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STELLAR REVIEW
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The role of infections in autoimmune disease

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Summary

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. 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.

Keywords: autoimmune disease, molecular mimicry, virus infection

Introduction

There are more than 80 identified autoimmune diseases [1]. Multiple factors are thought to contribute to the development of immune response to self, including genetics, age and environment. In particular, viruses, bacteria and other infectious pathogens are the major postulated environmental triggers of autoimmunity.

Multiple arms of the immune system may be involved in autoimmune pathology. Antigens are taken up by antigen-presenting cells (APCs) such as dendritic cells (DCs) and processed into peptides which are loaded onto major histocompatibility complex (MHC) molecules for presentation to T cells via clonotypic T cell receptors (TCRs). 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, the B cell secretes antibodies specific for the antigens. Antibody may bind its specific target alone or may bind to and activate macrophages simultaneously via the Fc receptor.

There are multiple mechanisms by which host infection by a pathogen can lead to autoimmunity (Fig. 1). The pathogen may carry elements that are similar enough in amino acid sequence or structure to self-antigen that the pathogen acts as a self-'mimic'. Termed 'molecular mimicry', T or B 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. The pathogen may also lead to disease via epitope spreading. In this model the immune response to a persisting pathogen, or direct lysis by the persisting pathogen, causes damage to self-tissue. Antigens released from damaged tissue are taken up by APCs, and this initiates a self-specific immune response. 'Bystander activation' describes an indirect or non-specific activation of autoimmune cells caused by the inflammatory environment present during infection. A domino effect can occur, where the non-specific activation of one arm of the immune system leads to the activation of other arms. Lastly, infection may lead 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 APCs.

In this review, we discuss the evidence available for the involvement of specific pathogens in the initiation or exacerbation of representative autoimmune diseases. As will be mentioned, there is evidence for the involvement of different arms of the immune systems by many mechanisms, in both human disease and in animal models.

Coxsackievirus B

Coxsackievirus B (CVB) is the most common cause of infectious myocarditis. Infectious virus and viral RNA can be isolated from patients' hearts [2–4]. CVB3 can cause myocarditis in mice; in most mouse strains, the virus titre peaks at day 4 post-infection and is undetectable after 14 days [5]. The chronic stage of the disease (day 28 onwards) is characterized by mononuclear cell infiltration into the myocardium and the production of antibodies to cardiac myosin which, because of the absence of virus, argues for autoimmunity as the pathophysiological mechanism at this stage of disease. *In vitro*, cardiac myocytes can be infected and lysed

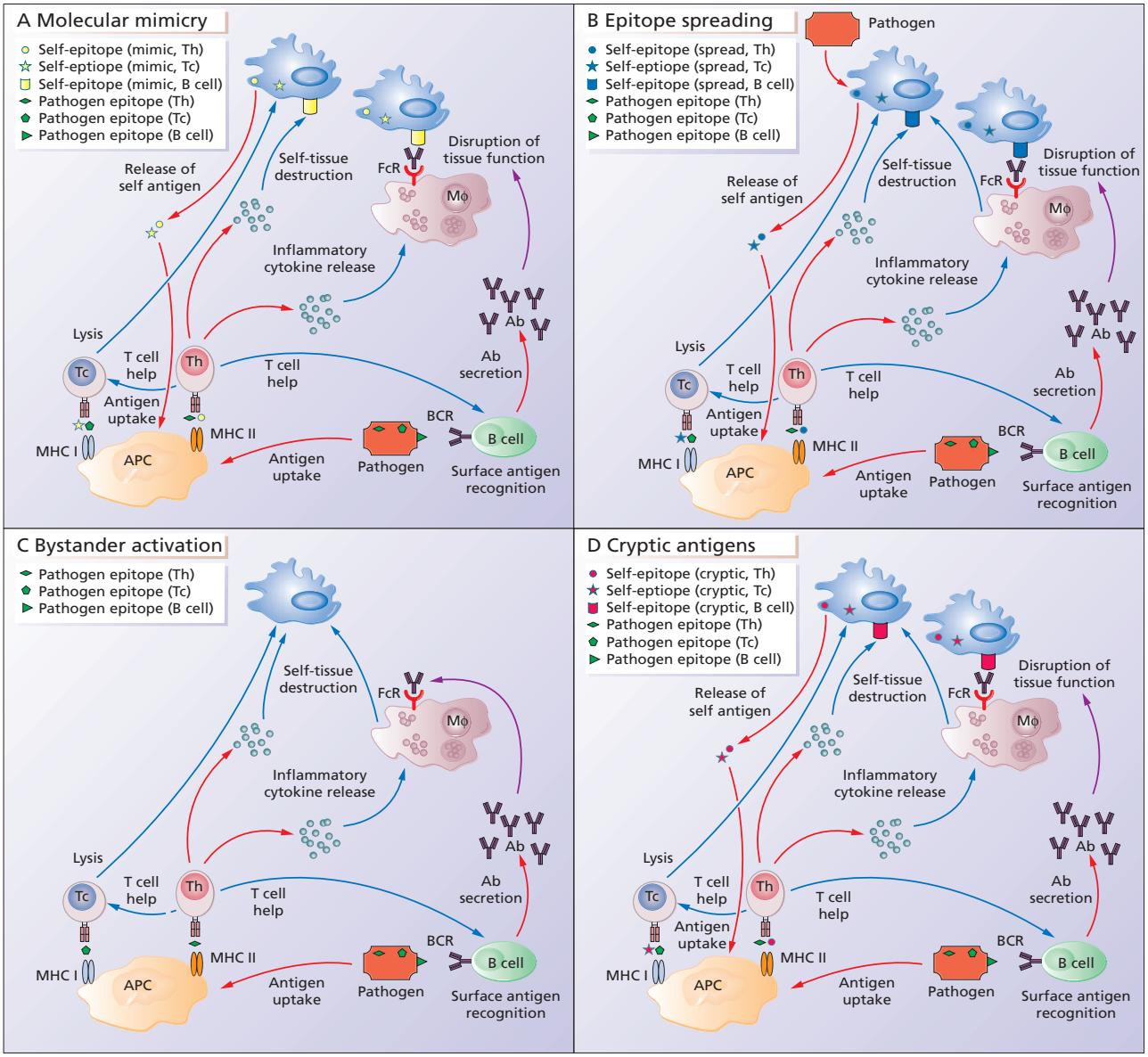

Fig. 1. Mechanisms by which pathogens may cause autoimmunity. (a) Molecular mimicry occurs when pathogen-derived epitopes are cross-reactive with self-derived epitopes. Pathogen-derived epitopes are taken up by antigen-presenting cells (APCs) and presented to cytolytic T cells (Tc) via major histocompatibility complex (MHC) class I or to helper T cells (Th) via MHC class II. T cells activated by pathogenic epitopes that are cross-reactive with self-epitopes can then damage self-tissue via lysis (Tc) or release of cytokines (Th). Cytokines released by activated Th cells can activate macrophages (Mϕ) or provide help to B cells. Pathogen-derived surface antigens are recognized by a B cell's B cell receptor (BCR), which triggers the secretion of antibodies. These antibodies can cause damage by binding to cross-reactive epitopes on the surface of tissues and disrupting tissue function, or the Fc portion of the antibody can bind simultaneously to the Fc receptor (FcR) on Mϕ; this will trigger the Mϕ to produce tissue-damaging cytokines. Damaged tissue will release more cross-reactive antigens, which will be taken up by APCs, propagating further damage. (b) In epitope spreading, the immune response to a persisting pathogen, or direct lysis of self-tissue by the persisting pathogen, causes damage to self-tissue. Antigens released from damaged tissue are taken up by APCs, and this initiates an immune response directed towards self-antigens. (c) In bystander activation, the various parts of the immune system respond to the invading pathogens. The inflammatory environment triggered by this response damages self-tissue in an antigen non-specific manner, and in addition triggers non-specific activation of immune cells. (d) 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 APCs.

by the virus [6] and CVB infection causes myocardial destruction in SCID mice (which lack T and B cells), showing that the virus can directly infect and lyse cells [7,8]. This damage may lead to autoimmunity via epitope spreading. In mice, virus-specific antibodies arise soon after infection, followed by antibodies to several cardiac proteins such as myosin, tropomyosin and actin [9–11]. T cells also play an important role, as T cells can transfer disease to naive recipients and athymic or T cell-depleted mice exhibit reduced disease following infection [12–15]. Depletion of $CD8^+$ T cells increases myocarditis in infected mice, showing the importance of this subset in mice [16]. Neutralizing anti-mCVB3 monoclonal antibodies (mAb), which could cause cardiac pathology when transferred into mice, were also cross-reactive to cardiac myosin and surface epitopes on cardiac fibroblasts, suggesting mimicry as a possible mechanism [17,18]. Similarly, T cell clones from infected mice proliferate in response to cardiac myosin [19,20]. Some studies have failed to detect cross-reactive T or B cells or mimic sequences within the virus capsid [21]. The same group found that tumour necrosis factor (TNF)-α or interleukin (IL)-1 treatment of genetically resistant mice could render them susceptible to cardiac disease, suggesting that bystander activation may be a mechanism of autoimmunity. CVB3 infection increases ubiquitinization of cellular proteins [9–11], and this increased cellular degradation may also lead to the release of cryptic epitopes. While these studies show that numerous autoimmune mechanisms can lead to cardiomyopathy in infected mice, it remains uncertain if autoimmunity accounts for the pathology seen in humans [22–24].

Streptococcus pyogenes: group A strepcococcus

Infection with *S. pyogenes* can lead to inflammation of the heart, and the involvement of lymphocytes in cardiac pathology has been suggested for some time [25,26]. Studies have shown that bacterial materials and DNA can persist in host tissue for some years after infection, so it is possible that ongoing immunity against the bacteria may lead to bystander damage to the organ [23]. However, it is accepted most predominantly that the autoimmune reaction is caused by molecular mimicry. Myosin has been identified as the dominant autoantigen in the heart, and myosin-reactive mAb derived from patients with acute rheumatic fever were shown be cross-reactive to both M protein (the major virulence factor of group A streptococci) [27] and the streptococcus carbohydrate epitope N-acetylglucosamine [28]. Similar cross-reactivity was seen with mAb derived from mice immunized with *S. pyogenes* membranes [29,30]. Cross-reactive mAb has been found to other heart proteins such as tropomyosin and laminin [31,32]. T cell clones from heart lesions of rheumatic heart disease patients, as well as their peripheral blood mononuclear cells (PBMC), can recognize simultaneously streptococcal M protein and heart tissue-derived proteins such as myosin, tropomyosin and laminin [33–36]. BALB/c mice immunized with human cardiac myosin developed T cells cross-reactive with M protein [37], and T cell lines from rats immunized with M protein were also cross-reactive with myosin [38]. These M protein-immunized rats develop cardiac lesions, presenting a good argument that mimicry is a major mechanism of pathology in human rheumatic heart disease. Cardiac lesions can also be induced in rabbits infected with the bacteria [39] and mice immunized with bacterial components [40].

Although somewhat controversial [41,42], infection with *S. pyogenes* has also been associated with the development of movement and behavioural disorders such as Sydenham chorea, Tourette's syndrome and obsessive–compulsive disorder [43,44]. Patients with these disorders often have antibodies to the basal ganglia in the brain, and molecular mimicry between basal ganglia and *S. pyogenes*-derived proteins remains the major postulated mechanism of disease induction. Rabbits immunized with streptococcal M protein developed antibodies cross-reactive with several human brain proteins, and synthetic M-derived peptides inhibited brain-cross-reactive antibodies from the serum of a patient with Sydenham chorea [45]. An early paper demonstrated antibody cross-reactivity between *S. pyogenes* membrane and neuronal cytoplasm in patients with Sydenham chorea [46]. Using serum, cerebrospinal fluid (CSF) and mAb derived from Sydenham chorea patients, dual-specific antibodies were found that react with both the immunodominant carbohydrate epitope on *S. pyogenes* cell wall (GlcNAc) and with lysoganglioside GM1 on the surface of neurones [47]. The same group demonstrated that GlcNAc-reactive antibodies from the sera of patients with paediatric autoimmune neuropsychiatric disorders associated with streptococci was inhibited by lysoganglioside GM1 [48], and that lysoganglioside GM1-reactive mAb from Sydenham chorea patients could also react with intracellular brain protein beta-tubulin [49]. Animal models are scarce, but Hoffman *et al.* showed that a subset of Swiss–Jackson Laboratory (SJL)/J mice primed with *S. pyogenes* homogenate developed movement and behavioural disorders [50]. These mice were found to have antibody deposits in their brains and serum antibody reactive to several regions of the brain.

Trypanosoma cruzi

Chagas disease is caused by infection with the protozoan parasite *T. cruzi* [51,52]; 10–30% of infected individuals develop the disease, which occurs in two major clinical phases, acute and chronic. The acute phase is characterized by parasitaemia, preferentially in heart muscle cells, and inflammatory infiltration of infected tissue. This is followed by an asymptomatic indeterminant phase, which can last up to 30 years [53]. Patients who progress to the chronic phase of the disease are affected mainly by irreversible cardiomyopathy.

Although it has been suggested that parasite persistence can contribute to chronic Chagas disease cardiomyopathy (CCC), *T. cruzi* antigens and DNA can also be detected in infected people who remain asymptomatic [54–56]. This suggests that the tissue destruction that characterizes this phase may be largely autoimmune. CCC is characterized histopathologically by mononuclear cell infiltrates, with $CD8^+$ T cells outnumbering $CD4^+$ T cells 2:1. Local production of interferon (IFN)-γ, TNF-α, IL-4 and IL-6 has been reported [57–59]. In addition, real-time polymerase chain reaction (PCR) analysis showed selective up-regulation of IFN-γ-inducible chemokines and chemokine receptors in CCC heart tissue [60]. Collectively, these data suggest that bystander tissue destruction mediated by inflammatory cytokines (especially IFN-γ) may play a role in CCC pathology. PBMC from CCC patients showed cytotoxicity against non-infected cardiac myocytes [61] and cytokine production against cardiac tissue homogenate [62,63], suggesting that the cell-mediated damage can also be tissue-specific. Antibodies to the cardiac protein Galectin-1 were found in both the sera and cardiac tissue of CCC patients; levels correlated with severity of cardiac damage, and interestingly were absent in cardiomyopathies that were not related to *T. cruzi* infection. There is also evidence for molecular mimicry in CCC. The *T. cruzi* protein B13 was found to elicit cross-reactive responses to cardiac myosin in from both the humoral [64,65] and $CD4^+$ T cell arms [66,67] of the immune system. Furthermore, cross-reactive antibodies were present in 100% of CCC patients but only 14% of asymptomatic infected individuals [65].

Most of the animal studies of CCC utilize *T. cruzi* infection of mice as a model. In the C3H/HeJ strain, the heart infiltrate of chronically infected mice is composed predominantly of $CD8^+$ T cells that secrete IFN-γ and TNF-α, which mirrors well the histopathology in humans [68]. In other strains, however, the $CD4^+$ compartment is responsible for the pathology. Chronically infected BALB/c or CBA mice develop $CD4^+$ T cells that proliferate in response to cardiac myosin, but not cardiac actin [69]. Chronically infected BALB/c mice rejected syngeneic newborn hearts unless treated with anti-CD4 (but not anti-CD8) antibody [70]. A $CD4^+$ T cell line derived from chronically infected DBA/2 mice, cross-reactive with both cardiac and *T. cruzi*-derived proteins, was able to cause intense heart inflammation when transferred into infected or heart-immunized BALB/c nude mice [71]. Girones *et al.* also published a study indicating that T and B cell mimicry existed between murine and *T. cruzi*-derived proteins. Here, they showed that T cells from *T. cruzi* infected mice were reactive to both the SAPA antigen on *T. cruzi* and the homologous, newly identified Cha autoantigen [72]. Transfer of these T cells into naive mice produced anti-Cha autoantibodies and heart lesions. Several other studies have demonstrated cross-reactive antibodies that recognize cardiac proteins such as myosin and *T. cruzi* antigens [73–77].

Although the chronic phase usually affects the heart, a subset of patients develop motor dysfunction of the gastrointestinal tract, essentially through the destruction of neurones of the enteric nervous system [78]. It was discovered that antibodies raised in rabbit against a flagellum-associated surface protein on *T. cruzi* (FL-160) are cross-reactive with a 48-kDa protein found exclusively in nervous tissue [79]. It was then found that antibodies raised against the amino terminus of FL-160 react to a different epitope on mammalian sciatic nerve than antibodies raised against the carboxyl terminus [80]. The medical relevance of this apparent mimicry is uncertain, as the ability of human sera to react to FL-160 did not correlate with clinical disease [81]. Other studies have also shown molecular similarity between *T. cruzi* antigens and antigens from mammalian nervous tissue [82,83].

Borrelia burgdorfeii

In the United States, Lyme disease is caused by the tick-borne spirochete *Borrelia burgdorfeii* (Bb). Sixty per cent of untreated patients develop arthritis that can last for several years, mainly in large joints such as the knee [84]. These patients have high titres of *Bb*-specific antibodies, and Bb DNA can be detected in the joint fluid by PCR [85]. Treatment of these patients with antibiotics usually ameliorates the arthritis, which indicates that bystander inflammatory response to the spirochete is responsible for early Lyme arthritis [86]. A subset of patients will progress from acute to chronic arthritis despite treatment with antibiotics and lack of detectable *Bb* DNA in synovial fluid [85–87]. Antibiotic-resistant Lyme arthritis is associated with the MHC class II alleles human leucocyte antigen (HLA)-DRB1*0401, *0101 and *0404, indicating that its mechanism is T cell-mediated and distinct from acute Lyme arthritis [88]. Cellular and humoral responses to outer surface protein A (OspA) of *Bb* develop in around 70% of patients with antibiotic-resistant Lyme arthritis, often at the beginning of prolonged arthritic episodes [89–92]. T cell and humoral responses to OspA, but not to other spirochete antigens, were found to correlate with the presence or severity of arthritis [92,93]. Specifically, antibiotic-resistant patients responded preferentially to the T cell epitope $OspA_{165–173}$, and T cells responsive to this epitope were expanded in the joint fluid compared with peripheral blood in HLA-DRB1*0401-positive patients [89,94,95]. An initial computer algorithm search identified lymphocyte function-associated antigen (LFA)$1\alpha_{L332–340}$, a peptide derived from the light chain of human leucocyte adhesion molecule, as homologous to $OspA_{165–173}$, and able to bind HLA-DRB1*0401 [96]. Synovial fluid mononuclear cells from patients with antibiotic-resistant arthritis produced IFN-γ in response to both $OspA_{165–173}$ and $LFA1\alpha_{L332–340}$, suggesting that mimicry between these two proteins may cause the inflammation associated with arthritis. LFA-1α has also been identified in the synovia of

patients with antibiotic-resistant Lyme arthritis [97]. However, other studies showed that in treatment-resistant patients, LFA1$\alpha_{L332–340}$ was a weak agonist for OspA$_{165–173}$-specific T cells and mainly induced the Th2-type cytokine IL-13 [98]. LFA1$\alpha_{L332–340}$ binds well to HLA-DRB*0401, but not to the more commonly associated allele HLA-DRB1*0101 [99]. In addition, although cross-reactive T cells were identified in the majority of patients in one study, there was no correlation between T cell response to LFA1$\alpha_{L332–340}$ and clinical status [100]. These studies weaken the argument that LFA1$\alpha_{L332–340}$ cross-reactivity is important in the pathology of antibiotic-resistant Lyme arthritis. On the other hand, Maier *et al.* identified 15 other human and murine self-peptides that could stimulate an OspA$_{165–173}$-specific T cell hybridoma [101], so other peptides may prove to be more important in disease pathology.

There are several rodent models in which arthritis is induced upon infection with *Bb* [102–105]. In C3H mice, joints are infiltrated with neutrophils 10–14 days after infection and, at the peak of arthritis (3–5 weeks), synovial lesions show leucocyte infiltration with mononuclear cells [103]. C57BL/6-*beige* mice, which have impaired macrophage motility and chemotaxis, develop severe arthritis [106], whereas C57BL/6 mice develop minimal arthritis unless deficient in IL-10 and IL-6 [107,108]. These studies indicate that macrophage-derived anti-inflammatory cytokines protect these mice from severe joint inflammation. Transferring *Bb*-specific T cells alone in the absence of B cells will exacerbate and accelerate the onset of arthritis in C57/BL6-SCID mice [109]. Rodent models are helpful only in studying acute Lyme arthritis, as the arthritis resolves within a few weeks and is not antibiotic-resistant.

Neurological complications, including myelitis and peripheral neuropathy, can occur in 10–12% of untreated patients infected with Bb and can arise even after antibiotic treatment [110]. Patients with chronic neuroborreliosis have been reported to have antibodies reactive to nerve axons in their serum [111], as well as antibodies and T cells specific for myelin basic protein (MBP) in spinal fluid [112,113]. Patient serum that was reactive to axons and neuroblastoma cells was also cross-reactive with *Bb* flagellin [111,114]. Next, it was discovered that a mAb for flagellin was cross-reactive with human heat shock protein 60 and with neuroblastoma cell lines [115,116] and slowed neurite outgrowth in culture [117]. Antibody cross-reactivity has also been described between human central nervous system (CNS) proteins and *Bb* OspA [118]. Several host neural peptides were identified as cross-reactive with *Bb*-specific T cells from CSF of a patient with chronic neuroborreliosis using peptide libraries and biometric data analysis [119]. However, studies such as those in non-human primates suggest that bystander inflammatory responses to the persistently infective pathogen may explain more clearly the CNS complications of this disease [120–122].

Herpes simplex virus

Herpetic stromal keratitis (HSK) is caused by corneal infection by herpes simplex virus (HSV) and can lead to blindness [123,124]. Whereas progression from epithelial infection to stromal keratitis is not prevented by anti-viral drugs, the symptoms of HSK can be alleviated with immunosuppressive drugs such as corticosteroids [125], indicating that HSK is an autoimmune disease. Because of the difficulties associated with studying the disease in humans, much of the characterization of HSK has utilized murine infection with HSV-1. Within 72 h of infection proinflammatory cytokines IL-1 and IL-6 are produced, which leads to influx of neutrophils into the corneal stroma [126–129]. Significantly, SCID mice reconstituted with CD4$^+$ T cells and depleted of neutrophils exhibit a lower incidence and severity of HSK [130]. Macrophage and natural killer (NK) cell influx follows subsequently in the cornea and may contribute to disease pathology directly or through the production of inflammatory cytokines [131–134]. Starting around 10 days after infection, a second wave of infiltration occurs, consisting mainly of neutrophils and CD4$^+$ T cells, which is heavily dependent on local production of IFN-γ [135,136]. Interestingly, the peak of HSK (day 14 post-infection) is 5–7 days after the infectious virus is typically detectable, suggesting that HSK pathology does not require the presence of the replicating virus [137,138]. However, viral DNA has been detected 37 or more days post-infection and could stimulate DCs and macrophages to activate T cells through bystander activation or the presentation of cryptic epitopes [139–141]. It was discovered early on that CD4$^+$ T cells were necessary for the development of HSK [135,136], and molecular mimicry has been postulated in addition to the mechanisms mentioned above. Cornea-specific T cell clones that cross-reacted with an epitope in the immunoglobulin (Ig)H locus (which was shown to defer susceptibility to HSK) were also found to recognize the HSV-1-derived protein UL6 [142,143]. Transfer of these cross-reactive T cells induced HSK lesions in nude mice, and HSV-1 viral mutants lacking the UL6 peptide did not induce HSK lesions in susceptible mice. However, in other studies employing a different susceptible mouse strain, infection failed to produce T cells reactive to either to UL6 or IgH [142,143]. In addition, T cell lines isolated from the cornea of HSK patients did not show reactivity to UL6 or other human corneal antigens [144–146]. This suggests that, in humans, T cells may cause pathology via bystander destruction.

Uveitis

Uveitis is a group of intra-ocular inflammatory diseases that are potentially blinding [147]. It is believed that many subgroups of this disease are autoimmune-mediated, in part because of the strong association with certain HLA alleles [148]. Humoral and cellular responses to the retinal antigens interphotoreceptor retinoid binding protein and S-antigen

are well characterized in humans [149,150] and animal models in rodents and primates (experimental autoimmune uveitis, EAU) are based on injecting these proteins in complete Freund's adjuvant. Singh *et al.* identified a $CD4^+$ T cell epitope in human S-antigen and several virus and *Escherichia coli*-derived peptides with sequence similarity [151,152]. Clinical and histological manifestations typical of EAU, including inflammatory infiltrates in affected eyes, were seen in Lewis rats immunized with these mimics. In addition, proliferation assays performed from lymph nodes demonstrated cross-reactive responses between the mimics and the retinal autoantigen. Starting with a different S-antigen $CD4^+$ T cell epitope, Wildner and Diedrichs-Mohring found mimics derived from rotavirus and bovine milk casein [153]. In the same study, patients with uveitis were found to have an increased T cell and antibody response to S-antigen and the two identified mimics compared with healthy donors. Aside for a report of an outbreak of uveitis in children after echovirus infection, no pathogen has yet to be associated epidemiologically with uveitis [154].

Diabetes

Type I diabetes (T1D) results from autoimmune destruction of pancreatic cells by autoreactive T cells and/or inflammatory cytokines. Although there is a definite genetic component to T1D, the concordance rate in monozygotic twins is only approximately 40% [155,156], and epidemiological evidence suggests that pathogens play a role in development. Many different viruses have been associated with T1D development [157]. Studies showed a higher incidence of T1D in people with congenital rubella [158] and antibodies to pancreatic islet cells in rubella-infected patients [159]. Similarly, cytomegalovirus (CMV) was isolated from T1D patients [160] and antibodies to pancreatic islet cells detected in CMV-infected patients [161]. It was also noted that mumps infection often preceded the onset of T1D in children [162,163]. A convincing study showed that CVB4 isolated from the pancreas of acute-onset patients could induce diabetes upon transfer into susceptible mice [163]. CVB4-specific IgM antibodies could be detected in children newly diagnosed with T1D [164,165]. There is some evidence that CVB4 may cause T1D via molecular mimicry. T cells isolated from T1D patients reacted with both glutamic acid decarboxylase (GAD-65) (an identified autoantigen in T1D) and protein 2C in CVB4. However, another study did not observe similar T cell cross-reactivity [166], and yet another showed that cross-reactivity was observed in both diseased patients and healthy controls [167]. *In vitro* studies suggest that rubella virus may act by producing antibodies and CTLs cross-reactive with islets [168,169]. There is also evidence that CMV can induce cross-reactive antibodies and Th cells [161,170]. *In vitro* studies showed that the mumps virus could infect and replicate in human cell lines, induce the release of IL-1 and IL-6 and up-regulate expression of MHC class I and class II antigens [171–173]. As the virus has also been shown to replicate in exocrine pancreas [174], it is possible that cytokine release and HLA up-regulation following mumps virus infection may lead to autoimmunity.

The non-obese diabetic (NOD) mouse model develops diabetes through the spontaneous destruction of pancreatic β cells. Similar to human T1D, the T cell response to GAD-65 appears to be important in disease pathogenesis, and epitope spreading may then result in responses to other autoantigens such as insulin [175]. Although in one study immunization of NOD mice with the CVB4-derived 2C protein induced T cells cross-reactive with GAD-65 (supporting the mimicry hypothesis) [176], in another study CVB4 infection did not induce cross-reactive T cells [177]. In a study where CVB4 accelerated the onset of diabetes, it was found that a threshold level of β cell-specific T cells needed to already be present for disease acceleration to occur [178]. Thus, bystander activation may be a more likely explanation than molecular mimicry in the NOD model. BDC2·5 mice are transgenic for a diabetogenic TCR. These mice develop diabetes similar to that seen following CVB4 infection after treatment with streptozotocin (which damages the pancreas) but not after treatment with poly I:C (a Toll-like receptor-3 agonist). This suggests that in this model, the release of cryptic antigens following viral infection may be the mechanism of diabetes induction [179]. Infecting diabetes-resistant BB (DR-BB) rats with Kilham's rat virus (KRV) induces diabetes in about 30% of these animals and insulitis without diabetes in an additional 30% [180]. Interestingly, unlike CVB4 in mice, KRV is not trophic for the pancreas but rather for lymphoid organs such as the spleen, thymus and lymph nodes. It is not very well understood how this virus causes diabetes without infecting β cells, but inactivating macrophages prevents diabetes in KRV-infected DR-BB rats [181]. There are also data that the virus may trigger previously quiescent β cell-specific T cells in DR-BB rats [182]. Finally, CVB4 was found to produce abnormalities in glucose tolerance tests and impaired insulin secretion in patas monkeys [183].

Guillain–Barré syndrome

Guillain–Barré syndrome (GBS) is a paralytic illness affecting both myelin and axons of the peripheral nervous system [184]. Several studies have demonstrated anti-glycolipid antibodies in the serum of a proportion of patients [185]. There are different clinical variants of the disease, which can correlate with the specific type of glycolipid targeted by the antibodies. Glycolipids found most commonly in neural tissues include the gangliosides and cerebrosides. Onset of GBS occurs days or weeks following an infection or immunization [186]. Although several microorganisms have been associated with GBS development, *Campylobacter jejuni* is the most extensively studied pathogen as it is a common

antecedent to GBS. In addition, there is mounting evidence suggesting that lipopolysaccharide (LPS) on the outer core of the bacteria can mimic host gangliosides. LPS from *C. jejuni* serotypes associated with GBS were shown to resemble human gangliosides structurally [187,188], and priming of mice, rats and rabbits with the above-mentioned LPS produced corresponding anti-ganglioside antibodies [189–191]. Several studies have shown that *C. jejuni* serotypes associated with GBS are more likely to contain ganglioside-like epitopes compared with serotypes isolated from *C. jejuni*-infected patients with gastroenteritis but no neurological symptoms, with one study linking ganglioside mimicry to specific GBS clinical subtypes [192,193]. Furthermore, Yuki *et al.* reported that rabbits immunized with *C. jejuni* LPS developed flaccid limb weakness that was associated with antibodies to the ganglioside GM1 and peripheral nerve pathology identical to that seen in GBS [194].

Patients infected with *Mycoplasma pneumoniae* prior to the development of GBS often have antibodies to galactocerebroside. These antibodies can cross-react with glycolipids on *M. pneumoniae* [195,196]. Associated antibodies to GM1 have also been reported [197]. Similar to what occurs following *C. jejuni* infection, patients infected with *Haemophilus influenzae* can develop antibodies to bacterial LPS that are cross-reactive with ganglioside [198]. The presence of a ganglioside-like structure on the surface of *H. influenzae* suggests that molecular mimicry may explain its association with GBS induction [199,200].

Multiple sclerosis

Multiple sclerosis (MS) is characterized by a loss of the myelin sheath surrounding axons in the CNS [201]. Demyelination is associated with elevated levels of $CD4^+$ T cells specific for major myelin proteins, and the disease is generally thought to be autoimmune [202–204]. Although it is not known precisely what triggers the development of MS, it is well established that relapses or disease flares in patients diagnosed with the relapsing–remitting form of MS are often associated with exogenous infections, particular upper respiratory infections. In total, more than 24 viral agents have been linked to MS [205,206]. Most of the associations have been circumstantial, but some studies have found evidence of specific pathogens in human tissue. Antigens from herpesvirus type 6 were found in MS plaques but not from tissues from other neurological disorders [207]. Similarly, compared with CSF from patients with other neurological diseases, CSF from MS patients was shown to have higher levels of the bacteria *Chlamydia pneumoniae* [208]. *In vitro* studies have also provided evidence linking MS and infectious agents. MS patients have activated T cells specific for MBP [209–211]. Eight pathogen-derived peptides, including epitopes from HSV, adenovirus and human papillomavirus, were identified that are able to activate MBP-specific T cell clones derived from MS patients [212]. Significantly, these peptides were found to be presented most efficiently by subtypes of HLA-DR2 that are associated with susceptibility to MS. Despite the difficulty in linking MS to any one pathogen, the amount of epidemiological evidence reported over the years shows that environmental factors play a strong role in disease development, and suggests that a cumulative lifetime exposure to certain microorganisms can influence disease development [213–216]. In addition, a recent study showed that the degree of concordance for monozygotic twins (generally reported at 40% or less) was influenced by environmental factors [217].

There are numerous rodent models of demyelination which, although not identical to the human disease, are used to study MS. The major infectious models in mice are Theiler's murine encephalomyelitis virus (TMEV), murine hepatitis virus (MHV) and Semliki Forest virus (SFV). Each has distinct immunopathological mechanisms and illustrate the various potential ways pathogens may induce MS. There are two strains of TMEV (TMEV-DA and TMEV-BeAn) which cause an initial acute grey matter disease followed by a chronic progressive demyelination in the white matter of the spinal chord known as TMEV-induced demyelinating disease (TMEV-IDD) [205,218,219]. Although the two strains induce slightly different diseases, the key characteristics of TMEV-IDD (abnormal gait and spastic hindlimb paralysis) remain the same. Intracerebral (i.c.) injection of virus leads to persistent CNS infection; the level of infectious virus is low during the chronic phase, but abundant amounts of viral RNA and viral antigen can be detected throughout the lifetime of the mouse [220–222]. The immune response is initiated by the presentation of persistent viral antigens by CNS-resident APCs to Th1-type $CD4^+$ T cells, but reactivity to myelin does not appear until after the onset of clinical symptoms (30–35 days post-infection) [223–226]. Thus, TMEV-IDD is caused by epitope spreading from viral determinants to self-myelin determinants. Interestingly, in SJL mice, reactivity appears to multiple myelin peptides starting with the immunodominant epitope and spreading at later time-points to other subdominant myelin determinants in a hierarchical manner [226,227]. In contrast to TMEV, mice inoculated with neurotropic strains of MHV will have a single major symptomatic episode (ataxia, hindlimb paresis, paralysis) from which the majority will recover [228]. CNS infection results in an influx of immune cells that for the most part will clear the virus, although virus does persist in low amounts [229]. Demyelination begins about 1 week post-infection and peaks at week 3, after which lesion repair and remyelination generally occurs [230–232]. The exact mechanism of demyelination in this model is somewhat controversial, but appears to be bystander myelin destruction by the immune response recruited initially to the CNS to control viral infection. There is no evidence of self-specific immunity in the CNS of MHV-infected mice [233]. T and B-cell deficient $RAG1^{-/-}$ mice, which were resistant to demyelination, developed histological disease after adoptive transfer with

splenoctyes from MHV-inoculated mice, which involved the recruitment of activated macrophages/microglia to sites of demyelination in the spinal cord [234]. Chemokine receptor knock-out mice ($CCR5^{-/-}$) showed reduced demyelination that correlated with reduced macrophage but not T cell infiltration into the CNS of MHV-infected mice [235]. CD4-deficient mice showed less severe disease than CD8-deficient mice [236,237]. Collectively, these studies suggest that macrophages are responsible primarily for myelin destruction in the MHV model, but that T cells are required to recruit macrophages into the CNS. Like MHV, SFV leads to a transient clinical disease [238,239]. The virus is, for the most part, cleared from the CNS by day 6 post-infection, while demyelination peaks at day 14 and then wanes [240,241]. Demyelination is not seen in nude or SCID mice, demonstrating that it is T cell-mediated [240,242]. In BALB/c mice it is thought that demyelination is due to cytolytic damage of virus-infected oligodendrocytes, although this has not been proved definitively. Depletion of $CD8^+$ T cells virtually abolished lesions of demyelination, whereas depletion of $CD4^+$ T cells did not have that effect [243]. Other studies in BALB/c mice have shown that Th1-type cytokines are involved in viral clearance but not demyelination [244,245]. In C57/Bl6 mice, molecular mimicry may also play a role in demyelination. Infected mice have MBP-reactive T cells [246], and antibodies reactive to MBP and myelin oligodendrocyte protein (MOG) [247]. Computer algorithms uncovered homology between an epitope in the SFV surface protein E2 and $MOG_{18–32}$ [248]. Mice primed with either peptide develop paralytic symptoms with histopathology resembling that of mice infected with SFV. The authors of that study concluded that the cross-reactive antibody response was mainly responsible for the demyelinating lesions.

Summary and perspectives

The immune system has evolved checks and balances to prevent the destruction of host tissue. It is perhaps not surprising that a strong immune response to an invading pathogen could disrupt this regulation and lead to autoimmunity. As outlined above, there is significant evidence suggesting that different classes of pathogens (bacteria, viruses and parasites) are involved in triggering or propagating self-reactive immune responses. However, the evidence for a definitive link for infection-induced autoimmunity is stronger for certain diseases than for others.

The argument for infection-induced pathology is much stronger for diseases associated with one or two specific pathogens than for diseases with multiple causal associations. For example, the fact that infection with *C. jejuni* is a common antecedent to GBS makes a strong argument that this disease is infection-triggered. In contrast, for diseases such as TID and MS that have been associated with dozens of pathogens, but none in particular, much more needs to be done to make a convincing case. The most compelling proof would be the disappearance of symptoms with the clearance of the infection. This is the case in Lyme disease, where treatment with antibiotics alleviates acute arthritis. However, as outlined previously in this paper, there are many ways a pathogen can cause disease even after the infection has been cleared. In these cases, epidemiological studies showing that people infected with a particular agent have an increased incidence of these diseases compared with people never infected, while not wholly definitive, would certainly strengthen the infection-induced autoimmunity argument.

In human autoimmune diseases, where direct evidence for a role for a particular pathogen is weak, it is all the more important to have supporting animal models. The strongest support comes from animal models in which infection with the agent thought to induce disease in humans causes similar symptoms in animals, as exemplified by induction of heart disease in mice infected with *T. cruzi* and CVB and arthritis in mice infected with *Bb*. In other animal models, disease can be shown to be induced by priming with a pathogen-derived antigen, thus strengthening the argument for the involvement of that pathogen in the human disease. The ability to induce heart disease in rats primed with *Streptococcal* M protein is strong evidence that *S. pyogenes* causes heart disease in humans via molecular mimicry. Although the link between *S. pyogenes* infection and neurological disorders in humans is uncertain, at best, the fact that movement and behaviour disorders can be induced in mice primed with *S. pyogenes* homogenate also lends credibility to that theory. In cases where it is uncertain whether a disease pathology is actually autoimmune (such as uveitis and myocarditis following CVB infection), animal models have played a crucial role in elucidating the potential mechanisms of disease induction.

The heterogeneity of the human population, rather than the weakness of the data, may be in play in instances where the evidence linking infection and autoimmunity is tenuous or even conflicting. It is not difficult to imagine that some people may be more susceptible to developing autoimmune disease following a particular infection than others, or that mimic peptides derived from different infectious agents may be able to trigger a particular autoimmune disease depending on the ability of the infected individual to present various epitopes in the context of their various HLA molecules. Defining the genetic markers that predispose patients to different autoimmune diseases with a suspected infectious trigger would be an important contribution to defining the underlying disease pathogenesis.

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