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Antiviral immune responses: triggers of or triggered by autoimmunity?

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Abstract

Several common autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and multiple sclerosis, are genetically linked to distinct human MHC class II molecules and other immune modulators. However, genetic predisposition is only one risk factor for the development of these diseases, and low concordance rates in monozygotic twins as well as geographical distribution of disease risk point towards environmental factors in the genesis of these diseases. Among these environmental factors, infections have been implicated in the onset and/or promotion of autoimmunity. In this review, we outline mechanisms by which pathogens can trigger autoimmune disease, and also pathways by which infection and immune control of infectious disease might be dysregulated during autoimmunity.

The immune system walks a fine line to distinguish self- from harmful non-self to preserve the integrity of the host. Deficits in this discrimination can result in susceptibility to infections or over-reactivity to harmless antigens, leading to immunopathology and autoimmunity. Therefore, it is not surprising that genetic factors that influence the sensitivity of the immune system are associated with autoimmune diseases, but might only manifest themselves as autoimmunity after stimulation by environmental factors, including viral infections. Unfortunately, this implies also that the over-reactive immune system of individuals susceptible to autoimmune disease might be triggered by more than one pathogen or even by more severe primary infections with common pathogens. Both factors make it difficult to associate distinct pathogens with particular autoimmune diseases. This review discusses the mechanisms by which pathogens could trigger autoimmune diseases and mechanisms by which autoimmune disease could alter the ability of the host to control infections and regulate the immune system. In discussing these aspects, we highlight recent studies showing the induction of autoimmune inflammation in the central nervous system (CNS) of mice following infection with Theiler's murine encephalomyelitis virus (TMEV), and the dysregulation of immune responses against Epstein–Barr virus (EBV) in humans with the autoimmune disease multiple sclerosis. The discussed mechanisms and correlations between altered immune responses to these pathogens and autoimmune diseases could be developed as therapeutic targets or as diagnostic markers in the future.

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How can antiviral responses trigger autoimmunity?

As we discuss here, several mechanisms have been described to explain how viruses might trigger autoimmune diseases, including virus-induced general activation of the immune system and provision of viral antigens that specifically stimulate immune responses, which cross-react with self-antigens and therefore cause autoreactive immunopathologies.

Adjuvant effect of pathogens in priming autoreactive immune responses

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 (PRRs). These molecules include Toll-like receptors (TLRs), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), (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 (reviewed in [1]). 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 antigen-presenting cells (APCs), 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 APCs, 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 and effector function (Figure 1). 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, but most evidence in animal models has been gathered to support the idea that cross-reactive immune responses cause autoimmunity due to similarities of viral and self antigens.

Molecular mimicry

The well-documented degeneracy of antigen recognition by the T-cell receptor (TCR), which allow T-cell activation by different peptides bound to one or even several MHC molecules [2], implies that responses to foreign antigens could result in the activation of T cells that are also cross-reactive with self antigens. Similarly monoclonal antibodies, reflecting B-cell receptor specificity were found to recognize both microbial and self-antigens [3]. This idea, known as molecular mimicry **(**Figure 2A**)**, was first put forward by Fujinami and Oldstone [4,5]. 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 [6-8]. 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. Vice versa the identification of such cross-reactivities can also help to uncover etiologic agents of autoimmune disease. In vitro studies have clearly shown that viral peptides with some degree of homology with self peptides can stimulate autoreactive T cells [6].

Animal models in which molecular mimicry can trigger autoimmune disease are abundant. These include: 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 [9]; herpes simplex virus (HSV)-associated stromal keratitis, in which HSV infection leads to T-cell-mediated blindness in both humans and mice [10-12]; diabetes model(s) [13]; autoimmune demyelinating disease associated with

Semliki Forest virus (SFV) [14]; autoimmune myocarditis associated with coxsackie virus infection [15] and murine cytomegalovirus [16] (Table 1). Even so we primarily focus on a possible role of viruses in autoimmune diseases, other microbial pathogens have also been implicated in contributing to autoimmune disease by molecular mimicry, like for example streptococcus in rheumatoid myocarditis [17]. There are also many less physiological scenarios that do not necessarily aim to closely model a particular disease but serve to reveal potential mechanisms through which immune responses to infections could lead to autoimmunity through molecular mimicry.

Along these lines, many investigations have used models of molecular identity, in which an exact microbial protein or epitope is transgenically expressed in a particular tissue. Under these conditions, animals are not generally susceptible to the development of spontaneous autoimmune disease. However, after infection with the microorganism containing the protein, autoimmunity in the transgenic protein-expressing organ ensues [18-21]. Although these approaches are clearly artificial, they do indicate that T cells specific for a “self” antigen can become activated by infection with a microorganism containing an identical antigen, which provides appropriate innate immune signals, resulting in overt autoimmune disease. Even when the transgene-expressed antigen is also expressed in the thymus, so that normal mechanisms of negative selection significantly decrease the number of high-affinity T cells specific for the viral/self antigen, infection eventually results in autoimmunity [20]. These experiments indicate that even T cells with low affinity for a self antigen and that have escaped negative selection, as would be the case for many self-antigen-specific responses, can be activated through molecular mimicry with a microbial antigen and cause disease. Similarly, in the TMEV-IDD model of multiple sclerosis, a severe rapid-onset demyelinating disease in the CNS is induced by intracerebral or peripheral infection with TMEV that has been engineered to express the immunodominant self epitope from myelin, proteolipid protein (PLP)139-151 [22].

Several bacterial and viral peptides that mimic $PLP_{139-151}$ [23] have been identified, and these have been used in models that more directly address the possibility of autoimmune disease induced by molecular mimicry. TMEV engineered to express peptides derived from *Haemophilus influenzae* that mimic $PLP_{139-151}$ (TMEV-HI, which shares 6 of 13 amino acids with $PLP_{139-151}$) or murine hepatitis virus (TMEV-MHV, which shares only 3 of 13 amino acids with $PLP_{139-151}$), induces a rapid onset, severe demyelinating disease that is similar to that induced by infection with TMEV expressing $PLP_{139-151}$ [22,24] itself. The *H. influenzae* mimic of $PLP_{139-151}$ can also be processed and presented out of its own native flanking sequences when larger portions of the bacterial protein are expressed in TMEV, which further supports the potential role for molecular mimicry in a natural infection [25]. Relevant to human disease, bacterial peptide mimics of the myelin basic protein (MBP) epitope 85-99, derived from such different pathogens as *Mycobacterium tuberculosis, Bacillus subtilis* and *Staphylococcus aureus*, induce demyelinating disease in mice that transgenically express a human MBP_{85-99}-specific TCR as well as an HLA class II molecule that can present the peptide [26]. Molecular mimicry was also shown in a model of diabetes in which lymphocytic choriomeningitis virus (LCMV) nucleoprotein was expressed under the control of the rat insulin promoter. Infection with Pichinde virus, which contains an epitope that mimics a subdominant epitope in the LCMV nucleoprotein, accelerated autoimmune disease that had already been established by previous infection with LCMV [13]. HSV-induced stromal keratitis is mediated by corneal-antigen-specific T-cell responses that are induced following corneal HSV infection. This is a non-synthetic, natural model of autoimmune disease in which molecular mimicry can occur in the absence of genetic manipulation [10]. The results from these experiments were called into question by a later study in which HSV-induced stromal keratitis could be induced in mice in the absence of T-cell responses against HSV [11]. However, the former model allows for efficient HSV specific immune control, whereas in the absence of HSV specific immune control in the latter model, keratitis could be caused by pathogen induced

immunopathology. Therefore, as different model systems with possibly different disease mechanisms were used to investigate HSV-induced stromal keratitis, the strong case for molecular mimicry put forth by the former study has yet to be ruled out [12].

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 SLE, rheumatoid arthritis and multiple sclerosis have been found to have higher frequencies and activation states and/or less co-stimulatory requirements of self-reactive lymphocytes [27-30]. In multiple sclerosis, receptor analysis of T and B cells in 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 [31-33]. 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 [34-36], indicating a strong, persisting memory response and/or ongoing autoantigen exposure at least for a subset of myelin-reactive T cells in multiple sclerosis.

We suggest that these memory responses reflect, at least in part, persisting clonal expansions of polyspecific T cells recognizing both self and virus antigens that have been found associated with human autoimmune diseases **(**Table 2**)**. 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 [37-39], 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 [40]. Notably, myelin and EBNA1 cross-reactive T cells produce interferon-γ (IFNγ) but differ from EBNA1-monospecific cells in their capacity to produce additional cytokines, such as interleukin-2, which is indicative of polyfunctional T cells. Because T cells successively use their ability to produce more than one cytokine during differentiation, polyfunctional T cells are thought to be particularly important under conditions of antigen persistence and high antigen load because they are less susceptible to clonal exhaustion or activation-induced cell death [41]. However, viral titres in circulating blood cells from patients with multiple sclerosis are similar to those detectable in healthy virus carriers [42] and patients with multiple sclerosis do not differ from healthy EBV carriers in the rate of EBV-induced B-cell transformation or in their ability to control the outgrowth of EBV-infected B cells *in vitro* [40], which argues against increased viral replication or impaired immune control of chronic EBV infection driving EBV-specific T-cell expansion in patients with multiple sclerosis. Instead, a more extensive priming of polyfunctional cross-reactive T cells during symptomatic primary EBV infection with high levels of viral load, and continuous restimulation caused by autoimmune tissue inflammation, could potentially establish and maintain a distinct repertoire of myelin-reactive virus-specific T cells, which could predispose for multiple sclerosis.

Bystander activation of autoreactive cells and epitope spreading

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 a process known as bystander activation. In this case, APCs present self antigen, obtained subsequent to tissue destruction and/or the uptake of local dying cells, to autoreactive cells [43,44] **(**Figure 2B**)**. In addition to autoimmune responses that are initially primed by APCs and stimulated by bystander activation, additional autoantigen-specific T or B cells can be primed through epitope spreading [45] — 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) **(**Figure 2B**)**. Activating a broader set of T cells through epitope spreading is helpful in an antipathogen or antitumour immune response, because the pathogen or tumour cannot easily escape immune control with a single mutation in an immunogenic epitope. However, disease potentially arises when spread to and within self proteins occurs subsequent to the destruction of self tissue. Epitope spreading in animal models proceeds in an orderly, directed 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 non-infectious model of multiple sclerosis [46,47], as well as in TMEV-IDD [9,48-50] and in the non-obese diabetic (NOD) mouse model of type 1 diabetes [51] (S.D.M., unpublished observations). While these examples document epitope spreading within autoantigens and to additional autoantigens, the inflammatory environment of viral infections could support these immune response cascades by increasing the presentation of self antigens via provision of signals through PRRs.

An even broader form of bystander activation is achieved by cross-linking MHC class II molecules on APCs with TCRs 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 [52]. 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 [53-55]. In these studies, staphylococcal, mycoplasma- and enteric microbiota-derived superantigens were shown to amplify, but not initiate, autoimmune T cell responses **(**Table 1**)**. Furthermore, the association of certain genotypes of the superantigen-encoding endogenous retrovirus HERV-K18, which is transactivated by EBV [56], with multiple sclerosis has been reported [57]. However, $V\beta7^+$ and $V\beta13^+$ T-cell populations, which are stimulated by the retroviral superantigen, do not seem to be selectively expanded in patients with multiple sclerosis. Nevertheless, viral-antigen-specific and/or superantigen-expanded T cells might participate in the development or maintenance of autoimmune disease. So 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.

Emerging 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. A recent study showed that in a spontaneous animal model of SLE, lipid raft aggregation on T cells, which was induced by Cholera toxin B from *Vibrio cholerae* in this particular study, but could be induced by several microorganisms or toxins, enhanced T-cell signalling and exacerbated SLE [58]. Furthermore, viral infections could also directly maintain autoreactive effector cells or autoantigen-presenting cells [59]. As one example, 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 APCs [60]. In another example, EBV immortalizes B cells and assists in their differentiation to long-lived memory B cells [61]. In addition, even in infected memory B cells, that usually do not express the latent EBV proteins that are associated with immortalization, non-translated viral RNAs contribute to resistance to cell death [62]. These mechanisms could preserve autoreactive B cells or a reservoir of APCs capable of presenting autoantigens to promote autoimmunity. For example, a reservoir of EBV-infected B cells was recently found in submeningeal aggregates of brains from patients with multiple sclerosis[63]. 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, at which time the pathogen might have already been cleared and/or the antiviral immune responses might have subsided, the so-called 'hit-and-run' hypothesis.

Reciprocal relationships of pathogen-derived mechanisms of autoimmunity

All of these mechanisms are interrelated, non mutually exclusive, and dynamic, so the idea of microbial infection eliciting autoimmunity must be viewed not as a defined event that occurs through a particular mechanism, but as a process that can occur through many pathways simultaneously and/or sequentially **(**Figure 2**)**. For example, epitope spreading can be initiated through molecular mimicry as illustrated by the activation of $PLP_{178-191}$-specific T cells in SJL mice in which autoimmunity was induced by infection with TMEV expressing either $PLP_{139-151}$ or a $PLP_{139-151}$ mimic peptide [22], or following bystander damage. Molecular mimicry can initially activate autoreactive T cells that then expand and become pathogenic through bystander activation, or vice versa. As a result, it can be difficult to distinguish between the postulated mechanisms, even in seemingly simple animal models [5,11,12,64].

How can these mechanisms lead to overt autoimmune disease?

Animal studies have made it clear that in principle, infections can trigger autoimmune responses. This must be distinguished, however, from the elicitation of overt autoimmune disease as a direct result of microbial infection, which might be more difficult to establish.

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. A cogent example is that although demyelinating disease is readily induced in mice either by priming with $PLP_{139-151}$ peptide in complete Freund's adjuvant (CFA), or by infecting with TMEV expressing a $PLP_{139-151}$ mimic, priming with $PLP_{139-151}$ mimics in CFA does not induce overt disease, despite the fact that T cells from mice primed with mimic peptides robustly respond to $PLP_{139-151}$ [23,24,44]. Presumably, TLR engagement and other innate immune stimuli that are present upon infection with TMEV expressing the mimic peptide allow APCs to provide the necessary signals for full-blown activation and optimal migration of autoreactive T cells [60]. So, the nature of a pathogen, which directs the type of immune response that is elicited, can profoundly influence the potential for development of autoimmune disease, and could in fact increase *or* decrease the likelihood of autoimmunity in the presence of autoreactive cells. In this regard, T helper 1 (T_H1)- and T_H17-polarized T-cell responses have been proposed to accelerate autoimmunity, whereas T_H2-polarized responses might confer protection [65]. Also, in the case of molecular mimicry, the virus-encoded mimic itself has an important role, as a peptide that partially mimics a self antigen (known as an altered peptide ligand), depending on the context of the infection, could have a tolerizing rather than an immunizing effect [60].

Even the presence of autoreactive T cells together with the presence of an appropriate infection might not lead to autoimmune disease. For example, in Pichinde virus infection of RIP-LCMV-

NP mice, although the mimic-encoding Pichinde virus was not sufficient to initiate overt autoimmunity, it was able to accelerate autoimmune disease that had already been established by infection with LCMV [13]. So, viral "adjuvant" and self mimics might in some cases be able to trigger autoimmune disease only if autoreactive cells are already 'primed' to some degree, such that the autoreactive T cells have been previously activated and exist at a higher precursor frequency [66]. The affinity of TCRs for various self-peptide–MHC complexes might also have a key role in the development of autoimmune disease. Indeed, a threshold level of TCR affinity has been shown to be important for the establishment of autoimmunity [67]. In RIP-LCMV mice, whether or not the self antigen was expressed in the thymus during development (which affects T-cell affinity) has a significant impact on the speed with which autoimmune disease develops [20]. TLR engagement alone can be sufficient to induce the correct environment for the development of autoimmune disease if autoreactive T cells are of high enough affinity for self antigen [20,68]. However, as most T cells will have low affinity for self under physiological situations, studies in which TCR affinity for self-antigen is low may have greater relevance to human autoimmune disease.

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 of 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.

Autoimmunity can occur at a site distal to the initiating infection

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 [10 11,12]. Along these lines, submeningeal reservoirs of EBV infected B cells have been reported in the brains of patients with multiple sclerosis [63], but it remains unclear if these focus pathogenic immune responses to the diseased tissue. Models in which infection directs autoreactive responses to distinct tissues provide a simple system in which to study the pathological mechanisms of infection-induced autoimmunity. However, in most cases a robust immune response to a pathogenic infection in the target organ is usually not associated with the development of autoimmunity in humans. 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 **(**Figure 3**)**. 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 [21]. In non-transgenically manipulated mice, pancreatropic Coxsackie virus engineered to express $PLP_{139-151}$, induces CNS demyelinating disease associated with $PLP_{139-151}$-specific T-cell responses, also in the absence of any apparent infection in the CNS itself (S.D.M.,unpublished observations).

The fact that the various mechanisms for infection-induced autoimmunity discussed here are 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 through the inflammatory environment of infections and/or superantigens might exacerbate autoimmune responses later on. However, as we consider the potentially multi-mechanistic and multi-step nature of autoimmunity, it is important to remember that an established autoimmune response can also have effects on pathogen-directed immune responses occurring in the same organ or elsewhere in the body.

How might antiviral responses be triggered by autoimmunity?

The flip side of autoimmunity being driven by viral infections is that autoreactive immune responses or even only predisposition to these might affect the development of antiviral immune responses. This might alter their composition, the viral set-point during chronic infections and the anatomical distribution of virus-specific lymphocytes. These alterations could be used as diagnostic markers for autoimmune disease activity, but might not regulate the autoimmune disease itself.

Bystander activation

The activation of innate immune cells can be initiated by both pathogen-associated "stranger" signals [69] and damage-associated, altered-self "danger" signals [70]. These apparently disparate mechanisms trigger inflammation through common means, as stranger and danger signals both ligate PRRs. TLRs have a particularly instructive role in innate immune responses against microbial pathogens, as well as the subsequent induction of adaptive immune responses. Both experimental infections in mice lacking individual TLRs and key molecules of the TLR signaling pathways [71] as well as natural infections in humans with primary immunodeficiencies that selectively impair TLR responses [72] clearly show the crucial role of TLRs in shaping protective antiviral immunity.

A role for TLR signaling in the induction and maintenance of autoimmune diseases was first highlighted by Leadbetter et al. [73] who showed that immunoglobulin in the blood provokes autoimmune responses when immune cells recognize it as a complex with self-DNA. In B-cell receptor (BCR)-transgenic mice in which most B cells express surface antibodies with low affinity for self-IgG2a, which is the rheumatoid-factor specificity, immunoglobulin neither activates the B cells nor makes them tolerant unless these mice are crossed onto an autoimmune-prone *lpr* background; self-IgG2a in the offspring of this cross is immunogenic, resulting in high titres of circulating rheumatoid-factor autoantibodies, a diagnostic marker of autoimmune disease [74]. This study found that immune complexes consisting of self-IgG2a and self-DNA, triggering both surface BCRs and endosomal TLRs, were necessary and sufficient for the loss of self-tolerance in this model. Similar models have been reported for RNA-containing immune complexes and TLR7/TLR8 activation [75,76]. So, endogenous TLR ligands such as self-DNA or RNA or nucleic acid-associated proteins could act as adjuvants in autoimmune diseases that are characterized by prominent tissue damage or impaired removal of apoptotic cell or necrotic debris [77], and could assist in the priming of anti-viral immune responses.

Furthermore, the induction and maintenance of autoimmune tissue inflammation crucially depends on the cytokine polarization profile of pathogenic T_H cells in animal models of T-cell-mediated autoimmune diseases [65,78,79]. Both T_H1 and T_H17 cells are thought to coordinate autoimmune inflammation in these diseases, presumably through distinct pathways [80]. Although the T_H1-cell cytokine IFNγ can inhibit the generation of T_H17 cells, it also reinforces T_H1-cell differentiation [78], which is instrumental in establishing protective antiviral immune responses. Therefore, the T_H1-polarizing milieu of autoimmune diseases might support superior anti-viral immune responses [81,82].

Although it has not yet been shown in experimental models, we suggest that the increased availability of intrinsic "danger-signals" released through autoimmune tissue damage probably both affects host responses to microbial pathogens at sites of autoimmune inflammation and enhances pathogen-specific innate and adaptive immune responses.

Increased pathogen replication

In addition to the adjuvant activity of autoimmunity, which might enhance pathogen-specific immune responses, autoimmunity can also affect pathogens that persist in lymphocytes. HTLV-1 and EBV are classical examples, with HTLV-1 persisting in memory T cells and EBV persisting in memory B cells. Both viruses seem to establish latency without detectable antigenic protein expression in these cellular reservoirs [83,84]. Reactivation of HTLV-1 occurs upon TCR and co-stimulatory molecule engagement [85]. Similarly, lytic replication of EBV can only be observed in plasma cells [86], and it can be induced by cross-linking of surface immunoglobulin on infected B cells [87]. Therefore, autoimmunity could trigger reactivation of these pathogens **(**Figure 4**)**, as has been documented in the case of EBV reactivation by malaria antigens [88]. Indeed, patients with SLE have abnormally high frequencies of EBV-infected cells that have aberrant expression of the immediate early lytic antigen BZLF1 in peripheral blood [89]. Interestingly, increased cell-associated viral loads correlated with autoimmune disease activity. Moreover, increased EBV loads correlated with EBV-specific $CD8^+$ T-cell responses in patients with SLE [90], which had decreased cytotoxicity as a sign of exhaustion [91], possibly due to persistent restimulation by the high antigenic load. By contrast, $CD4^+$ T-cell responses to EBV were also upregulated in patients with SLE, but negatively correlated with viral loads, suggesting enhanced immunoprotection by these cells [90]. Whereas EBV viral loads are up to 40-fold increased in patients with SLE, they are 10-fold increased in patients with rheumatoid arthritis [92]. Again, $CD8^+$ T-cell responses to EBV antigens positively correlate with these increased viral loads [93]. Also in rheumatoid arthritis the increased antigen load seems to cause further differentiation of EBV-specific $CD8^+$ T cells, resulting in the presence of a subpopulation of terminally differentiated, and presumably costimulation-insensitive, $CD27^-CD28^-$ cells that are rarely observed in healthy EBV carriers [93,94]. In addition to EBV-specific T-cell responses, subdominant antibody responses and broadened responses to dominant EBV antigens are also observed in patients with rheumatoid arthritis[93], again suggesting that the increased EBV antigen load in these patients hyperstimulates EBV-specific humoral and cell-mediated immune responses. Although these increased immune responses maintain EBV-specific immune control in most cases, the increased autoantigen-mediated stimulation of the B-cell compartment can even result in lymphoma development by driving B cells to hypermutation and germinal centre reactions, which increases the risk of acquiring transforming mutations. In the case of rheumatoid arthritis, Hodgkin lymphomas, including EBV^+ tumours, are more strongly associated with the autoimmune disease than non-Hodgkin lymphomas [95]. These studies suggest that lymphotropic pathogens such as EBV can be affected by autoimmune stimulation of host immune cells, leading to increased viral titres, increased immune responses against the pathogen and even pathogen-associated malignancies. Collectively, the evidence indicates that dysregulation of EBV-specific immune responses is a feature of rheumatoid arthritis and SLE, and is probably driven by autoantigen-mediated activation of EBV-infected B cells.

Genetic factors—Family-based genetic epidemiological studies provide unequivocal evidence that the susceptibility for autoimmune diseases is inherited, and genome-wide microsatellite screens and large-scale single nucleotide polymorphism (SNP) association studies have identified chromosomal loci that are associated with specific disorders such as SLE, rheumatoid arthritis, type 1 diabetes and multiple sclerosis. HLA-DR and -DQ alleles within the HLA class II region on chromosome 6p21 are by far the strongest risk-conferring genes for all of the aforementioned conditions [96,97,98,99]. Although the MHC region has proven

difficult to dissect because of its intense and variable patterns of linkage disequilibrium, there is evidence that additional loci in the HLA class III and HLA class I genomic regions and loci telomeric of genes encoding the classical MHC might have independent associations with autoimmune disease [96]. Furthermore, less robust susceptibility effects have been identified in non-MHC regions. Among these, the ITGAM-ITGAX region on chromosome 6p11, which encodes the α-chain of the $\alpha_M\beta_2$-integrin (also known as Mac-1, CR3 and CD11b), which is important for neutrophil and monocyte adherence to stimulated endothelium as well as the clearance of immune complexes, was associated with SLE in multiple studies [97,100,101], and the IL7RA region on chromosome 5p13 and IL2RA on 10p15 were identified as loci associated with multiple sclerosis [102-104]. Epistatic interactions between these risk-conferring and protective allelic variants are thought to define the overall genetic threshold for disease susceptibility [8].

We propose that immune functions of autoimmune susceptibility genes and their products probably affect host-pathogen interactions in patients with autoimmune diseases [72]. Along these lines, it was shown that $CD8^+$ T cells recognizing an immunodominant EBV epitope, restricted by HLA-B8, cross-reacted on HLA-B*4402, presumably presenting a self-peptide [105]. This cross-reactivity was strong enough to mediate alloreactivity against HLA-B*4402^+ cells, and result in deletion of this EBV specificity in HLA-B*4402^+/HLA-$B8^+$ individuals by negative selection, which ablates T cells of this specificity from the repertoire of EBV-specific immune responses in these individuals. Incomplete deletion of these alloreactive T cells in genetically susceptible individuals could however result in autoreactive and EBV-specific T cells. Similar to the genetic variation of the host predisposing for particular viral peptide presentation and recognition, as documented by the just discussed example, genetic variation of viruses might also favour peptide presentation that can stimulate cross-reactive T cell specificities. For example, the EBV strain B95-8 carries a point mutation in the HLA-B8 restricted $CD8^+$ T-cell epitope discussed above, which affects T-cell recognition of the virus through inefficient binding to HLA-B8 [106]. Vice versa, autoreactive T cell specificities could be preferentially triggered by certain virus strains encoding peptide epitopes that stimulate cross-reactive T cell specificities. With increased sequence variation also mapping to EBNA1 [107], especially an association between multiple sclerosis and a particular EBV strain remains possible, and sequence variation in the viral strain might enhance particular EBV-specific T- and B-cell responses that could participate in the autoimmunity. Therefore, the particular HLA background of an individual and the distinct viral strains carried by the individual could select for T-cell specificities with autoreactive capacity during anti-viral immune responses.

Considering this potential mechanism, it is apparent that disease promoting or protective effects of gene-environment interactions should ideally be investigated in patients with autoimmune diseases in comparison to syngeneic controls such as non-affected monozygotic twins [108]. As this is not feasible, we suggest that patients and controls should at least be matched for expression of large-size risk alleles such as HLA-DR and HLA-DQ allelic variants as this strategy minimizes the risk that detected differences in pathogen-specific immune responses are consequence rather than cause of disease susceptibility.

Redistribution of antiviral immune responses to sites of autoimmune inflammation

Besides genetic factors on both the pathogen and the host side that might boost distinct virus-specific immune responses, the preferential homing of primed antiviral T cells might also falsely implicate pathogens in the immunopathology of autoimmune diseases **(**Figure 5**)**. For example, 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 [109]. Indeed $CD8^+$ T cells specific for immediate early and early lytic EBV antigens were first cloned from the synovial fluid of patients with rheumatoid arthritis [109]. These specificities, which are now

recognized to be among the most frequent T-cell responses, develop during persistent infection with EBV [110]. Similarly the first lytic EBV antigen-specific $CD4^+$ T-cell responses were also cloned from this source [111]. Interestingly, it was later found that these lytic EBV antigen-specific T cells home to a variety of autoimmune inflamed tissues [112], 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. Similarly pathogen infected lymphocytes could preferentially migrate to inflamed tissues and this localization could be erroneously interpreted as a contribution of the pathogen in the autoimmune pathology, whereas it reflects in reality only the normal migratory behavior of infected host cells. The enrichment of EBV infected B cells in tertiary lymphoid tissue in post mortem CNS tissue form patients with multiple sclerosis might result from changes in the migratory behaviour of infected B cells [63], and needs to be further evaluated. In particular, CXCL13-mediated recruitment of $CXCR5^+$ B cells to multiple sclerosis lesions should be evaluated along these lines [113]. Therefore, the enrichment of both pathogen-specific and pathogen-infected lymphocytes at sites of autoimmunity might be informative with respect to the migration behaviour of pathogen-infected host cells and lymphocytes targeting them, rather than indicating the involvement of the respective pathogens in the immunopathology of autoimmune diseases. Nevertheless, a better understanding of these mechanisms could suggest how certain pathogens focus the autoimmune reactivity of a sensitized immune system to certain organs and reveal the diagnostic usefulness of monitoring antiviral immune responses in patients with autoimmune diseases.

Concluding remarks

Besides genetic predisposition to autoimmunity, environmental factors are known to be involved in the initiation and promotion of autoimmune diseases. Among these, viral infections are 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 viruses with autoimmune diseases in humans, as described in the recent studies highlighted in this review. These studies suggest that viruses 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. These changes might prove to be useful as diagnostic markers for autoimmune reactivity, and might be harnessed therapeutically. However, any therapeutic approach that targets these responses should be done with caution so that immune control against the pathogen is not compromised.

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Glossary

Pattern-recognition receptors (PRRs)	A host receptor (such as Toll-like receptors) that can sense pathogen-associated molecular patterns and initiate signalling cascades (which involve activation of nuclear factor-κB) that lead to an innate immune response.
Adjuvant	A non-infectious form of immune activation that is used to increase immune responses to antigen.
Molecular mimicry	A term used to describe what happens when a T- or B-cell receptor recognizes a microbial peptide that is structurally similar to a self peptide. The immune response initially directed at the microbial peptide spreads to tissues presenting the crossreactive self peptide, resulting in autoimmunity.
Negative selection	The intrathymic elimination of double-positive or single-positive thymocytes that express T-cell receptors with high affinity for self antigens.
*Polyfunctional T cell*s	T cells that have two or more functions including, but not limited to, degranulation or production of cytokines or chemokines. The development of multiparameter flow cytometry has facilitated the extensive analysis of T-cell effector functions at the single-cell level.
Clonal exhaustion	A state of non-reactivity when all precursor lymphocytes are induced by persistent antigen(s) to become effector cells, purging the immune-response repertoire of this specificity(s).
Activation-induced cell death (AICD)	A process by which fully activated T cells undergo programmed cell death through engagement of cell-surface-expressed death receptors such as CD95 (also known as FAS) or the tumour-necrosis-factor receptor.
*Bystander activatio*n	Activation and/or expansion of an immune response at a site of direct inflammation-induced tissue damage.
Epitope spreading	The *de novo* activation of autoreactive T cells or B cells to epitopes within the same or different self antigens that have been released after T-cell or B-cell-mediated bystander tissue damage.
Immunodominant epitope	A portion of an antigen that is targeted preferentially or to a greater degree during an immune response.
Superantigens	A microbial protein that activates all T cells expressing a particular set of T-cell receptor (TCR) Vβ chains by crosslinking the TCR to a particular MHC regardless of the peptide presented.
Altered peptide ligand (APL)	APLs are peptide analogues that are derived from the original antigenic peptide. They commonly have amino-acid substitutions at T-cell receptor (TCR) contact residues. TCR engagement by these APLs usually leads to partial or incomplete T-cell activation. Antagonistic APLs can specifically antagonize and inhibit T-cell activation that is induced by the wild-type antigenic peptide.

Rheumatoid factor	An antibody (usually IgM) that binds to the Fc region of IgG thereby forming immune complexes. Rheumatoid factors are sometimes found in patients with rheumatoid arthritis and other autoimmune diseases such as systemic lupus erythematosus.

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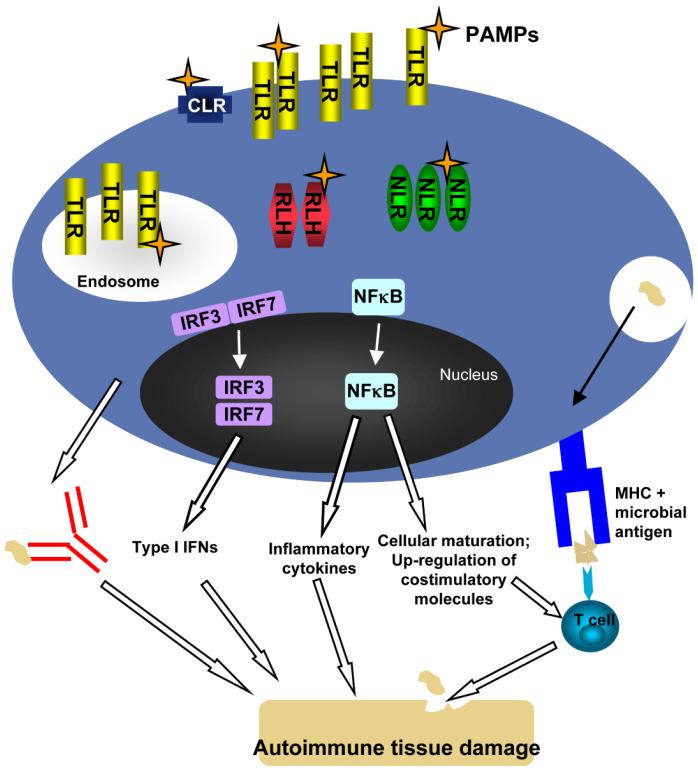

Figure 1. Infectious agents act as adjuvants for the activation and potentiation of immune responses, fostering induction of autoimmune diseases

Detection of pathogen-associated molecular patterns (PAMP) occurs via pattern recognition receptors (PRR). These include Toll-like receptors (TLRs), a set of receptors that sense a variety of molecules associated with bacteria and viruses outside or within endosomes or phagosomes of cells; nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), which detect similar molecules found within the cytoplasm; retinoic acid-inducible gene-I (RIG-I)-like helicases (RLH), which detect viral RNA within the cytoplasm; and a subset of C-type lectin receptors (CLR), which detect microbial DNA, RNA, or cell wall components. Activation of these PRRs results in a cascade of events culminating in the activation of interferon response factors (IRF) and NFκB, which trigger release of Type I Interferons and inflammatory cytokines, respectively. PRR ligation also results in cellular maturation and activation, including the upregulation of costimulatory molecules to allow efficient T-cell activation. Autoreactive T cells, activated in this fashion, could then cause autoimmune tissue damage. In addition, PRR stimulation can result in class switching and upregulation of antibody production in B cells [114]. Thus for autoreactive B cells, PRR triggers can directly augment autoimmune responses. Finally, the presence of a microbial infection provides antigen for activation of microbe-specific T and B cells that potentiate the inflammatory response, or for activation of T and B cells specific for antigens that are cross-reactive with self antigens.

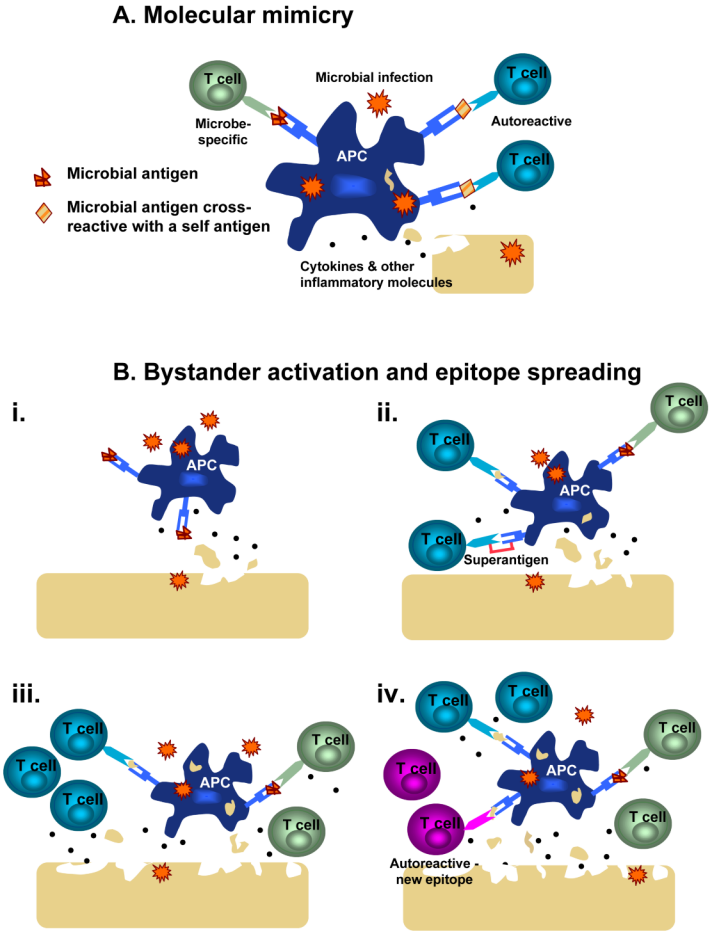

Figure 2. Mechanisms of infection-induced autoimmunity

A) ***Molecular mimicry*** occurs through cross-reactive recognition between a microbial antigen/MHC and a self antigen/MHC complex. **B) i,** Microbial infection stimulates TLRs, NLRs, *etc*., leading to tissue destruction via inflammatory mediators originating from cells of the innate immune system. **ii,** During ***bystander activation*,** engulfment of self antigen by activated APC is followed by presentation to autoreactive T cells (concomitant with presentation of virus antigen to virus-specific T cells). Alternatively an infection can lead to microbial ***superantigen***-induced activation of a subset of T cells, some of which are specific for self antigen. **iii,** T cell-mediated tissue destruction along with inflammatory molecule-mediated destruction releases more self antigen from tissues. **iv,** During ***epitope spreading*,** the response spreads to T cells specific for other self antigens.

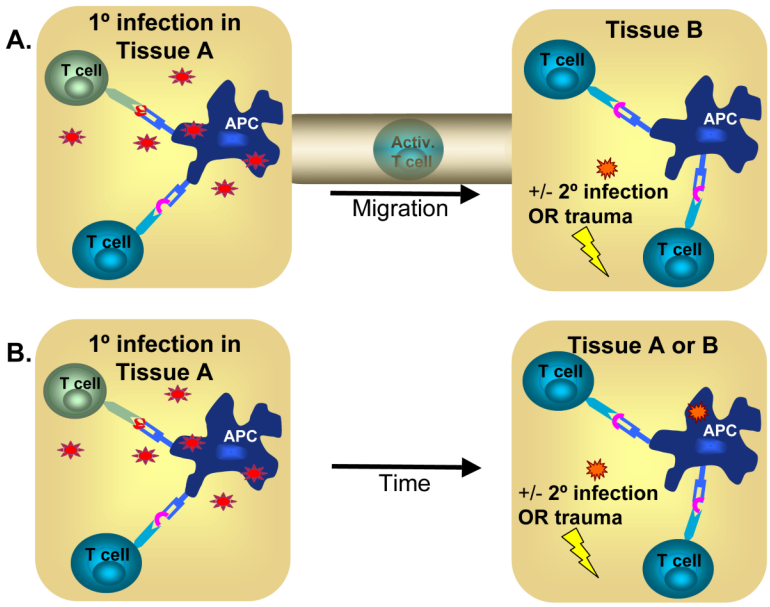

Figure 3. Mechanisms by which infection-induced autoimmune disease can occur in an organ distant from that of the initial infection, and/or subsequent to pathogen clearance

Autoreactive T cells can be activated via molecular mimicry or bystander activation in a tissue undergoing infection, without eliciting overt autoimmune disease before the infection is resolved. **A)** After migrating to a distant site, if sufficient antigen is available at this site, these previously activated T cells can trigger autoimmune disease. If sufficient self-antigen is not present, the induction of overt autoimmune disease may require a secondary infection or trauma. **B)** Similarly, T cells that were activated during infection in a particular tissue can become re-activated at a later date by a secondary infection with the same or a new microbe, or by a trauma. Presumably, autoimmune disease subsequent to microbial clearance can occur in the initial tissue or in a secondary site, if enough self-antigen is available for presentation.

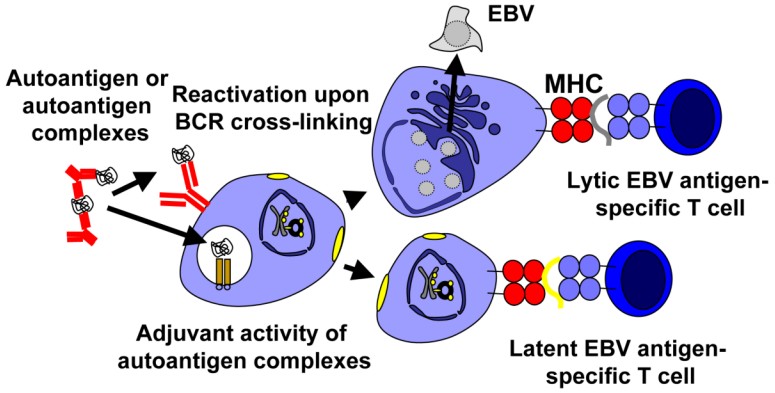

Figure 4. Adjuvant activity and cognate autoantigen recognition in autoantigen complexes can lead to the reactivation of lymphotropic viruses like EBV

B cell receptor cross-linking triggers lytic infection in EBV positive B cells, increasing viral load and lytic EBV antigen presentation to specific T cells. This might lead to elevated EBV specific immune control in patients with autoimmune disease. The adjuvant activity of autoantigen complexes might sustain or reactivate latent EBV antigen expression, resulting in the expansion of latent EBV specific T cell responses.

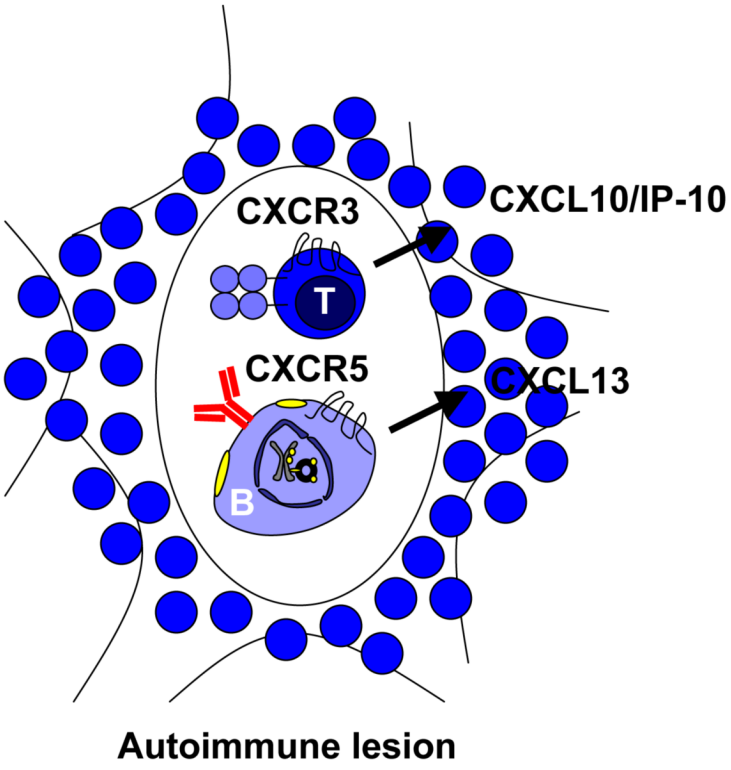

Figure 5. Primed T and B cells might accumulate in autoimmune lesions due to their migratory behaviour to inflamed tissues

The chemokine CXCL10/IP-10 binding to CXCR3 has been implicated in effector T cell recruitment to inflamed tissues, and the chemokine CXCL13 has been implicated in CXCR5-dependent attraction of B cells to multiple sclerosis lesions.

Table 1

Selected pathogen-induced murine models of human autoimmune disease

Relevant Human Disease	Mouse Model/ Infectious agent	Proposed Mechanism(s) of autoimmunity	Comment	References
Multiple sclerosis	TMEV-IDD	Bystander activation/ Epitope spreading	Natural virus-induced autoimmune disease of mice	9
	TMEV transgenically expressing PLP_{139}	Molecular identity		22
	TMEV transgenically expressing PLP_{139} mimics	Molecular mimicry		22,24,25
	Coxsackievirus B4 transgenically expressing PLP_{139}	Molecular identity	Infection can be at a site distant from where autoimmunity occurs	In preparation (SD Miller)
	LCMV infection of mice expressing LCMV proteins in the CNS	Molecular identity		21
	Semliki forest virus (SFV) infection	Molecular mimicry		14
T1D	Coxsackie B4 virus infection	Bystander activation		115
	LCMV infection of mice expressing LCMV protein in the pancreas	Molecular identity	TCR affinity for the LCMV peptide determines rapidity and severity of autoimmune disease	18-20
	Pichinde virus infection of mice expressing LCMV protein in the pancreas	Molecular mimicry	Autoimmunity can only be accelerated, not initiated de novo, in this model	13
Myocarditis	Mouse cytomegalovirus infection	Bystander activation or molecular mimicry	Circumstantial evidence points to molecular mimicry, but does not exclude bystander activation	16,116,117
	Coxsackievirus B3 infection	Molecular mimicry		15,16,117
Stromal Keratitis	Corneal HSV infection – induced stromal keratitis (HSK)	Molecular mimicry/bystander activation	Some controversy over which mechanism is responsible	10-12

Table 2

Some viral pathogens implicated in human autoimmune diseases

Pathogen	Autoimmune disease	Evidence	Selected references
RNA viruses			
Coxsackievirus	T1D	• Altered Immune responses • Enterovirus positive beta cells detected in pancreata from T1D subjects • Experimental infection causes T1D	115,118119,120
Rubella virus	T1D	• Tropism for pancreatic beta cells • Molecular mimicry	121,122
HTLV-1	HTLV-1 associated myelopathy	• Molecular mimicry	123
Measles virus	multiple sclerosis	• Infection can result in demyelination Higher titres of virus-specific IgG and increased frequencies of virus-specific T cells in the CSF	124,125126
DNA viruses			
HHV1/HSV1	Autoimmune stromal keratitis	• Molecular mimicry	10
HHV4/EBV	multiple sclerosis	• Increased risk to develop multiple sclerosis after primary symptomatic infection • Increased antibody responses in healthy individuals who will develop multiple sclerosis • Increased seroprevalence • Altered T cell and humoral immune responses • Molecular mimicry • Localization in diseased tissue	127128,129 37,38,42,63 40,130
	rheumatoid arthritis	• Altered immune responses • Higher viral loads in circulating blood cells • Localization in diseases tissues	131109,132,133 9293
	SLE	• Increased seroprevalence • Altered immune responses • Increased viral load • Molecular mimicry	90 89134
HHV6	multiple sclerosis	• Localization in diseased tissue • Heightened Immune Responses	135,136
Torque Teno virus	multiple sclerosis	• Localization in diseased tissue	137

Pathogen	Autoimmune disease	Evidence	Selected references
		• Clonally expanded CSF-infiltrating T cells recognize virus-encoded antigen	
Parvovirus B19	rheumatoid arthritis	• Phenotype of acute infection can mimic early rheumatoid arthritis • Detection of viral DNA in synovial tissue	138,139
	SLE	• Phenotype of acute infection can mimic early SLE • SLE patients Increased frequency of virus carriers	140 140