune disease. In many animal models, autoimmune responses are triggered during the initial or acute response to an infection, and autoimmune disease occurs exclusively in the infected organ, such as during corneal HSV infection leading to stromal keratitis [13,30,31]. However, none of the proposed mechanisms for the development of infection-induced autoimmunity excludes the possibility that disease can occur temporally and/or spatially distal from the site of the initiating infection. Animal models that allow investigators to study this aspect of infection-induced autoimmune disease are few, but they might provide important insights relevant to human disease. Autoimmune CNS demyelinating disease can be triggered by molecular mimicry when the pathogen containing the mimic epitope does not infect the CNS

itself. When mice that express an LCMV protein in the CNS were peripherally infected with LCMV, autoimmune responses occurred in the CNS despite the fact that LCMV was not detectable in that organ [75].

Finally it is of interest to emphasize that the preferential homing of primed antiviral or antibacterial T cells might also falsely implicate pathogens in the immunopathology of autoimmune diseases. Lytic EBV infection was suspected to contribute to rheumatoid arthritis after it was found that lytic EBV antigen-specific T cells were enriched in inflamed joints [76]. It was later found that these lytic EBV antigenspecific T cells were home to a variety of autoimmune inflamed tissues [77], including knees affected by rheumatoid arthritis, eyes of patients with uveitis, and the brains of patients with multiple sclerosis. These data were interpreted as primarily reflecting the migration of EBV-specific T cells in response to inflammatory chemokines, such as the CXCR3 ligand CXCL10, rather than a direct involvement of EBV-directed immunity in the immunopathology of the autoimmune diseases.

Conclusions

Besides genetic predisposition to autoimmunity, environmental factors are known to be involved in the initiation and promotion of autoimmune diseases. Among these, viral and bacterial infections are the main candidate environmental factors due to their capacity to elicit strong immune activation and to induce autoimmune diseases in animal models, as well as the correlation of several pathogens with autoimmune diseases in humans. These studies suggest that pathogens can trigger autoimmunity through molecular mimicry and their adjuvant effects during initiation of disease, and can promote autoimmune responses through bystander activation or epitope spreading via inflammation and/or superantigens. However, an association of dysregulated antiviral immune responses with a given autoimmune disease has to be interpreted with caution, because these can be differently primed in individuals with ongoing autoimmune disease or with a genetic predisposition to autoimmune disease. Furthermore, the autoimmune disease can alter virus infection by affecting its host cells, and might lead to redistribution of antiviral lymphocytes to sites of autoreactive tissue inflammation.

Dedication

The news that you never want to hear: the passing of a good friend, mentor and scientist. Gianfranco Del Prete said goodbye to this world in November 2010.

Here we would like to remember Gianfranco Del Prete not just because he was a full professor of medicine in the University of Florence or because of his large number of important publications in the immunology field, where one of his major research goals of was the study of important scientific issues related to developing countries. Here we would like to remember Gianfranco as a person able to dedicate himself to research, until the end of his life, with always a very impressive energy, passion and curiosity. He was straightforward but always honest and he had the gift of being able to involve everyone in a magical feeling: the feeling of science … where you think that with your job, your mind, doing research, working hard with passion, you can improve someone else's life … you can give new knowledge to the community. A fruitful life of achievement makes Gianfranco Del Prete a Man to be remembered in science.

For all you gave us and to the world it is with great emotion that we say, *Thank you, Gianfranco!*

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