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Virus infection, antiviral immunity, and autoimmunity

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Summary

As a group of disorders, autoimmunity ranks as the third most prevalent cause of morbidity and mortality in the Western World. However, the etiology of most autoimmune diseases remains unknown. Although genetic linkage studies support a critical underlying role for genetics, the geographic distribution of these disorders as well as the low concordance rates in monozygotic twins suggest that a combination of other factors including environmental ones are involved. Virus infection is a primary factor that has been implicated in the initiation of autoimmune disease. Infection triggers a robust and usually well-coordinated immune response that is critical for viral clearance. However, in some instances, immune regulatory mechanisms may falter, culminating in the breakdown of self-tolerance, resulting in immune-mediated attack directed against both viral and self-antigens. Traditionally, cross-reactive T-cell recognition, known as molecular mimicry, as well as bystander T-cell activation, culminating in epitope spreading, have been the predominant mechanisms elucidated through which infection may culminate in an T-cell-mediated autoimmune response. However, other hypotheses including virus-induced decoy of the immune system also warrant discussion in regard to their potential for triggering autoimmunity. In this review, we discuss the mechanisms by which virus infection and antiviral immunity contribute to the development of autoimmunity.

Keywords

autoimmune disease; molecular mimicry; epitope spreading; bystander activation; T-cell receptor affinity; microbial superantigens

Introduction

The ability to recognize self and non-self is a pillar of the adaptive immune response, with deficiencies in these mechanisms leading to increased susceptibility to infection and cancer, or conversely, aberrant immune responses resulting in immunopathology and autoimmunity (1–4). Genome-wide association studies have identified polymorphisms in numerous genes associated with immune activation and regulation predisposing to development of autoimmune disease (5, 6); however, manifestation of autoimmunity may only occur after infection with certain pathogens (7). A precise set of pathogens as well as distinct autoimmune-associated immune responses remain to be elucidated (8). To the contrary, data suggest that autoimmunity may result from numerous immune pathways triggered by a plethora of microorganisms (9). In the case of multiple sclerosis (MS), viruses such as

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Epstein–Barr virus (EBV) and measles virus (MV) have been implicated in humans; however, a precise causal relationship between these ubiquitous viruses and MS has yet to be elucidated (10, 11). On the other hand, there are clear examples of rodent neurotropic viruses, such as Theiler's murine encephalomyelitis virus (TMEV) and mouse hepatitis virus (MHV), which infect neurons and other cells within the central nervous system (CNS) resulting in deregulation of antiviral immune mechanisms and culminate in development of autoimmunity (12–14). It remains to be confirmed whether exposure of the brain parenchyma to pathogenic infection is critical for autoimmune induction in humans, or whether infection of the periphery is a sufficient trigger. However, following TMEV infection, viral persistence in the CNS is an essential requirement for autoimmunity induction (15). Using such surrogate virus-induced rodent MS models, numerous aberrant innate and adaptive immune responses that are associated with or support the breakdown of self-tolerance and subsequent propagation of autoimmunity have been discovered. These pathways, including how pathogens circumvent or trigger certain innate immune system functions, as well as the intricate interplay between professional antigen-presenting cells (APC) and elements of the cellular immune response, are discussed in this review. Based on our experience and that of others, it is clear that infection-triggered autoimmune disease is the result of dynamic, interrelated, and non-mutually exclusive mechanisms. Understanding how viral infection results in autoimmunity must be viewed as a process that can occur through numerous simultaneous and/or sequential pathways, which depend on the nature of the pathogen as well as the genetics and the immune response of the host.

Viruses associated with CNS autoimmunity

While this review focuses on viruses associated with triggering CNS autoimmune disorders, there are a number of bacteria and other microbes that have been associated with peripheral autoimmune disease, for example the Group A Streptococcus family can cause heart, joint, or brain autoimmunity (16). A significant amount of our current understanding of how self-tolerance is overcome comes from viral models of CNS infection and other rodent models of MS.

Infection of the CNS represents the failure of critical immune surveillance mechanisms and is most common in immune-compromised individuals, often times leading to morbidity in survivors (17–19). Numerous highly pathogenic viruses, including those from the *paramyxoviridae*, *flaviviridae*, and *herpesviridae* families are known to infect cells within the brain (Table 1); however, only a handful including EBV, MV, and HTLV-1 have been linked with MS or other demyelinating disorders (10, 11, 20).

The association of EBV with MS remains controversial. EBV is a double-stranded DNA human herpes virus that primarily not only infects B cells (21) but can also infect endothelial cells (22). Approximately 95% of the general population is infected with EBV, and EBV remains latent within B cells for the life of the individual (23, 24). The incidence of MS is increased in those who are seropositive for EBV compared to those who are seronegative (25, 26). Also, there is evidence supporting a potential role for molecular mimicry in activation of myelin-specific T cells in MS patients (27). However, considering the large number of seropositive patients that do not have MS and the difficulty in isolating infected B cells from the CNS, the link is arguably weak (25, 28–30).

In addition to EBV, MS patients generally have higher titers of MV, an RNA virus (31). Unlike EBV, a cause-and-effect relationship for MV has been shown, with 1 in 1000 patients likely to suffer a myelin basic protein (MBP)-specific postinfectious encephalomyelitis (32).

While HTLV-1 is not directly associated with MS, infection can result in a very similar disease, known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/ TSP) (20). Autoimmunity and molecular mimicry are believed to play a role in the pathogenesis of HAM/TSP, as antibodies cross-reactive to both HTLV-1 and neurons have been found in HAM/TSP patients (33).

Although direct evidence linking certain CNS infections with autoimmune disease in humans is correlative and non-definitive, strong support for virus-triggered CNS autoimmunity is derived from animal models. This includes infection with TMEV, Semliki Forest virus (SFV), Sindbis virus (SV), and MHV (34). Furthermore, using such tools as tetramers and transgenic mice, it has been elegantly shown that TMEV infection of the brain, as an example, is a critical step in the initiation of full-blown T-cell-mediated autoimmunity (13, 35)

While RNA viruses have been primarily used to investigate CNS infection and the development of autoimmunity, they represent a group of diverse pathogens, which are capable of eliciting an array of innate and adaptive immune responses. Using TMEV, we and others have unearthed numerous mechanisms through which viral infection of the CNS can initiate autoimmunity (35–37). TMEV is a single strand RNA virus of the picornovirdae family. A number of strains of TMEV have been characterized and differ in infectivity and pathogenicity. The GDVII strain is extremely neurovirulent and causes acute encephalitis typically resulting in mortality (38). The BeAn and DA strains, however, are able to persist in the CNS after their initial acute encephalitis and cause chronic immune-mediated demyelinating disease (39).

The ability of TMEV to chronically persist is evidently required for the eventual induction of CNS autoimmunity. A natural murine pathogen, TMEV is transmitted via the fecal-oral route (40). In laboratory models, the virus is usually injected into the CNS via intracranial injection. In many strains of mice, including C57BL/6, the innate immune and adaptive immune responses adequately resolve the infection with no lasting sequelae. However, in other strains that are deficient in certain elements of the immune response, such as SJL/J mice that lack natural killer dendritic cells (E. M. L. Chastain, D. R. Getts, S. D. Miller, unpublished observation), the virus establishes a long-term persistent infection within the CNS. In such situations, the infection leads to a chronic antiviral immune response, which at some point moves from a centrally focused antiviral response, to one that also targets myelinated axons. At this point, a fulminant autoimmune disorder characterized by CNS-infiltrating myelin specific $CD4^+$ T cells develops and is referred to as TMEV-induced demyelinating disease (TMEV-IDD).

In addition to TMEV, the positive-stranded RNA alphavirus SFV results in acute encephalitic disease that lasts 7 days, after which time the virus is cleared. Interestingly, a week to several weeks later, cytotoxic $CD8^+$ T cells as well as antibodies reactive to MBP and MOG epitopes are found in the brain and periphery. Together these cause CNS demyelination that is observed clinically with symptoms such as aberrant gate, reduced activity, and even death (41, 42). Similarly to SFV virus, in which autoimmunity appears secondary to the primary infectious process, SV infection results in rapid paralysis within 6 days post infection. In the case of this positive-stranded RNA alphavirus, the initial immune responses are specific for SV; however, auto-specific immunity arises via epitope spreading (34).

JEV is a positive-sense strand RNA flavivirus that is closely related to WNV and St. Louis encephalitis virus. JEV spreads to the CNS after amplification in peripheral lymph nodes and can infect both neurons and astrocytes. Clinical symptoms in mice occur within the first

week of infection and results in abnormal gait and hind limb paralysis (43, 44). Autoimmunity may contribute to disease progression as both MPB-specific antibodies and T cells were observed in infected mice (43). In addition to experimental models of JEV infection, clinical myasthenia gravis development has been described in patients previously exposed to WNV. Together the data show that there are a number of viruses that may increase, if not directly trigger autoimmunity in humans.

General pathogenesis of viral infection of the brain

Although plastic and physiologically well supported, the neuron, the central player in the organization of the CNS, is not readily replenished after development early in life (45). Thus, it is not surprising that infection of CNS, especially the brain, represents a potentially life-threatening event. The outcome of CNS infection is dependent on the interaction of the immune system, the nervous system, and the invading pathogen. A battle driven by the primal evolutionary need for survival of both virus and host, ultimately determines the fate of the challenged host. In many cases, this interaction has been optimized over time by coevolution of virus and host, resulting in the survival of both at the population level. However, in individual cases, the outcome may be dire, with, at best survival with severe neurological sequelae, and at worst, significant neurochemical disturbance leading to coma and death (46, 47). Historically, the CNS has been described as an immune privileged organ; however, it is now well known that the brain is more than capable of eliciting an internal immune response, as well as calling upon peripheral immune elements as needed.

The development of autoimmunity as result of CNS infection requires a significant number of events to occur (Fig. 1). The mechanisms by which viruses gain access to the CNS, directly/indirectly cause cell damage and death, activate the immune response, and initiate autoreactive responses are discussed here.

Viral access into the CNS

Not only is the CNS encased inside the skull, it also lies behind a sophisticated blood brain barrier (BBB). The BBB is a unique endothelial barrier that is comprised of specialized tight junctions between endothelial cells, which limit the permeability of the membrane (48, 49). In addition, on the parenchymal side, podocytes, and astrocytic foot processes surround the BBB. Together these factors form a practically impenetrable physical wall between the circulatory system and the CNS (50). Excluding the potential for direct head trauma, viruses have adapted to overcome this barrier through numerous mechanisms including the following: (i) direct penetration across the BBB; (ii) the ‘Trojan Horse’ method; (iii) axonal transport via peripheral nerves; and (iv) access via the ‘leaky’ choroid plexus responsible for cerebrospinal fluid production.

Penetration directly across the BBB

Infection of the endothelial cells that line the BBB represents a direct path into the brain and is the primary path for viruses capable of generating significant viremia. For example, JEV, a lytic virus, has been observed in the endothelium of postmortem human brain tissue (51). Experimentally, intravenous infection of mice with JEV results in endothelial infection and subsequent disruption of the BBB (44). Also, EBV has been shown, *in vitro*, to infect brain microvascular endothelial cells (HBMECs) (22). Importantly, infection of HBMECs resulted in increased leukocyte adherence to endothelial monolayers, a process argued to be mediated by increased expression of the adhesion molecule, intercellular adhesion molecule-1 (ICAM-1), and the chemokine CCL5 by the infected cells (22). The ability for viral infection to increase ICAM-1 expression after BBB endothelial infection has also been observed with SFV (52). Interestingly, even non-neurotropic viruses, such as HTLV-1, have

been demonstrated to directly infect human endothelial cells (53, 54). In the case of HTLV-1, it is presumed that endothelial infection is a result of contact with infected T cells. Romero and colleagues (55) observed this phenomenon *in vitro*, using differentially fluorescently labeled lymphocytes and endothelial cells. They observed transfer of membrane from the infected lymphocytes, indicative of virus budding, thus this may be a secondary route of infection for HTLV-1 into the CNS (55).

The Trojan horse

Similar to the Greeks, who in the tale hide within a large wooden horse to enter the city of Troy, viral subterfuge may include hiding in mobile immune cells, such as activated T cells, which migrate into the CNS as a consequence of their normal role in immune surveillance. Human immunodeficiency virus (HIV) is often described as the prototypical Trojan horse virus. Through its infection of T cells and macrophages, it can be transported into the brain and go on to infect cells of the CNS resulting in HIV encephalitis and dementia. Another virus that may enter the CNS via infected leukocytes is EBV (56). Although, it must be noted that isolation of EBV-infected B cells from the CNS is a rare event in MS patients, it is still possible to envision that B cells harboring the virus enter the CNS potentially contributing to disease initiation or progression.

Axonal transport via peripheral nerves

Potentially the most common pathway for CNS access, retrograde axonal viral transport, has been described for viruses such as MV, TMEV, and WNV (57–59). To support their cell bodies and processes, neurons have a complex system of transport. Retrograde transport employs dynein motors, while anterograde transport uses kinesin motors (60). Not surprisingly, viruses may hijack motor and/or sensory neurons as a means to enter the CNS. In rodent models, viruses that are inoculated via the olfactory route or the mouth may infect olfactory epithelium or the tongue and enter the brain along the neuronal tracts serving both bulb regions (59, 61, 62) (D. R. Getts, S. D. Miller, N. J. King, unpublished observation). It is presumed that viral budding occurs within the synapse, with receptors for virus expressed within the synaptic region. In the case of MV, CD46 acts as the receptor through which CNS propagation is mediated (31, 63).

TMEV enters the brain via axonal transport after natural and experimental inoculation (59). Footpad inoculation with the non-persistent strain of TMEV, GDVII, results in extremely efficient infection of the sciatic nerve and spinal cord (59, 64). Infection with this highly neurotropic strain via the intramuscular, intravenous, intratongue or intraperitoneal routes also results in spinal cord infection and limb paralysis in 80–100% of animals (64).

Across the choroid plexus

Viruses including mumps, HIV, and HTLV-1 are able to gain entry into the CNS by productively infecting choroid plexus epithelium (65–69). The choroid plexus is a highly vascularized fenestrated epithelial structure that is located within the ventricles, forming a barrier between the blood and the cerebrospinal fluid (CSF). The epithelium of the choroid plexus is responsible for the production of CSF and thus is naturally permeable allowing for the transport of blood components required for CSF production. These factors may allow for viral entry across the choroid plexus, into CSF. From there, the virus is able to infect the ependymal cells lining the ventricles and to invade the underlying CNS tissue (reviewed in 50).

Defending against CNS infection

Once viruses have gained access to the CNS, they may use different mechanisms to spread to new host cells. In the case of TMEV, viral RNA was found in the absence of axonal degradation, suggesting that the non-enveloped virus is capable of spreading via a cell-to-cell transfer method (59). MV also spreads in a cell contact-dependent manner. It does not bud from neurons, but is transmitted via trans-synaptic spread (70). The entry and spread of viruses within the CNS requires a multitude of innate and adaptive immune responses to ensure host survival. However, during the process through which viral eradication or latency is induced, significant tissue damage may occur. This may result directly from virus-mediated host cell lysis or indirectly from bystander damage due to the pro-inflammatory products of host antiviral immune responses. Both situations, virus-mediated lysis as well as immune-mediated pathology, may potentiate viral spread to non-infected cells/tissues as well as promote further activation of the immune system against self-antigens by serving an adjuvant function, respectively (50, 71).

Direct Viral CNS damage

Although cell death can play an important role in restricting the replication and transmission of some viruses, for others the death of host cells is critical for the effective spread of progeny to new targets (reviewed in 72). In the CNS, damage and loss of vital and largely irreplaceable resident cells can have permanent and severe consequences, including the development of seizures, paralysis, and multiorgan failure. Furthermore, excessive cell damage and death likely contributes to the initiation of self-reactive responses against CNS antigens that progresses into autoimmune disease (73).

Cell death can occur through two main pathways. Apoptosis is the process by which cells undergo programmed self-destruction in a systematic and genetically controlled manner, typically in response to stress, damage or infection (reviewed in 74). Cellular contents are contained in apoptotic bodies that are readily engulfed by phagocytic cells. Regulation of apoptosis is critical for the pathogenesis of a number of viral infections. Although some viruses actively prevent the induction of apoptosis to allow for the generation of large numbers of progeny or to maintain latency within host cells, others deliberately induce apoptosis in late stages of infection to promote the dissemination of progeny and to limit the induction of the host immune response (72). In comparison, necrosis is the process of cell death that occurs independently of the apoptotic pathway, in which cell membrane integrity is lost, resulting in the uncontrolled release of cellular contents into the extracellular space (reviewed in 75). Necrosis differs from apoptosis in that it often causes significant damage to surrounding tissues and induces inflammation.

Whether a virus inhibits or induces apoptotic or necrotic pathways in infected cells is often dependent on the type of host cell. For example, Varicella zoster virus induces apoptosis in most cell types, including human epithelial cells, fibroblasts, and peripheral blood mononuclear cells; however, neurons are protected to allow for viral latency (76–78). In comparison, the induction of apoptosis and necrosis in infected neurons is characteristic of SV and TMEV-DA infection of the murine CNS and may be important for neurovirulence (79–84). Furthermore, the mechanism of SV-induced cell death depends on the type, location, and maturity of the infected neuron (79, 80, 85).

Immunopathology resulting from viral infection

It is clear that viruses that are capable of directly infecting neurons are positioned to cause significant neuronal dysfunction and even death. However, the other primary cause of

damage in the CNS during viral infection results from both innate and adaptive antiviral immune responses.

The brain is equipped with numerous receptors that monitor the extracellular and intracellular milieu for potential invaders. These innate immune receptors are important for defense against invading pathogens and are often referred as pattern recognition receptors (PRRs), which recognize various pathogen-associated molecular patterns and include Toll-like receptors (TLRs), nucleotide-binding and oligomerization domain (NOD)-like receptors, (RIG-I)-like helicases, and a subset of C-type lectin receptors (reviewed in 86). By triggering PRRs, stimulating early cytokine responses by the innate immune system and enhancing 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 activation and effector function. Within this highly inflammatory environment, regulation is critical, with the failure of immune checkpoint regulation potentially resulting in bystander tissue damage and even death (87).

The ability for pro-inflammatory cytokines that are produced as part of the antiviral response to cause neuronal cell dysfunction and potentially death may play a role in the early stages of autoimmunity. This is demonstrated by the infection of transgenic animals that are deficient in specific factors. For example, animals lacking the proinflammatory cytokine IL-1β are resistant to fatal neurovirulent SV encephalitis (88). Also, IL-6-deficient mice showed significantly reduced seizures in TMEV-DA encephalitis (89). Mice lacking IL-12 show reduced clinical scores in MHV (JHM virus) encephalitis (90). Also, animals that lack expression of nitric oxide synthase-2, the enzyme that catalyzes nitric oxide (NO) production, show improved outcomes and reduced neuronal death during MHV encephalitis (91). Timing has also been shown to be important. Long-term aminoguanidine-mediated neutralization of NO in WNV-infected animals resulted in increased mortality (92); however, temporal aminoguanidine treatment at the time of acute disease symptom development promoted survival (92). Soluble mediators can mediate CNS pathology through numerous mechanisms. These include the induction of seizures and neuronal dysfunction (61, 93) as well as promoting the influx of leukocytes into the brain. Many leukocyte subsets have been shown to directly contribute to neuronal damage and death and thus play an immunopathogenic role in disease (36, 61, 92) For example, studies using anti-CCL2 antibody or mice deficient in the chemokine receptors CCR2 and CCR5, critical for inflammatory monocyte trafficking to the CNS, demonstrate improved outcomes for both TMEV (15, 94), MHV encephalitides (95), and WNV (61). Also, depletion of $CD4^+$ T cells but not $CD8^+$ T cells significantly reduced the incidence and severity of demyelination in TMEV-infected animals (36). In comparison, the presence of either $CD4^+$ or $CD8^+$ T cells was sufficient to initiate demyelination in T-cell-deficient MHV-infected mice (96).

Mechanisms of virus-induced autoimmunity

Excluding pathogenic mechanisms driving immune pathology that do not have an antigen-specific component, there are several postulated mechanisms by which pathogenic infections can trigger autoimmune disease, most of which are supported by substantial evidence from animal models.

Molecular mimicry

Fujinami and Oldstone (97, 98) originally conceptualized the potential for T-cell receptors (TCRs) specific for certain microbial epitopes to potentially cross-react with self-antigens that have similar molecular patterns or mimics. Subsequent investigations have shown that TCR antigen recognition is a highly degenerative process, in turn suggesting that there is a high probability that T cells specific for certain foreign antigens may also be cross-reactive

for self-antigens. The TCR structure allows for cross-recognition of an array of different unrelated peptide sequences bound to distinct major histocompatibility complex (MHC) molecules, when the complexes share similar shape and overall charge distribution (5, 27, 99–103). This inherent TCR flexibility is important for many homeostatic immunologic processes, such as thymic selection and the generation of a comprehensive TCR repertoire capable of recognizing viral-derived peptides. However, certain viral peptides that share some degree of homology with self-peptides are capable of stimulating autoreactive T cells *in vitro* (27).

Molecular mimicry is a predominate feature of autoimmune development in numerous animal models. These include TMEV-IDD (104), *Acanthamoeba castellanii*-induced experimental autoimmune encephalomyelitis (EAE) in SJL mice (105, 106), herpes simplex virus (HSV) stromal keratitis, in which HSV infection leads to T cell-mediated blindness in both humans and mice (107), diabetes model(s) (108), autoimmune demyelinating disease and SFV infection (109), autoimmune myocarditis associated with Coxsackie virus infection (110), and others (111). These viral models as well as a number of less physiological models have been used to help define the conditions through which autoimmunity may arise through infection-induced molecular mimicry (Table 1). Less physiological models include the transgenic expression of microbial proteins/epitopes in particular tissues and organs. Of course, thymic and peripheral immune regulatory mechanisms prevent autoimmunity under homeostatic conditions; however, infection with the microbe containing the self-protein is capable of breaking-self-tolerance and triggering autoimmunity in the organ with the targeted transgene expression (112–115). Furthermore, additional forced expression of the transgenic viral/ self protein within the thymus to ensure negative selection of high affinity transgenic protein-specific T cells is unable to prevent autoimmunity development caused by such infection (114). Together, these data show that even T cells with low affinity for a self-antigen, as would be the case for many self-antigen-specific responses, can be activated through molecular mimicry by microbial antigens and cause autoimmune disease.

In the TMEV-IDD model of MS, the onset and severity of autoimmunity is significantly enhanced in rodents infected with TMEV that has been engineered to express the immuno-dominant myelin proteolipid protein (PLP) 139–151 epitope ($PLP_{139–151}$) (116). In addition, a number of other viral-derived peptides have been shown to mimic $PLP_{139–151}$ (117). For example, TMEV engineered to express peptides from murine hepatitis virus (with TMEV and MHV only sharing 3/13 amino acids), induces a severe demyelinating disease, resembling that caused by infection with TMEV engineered to express $PLP_{139–151}$ itself (116, 118). Expanding into bacterially derived peptides, a number of human $MBP_{85–99}$ epitope mimics have been shown capable of inducing demyelinating disease in rodents that express both human MHC II as well as the human $MBP_{85–99}$-specific TCR (119).

While this review focuses on CNS autoimmunity, autoimmune diseases targeting other organs have also been shown to be a result of molecular mimicry. For example, expression of the LCMV nucleoprotein (NP) under the rat insulin promoter (RIP) induces molecular mimicry-mediated Type 1 diabetes in rodents infected with Pichinde virus engineered to express LCMV NP (120). Interestingly, patients with certain autoimmune diseases also show higher frequencies and/or activation states of self-reactive lymphocytes (121–125). Receptor analysis showed clonal expansion of both T and B cells in CNS tissue and CSF of MS, indicating clonal reactivity to a restricted number of disease-relevant antigens (126–128) with longitudinal studies MS patient studies supporting the persistence of individual myelin-specific T-cell clones for several years (129–131), highlighting the continued memory response and/or ongoing auto-antigen exposure at least for a subset of myelin-reactive T cells in MS. These memory responses may reflect autoimmune disease associated polyspecific T cells capable of recognizing self as well as virus antigens. This is supported,

at least in part, by the fact that high viral loads observed during symptomatic primary EBV infection in infectious mononucleosis are associated with an increased risk of developing MS (132, 133). Generally speaking, however, the EBV levels in MS patient peripheral blood leukocytes are similar to those found in normal virus carriers (134). Furthermore, EBV-positive MS patients do not have an elevated rate of EBV-induced B-cell transformation or a difference in their ability to control outgrowth of EBV-infected B cells *in vitro* (135). While this argues against an increased viral replication or impaired immune control of chronic EBV infection in MS, these patients often do have expansions of T cells specific for the EBV-encoded nuclear antigen 1 (EBNA1), the most consistently recognized EBV-derived $CD4^+$ T-cell antigen in healthy virus carriers. Importantly, EBNA1-specific T cells have a higher affinity to myelin antigens responding to such antigen more frequently than other non-MS related virus antigens (135). When stimulated with myelin, cross-reactive T cells produce IFN-γ but differ from EBNA1-monospecific cells in their capability to produce IL-2. This is indicative of polyfunctional T cells, which are thought to be less susceptible to exhaustion or activation-induced cell death (136). Consistent with these observations, a more extensive priming of polyfunctional cross-reactive T cells during symptomatic primary EBV infection with high viral loads 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 to MS.

Bystander activation of autoreactive cells

An over-aberrant antiviral immune response may result in the liberation of self-antigen(s) not usually exposed to the immune system. Bystander T-cell activation may result from these antigens being taken up, processed, and presented by local and inflammatory monocyte-derived APCs to autoreactive T cells (61, 92, 137–140). T cells activated in a bystander fashion are thought to have low affinity for self-antigen, with subsequent activation requiring some form of immunological adjuvant, with viral infection a primary candidate (139).

Related to the concept of bystander activation, epitope spreading is a situation whereby an immune response, triggered by a number of stimuli including viral infection, triggers the release of self-antigen(s) and *de novo* activation of autoreactive responses, which then spread to include responses directed against additional self epitopes on the same protein (intramolecular spreading) and/or different proteins (intermolecular spreading). In the context of antiviral immunity, activation of a broad set of viral-specific T cells is potentially a helpful event, however, destruction of host tissue and autoimmunity may result should the spread happen to include epitopes expressed by host tissues. We and others have shown that epitope spreading occurs in EAE, a non-infectious model of MS (141, 142), as well as in TMEV-IDD (143–146) and in the non-obese diabetic (NOD) mouse model of type 1 diabetes (147, 148). In these rodent models, epitope spreading occurs in a hierarchical, orderly and directed fashion, with immunodominant TCR epitopes activated prior to the activation of T cells expressing less dominant epitopes.

Bystander activation may also be achieved by microbial derived superantigens, which are presented by APCs in the context of MHC II to Vβ TCR-expressing T cells. The poly-clonal population of T cells activated by super-antigen has the potential to contain a T cells specific for a self-antigen (149). Considering the ability of human T cells to express human leukocyte antigen, this mechanism is likely to be relevant in the context of human autoimmunity. Furthermore, superantigens have been shown to exacerbate and/or alter the pathogenesis of rodent autoimmune diseases such as EAE, arthritis, and inflammatory bowel disease (150–152) (Table 1). Collectively, these data indicate that superantigens can trigger

bystander activation culminating in the development of autoimmunity or, at minimum, exacerbate autoimmune symptoms.

Other infection-related autoimmunity hypotheses

When considering the large number of viruses and the multiple mechanisms they employ to evade or subvert the immune system, it is not surprising that mechanisms other than molecular mimicry and bystander activation may exist for triggering autoimmune disease. One example may include the ability of viruses to immortalize autoreactive effector cells or autoantigen-presenting cells (153, 154). This has been observed in EBV-infected memory B cells, whereby non-translated viral RNAs increase resistance to cell death (155). Together these mechanisms may promote the survival of autoreactive B cells, potentially including those found in the submeningeal aggregates of MS brains (56).

An important consideration is the fact that in most cases viruses and other microbes can infect a host without triggering any clear clinical symptoms. This has further hampered direct linkage of infection with specific autoimmune disease development. This fact suggests that consideration of other viral infections and potential pathogen-host interactions should also be taken into account when investigating infection-induced autoimmunity. One potential emerging pathogen may include WNV (57). WNV employs some paradoxical immune evasion strategies that may consequently trigger self-reactive bystander T-cell activation. While WNV replicates most efficiently in dividing cells, it paradoxically increases MHC expression as well as expression of adhesion molecules like ICAM-1 in quiescent non-dividing cells (57). This is thereby proposed to result in increased immune focus on low virus yielding G_0 cells rather than those capable of generating high viral titers. Therefore, along the lines invoked for EBV infection, this raises the possibility that WNV infection generates polyspecific T cells, by increasing the avidity of interaction between T cells and infected cells via increased MHC expression and that infection activates an array of T-cell clones that range from those with high affinity for MHC/virus peptide to those with significant cross-reactivity for self (156, 157). Recently, a potential link between WNV infection and subsequent development of myasthenia gravis was described (158). In this report, disease development occurred several months after disease resolution, highlighting an important point that autoimmunity development may require significant time to evolve, becoming clinically evident months if not years after the triggering pathogenic infection has been resolved. Together these findings not only highlight the array of potential mechanisms through which infection may trigger the breakdown of self-tolerance, but also the difficulty associated with attempting to identify viruses capable of triggering autoimmunity.

How do these mechanisms lead to autoimmune disease?

The precise reason for the existence of autoreactive adaptive immune cells in the periphery remains unexplained. They may be the result of a lack of cognate self-antigen expression in the thymus during T-cell development, becoming evident only after viral infection. Alternatively, strong anti-microbial T-cell epitopes may not only share low affinity for certain microbial antigens but also share low affinity for self-antigens, and as such may avoid thymic deletion. Notwithstanding the presence of autoreactive T cells in the periphery, the development of autoimmunity is not certain. In a number of rodent models, infection is required for overt autoimmunity to be triggered. Indeed this has been shown elegantly using TMEV and $PLP_{139–151}$ mimics. While both infection with TMEV and parallel immunization with $PLP_{139–151}$ peptide in complete Freund's adjuvant rapidly induce CNS demy-elinating disease, immunization with $PLP_{139–151}$ mimics alone without infection does not induce disease, even though T cells in these mice are highly responsive to $PLP_{139–151}$ (117, 118, 138). Presumably, TMEV infection results in the expression of critical factors including chemokines and costimulatory and adhesion molecules that are necessary for the induction

and migration of pathogenic Th1 and Th17 autoreactive T cells into the CNS (159). The nature of a pathogen clearly has a significant impact on the development of autoimmunity; in fact, it may enhance or may even inhibit the activation of autoreactive T cells. In the case of molecular mimicry, virus-encoded mimics may also be perceived by the immune system as altered peptide ligands, and depending on the infection, may result in the induction of T-cell tolerance instead of triggering autoimmunity (159).

An important consideration may also include the exposure of the host to previous pathogens and the impact that they have on circulating autoreactive T cells. For example, the development of autoimmunity in RIP-LCMV-NP mice could not be elicited by infection with the mimic-encoding Pichin-de virus; however, this virus was capable of accelerating disease in animals that had been previously infected with LCMV (120). This finding suggests that the stimulating capability of self-mimicking viruses may only effectively induce autoimmunity if self-reactive T cells have already been activated (160). The affinity of TCRs for various self-peptide/ MHC complexes may also play 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 (161). In RIP-LCMV-NP mice, whether or not the self-antigen was expressed in the thymus during development (thus affecting T-cell affinity) had a significant impact on the speed with which autoimmune disease developed (114). TLR engagement alone can be sufficient for the development of autoimmune disease if autoreactive T cells are of high enough affinity for self-antigen (114, 162). However, since most T cells will have low affinity for self, 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 dependent on the presence of autoreactive T cells. However, whether overt disease actually occurs may depend on various other coincident events, including the number, avidity, and affinity of autoreactive T cells 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 apparent that these events do not necessarily need to happen at the same time or in the same place to elicit autoimmune disease.

Conclusions

Inherent genetic susceptibility plays a major role in determining susceptibility to development autoimmune diseases; however, epidemiological and animal studies have clearly shown that infection is likely to be an additional environmental factor required for autoimmunity. There is a cadre of potential pathogens that may trigger autoimmunity. Furthermore, there a numerous non-mutually exclusive immunological mechanisms that may result in the breakdown of immune tolerance. These include bystander activation, epitope spreading, molecular mimicry, and even immune decoy. The precise contribution of each of these mechanisms to the development of autoimmunity is not known and is likely to hinge on the underlying viral trigger. This review highlights the importance for further investigation into the mechanisms associated with virus-host interactions and the mechanisms that may result in the breakdown of self-tolerance.

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References

1. Graus F, Dalmau J. CNS autoimmunity: new findings and pending issues. Lancet Neurol. 2012; 11:17–19. [PubMed: 22172617]

2. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010; 464:1293–1300. [PubMed: 20432533]
3. Sollid LM, Jabri B. Triggers and drivers of autoimmunity: lessons from coeliac disease. Nat Rev Immunol. 2013; 13:294–302. [PubMed: 23493116]
4. Goverman J. Autoimmune T cell responses in the central nervous system. Nat Rev Immunol. 2009; 9:393–407. [PubMed: 19444307]
5. Gregersen PK, Behrens TW. Genetics of autoimmune diseases–disorders of immune homeostasis. Nat Rev Genet. 2006; 7:917–928. [PubMed: 17139323]
6. Zhernakova A, van Diemen CC, Wijmenga C. Detecting shared pathogenesis from the shared genetics of immune-related diseases. Nat Rev Genet. 2009; 10:43–55. [PubMed: 19092835]
7. Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity–friends or foes? Trends Immunol. 2009; 30:409–414. [PubMed: 19643667]
8. Sfriso P, et al. Infections and autoimmunity: the multifaceted relationship. J Leukoc Biol. 2010; 87:385–395. [PubMed: 20015961]
9. Pollard KM, Kono DH. Requirements for innate immune pathways in environmentally induced autoimmunity. BMC Med. 2013; 11:100. [PubMed: 23557436]
10. Lunemann JD. Epstein-Barr virus in multiple sclerosis: a continuing conundrum. Neurology. 2012; 78:11–12. [PubMed: 22156986]
11. Tucker WG, Andrew Paskauskas R. The MSMV hypothesis: measles virus and multiple sclerosis, etiology and treatment. Med Hypotheses. 2008; 71:682–689. [PubMed: 18703291]
12. Chastain EM, Duncan DS, Rodgers JM, Miller SD. The role of antigen presenting cells in multiple sclerosis. Biochim Biophys Acta. 2011; 1812:265–274. [PubMed: 20637861]
13. Chastain EM, Miller SD. Molecular mimicry as an inducing trigger for CNS autoimmune demyelinating disease. Immunol Rev. 2012; 245:227–238. [PubMed: 22168423]
14. Das Sarma J, et al. Demyelinating and nondemyelinating strains of mouse hepatitis virus differ in their neural cell tropism. J Virol. 2008; 82:5519–5526. [PubMed: 18385249]
15. Christophi GP, Hudson CA, Panos M, Gruber RC, Massa PT. Modulation of macrophage infiltration and inflammatory activity by the phosphatase SHP-1 in virus- induced demyelinating disease. J Virol. 2009; 83:522–539. [PubMed: 18987138]
16. Dale RC. Post-streptococcal autoimmune disorders of the central nervous system. Dev Med Child Neurol. 2005; 47:785–791. [PubMed: 16225745]
17. McArthur JC. HIV dementia: an evolving disease. J Neuroimmunol. 2004; 157:3–10. [PubMed: 15579274]
18. Ito Y, et al. Exacerbation of herpes simplex encephalitis after successful treatment with acyclovir. Clin Infect Dis. 2000; 30:185–187. [PubMed: 10619751]
19. Utley TF, Ogden JA, Gibb A, McGrath N, Anderson NE. The long-term neuropsychological outcome of herpes simplex encephalitis in a series of unselected survivors. Neuropsychiatry Neuropsychol Behav Neurol. 1997; 10:180–189. [PubMed: 9297711]
20. Oger J. HTLV-1 infection and the viral etiology of multiple sclerosis. J Neurol Sci. 2007; 262:100–104. [PubMed: 17688886]
21. Faulkner GC, Krajewski AS, Crawford DH. The ins and outs of EBV infection. Trends Microbiol. 2000; 8:185–189. [PubMed: 10754578]
22. Casiraghi C, Dorovini-Zis K, Horwitz MS. Epstein-Barr virus infection of human brain microvessel endothelial cells: a novel role in multiple sclerosis. J Neuroimmunol. 2011; 230:173–177. [PubMed: 20826008]
23. Williams H, Crawford DH. Epstein-Barr virus: the impact of scientific advances on clinical practice. Blood. 2006; 107:862–869. [PubMed: 16234359]
24. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer. 2004; 4:757–768. [PubMed: 15510157]
25. Owens GP, Bennett JL. Trigger, pathogen, or bystander: the complex nexus linking Epstein-Barr virus and multiple sclerosis. Mult Scler. 2012; 18:1204–1208. [PubMed: 22685062]
26. Ascherio A, Munch M. Epstein-Barr virus and multiple sclerosis. Epidemiology. 2000; 11:220–224. [PubMed: 11021623]

27. Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell. 1995; 80:695–705. [PubMed: 7534214]
28. Willis SN, et al. Epstein-Barr virus infection is not a characteristic feature of multiple sclerosis brain. Brain. 2009; 132:3318–3328. [PubMed: 19638446]
29. Peferoen LA, et al. Epstein Barr virus is not a characteristic feature in the central nervous system in established multiple sclerosis. Brain. 2010; 133:e137. [PubMed: 19917644]
30. Sargsyan SA, et al. Absence of Epstein-Barr virus in the brain and CSF of patients with multiple sclerosis. Neurology. 2010; 74:1127–1135. [PubMed: 20220124]
31. Ahlgren C, Oden A, Bergstrom T, Lycke J. Serum and CSF measles antibody levels increase over time in patients with multiple sclerosis or clinically isolated syndrome. J Neuroimmunol. 2012; 247:70–74. [PubMed: 22498098]
32. Young VA, Rall GF. Making it to the synapse: measles virus spread in and among neurons. Curr Top Microbiol Immunol. 2009; 330:3–30. [PubMed: 19203102]
33. Lee SM, Morcos Y, Jang H, Stuart JM, Levin MC. HTLV-1 induced molecular mimicry in neurological disease. Curr Top Microbiol Immunol. 2005; 296:125–136. [PubMed: 16323422]
34. Mecha M, Carrillo-Salinas FJ, Mestre L, Feliu A, Guaza C. Viral models of multiple sclerosis: Neurodegeneration and demyelination in mice infected with Theiler's virus. Prog Neurobiol. 2013; 101–102:46–64.
35. McMahon EJ, Bailey SL, Castenada CV, Waldner H, Miller SD. Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis. Nat Med. 2005; 11:335–339. [PubMed: 15735651]
36. Gerety SJ, et al. Class II-restricted T cell responses in Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease. V. Mapping of a dominant immunopathologic VP2 T cell epitope in susceptible SJL/J mice. J Immunol. 1994; 152:908–918. [PubMed: 7904291]
37. Olson JK, Croxford JL, Miller SD. Virus-induced autoimmunity: Potential role of viruses in initiation, perpetuation, and progression of T cell-mediated autoimmune diseases. Viral Immunol. 2001; 14:227–250. [PubMed: 11572634]
38. Reddi HV, Kumar AS, Kung AY, Kallio PD, Schlitt BP, Lipton HL. Heparan sulfate-independent infection attenuates high-neurovirulence GDVII virus-induced encephalitis. J Virol. 2004; 78:8909–8916. [PubMed: 15280499]
39. Zoecklein LJ, et al. Direct comparison of demyelinating disease induced by the Daniel's strain and BeAn strain of Theiler's murine encephalomyelitis virus. Brain Pathol. 2003; 13:291–308. [PubMed: 12946019]
40. Kang BS, Yahikozawa H, Koh CS, Kim BS. Oral administration of live virus protects susceptible mice from developing Theiler's virus-induced demyelinating disease. Virology. 2007; 366:185–196. [PubMed: 17507073]
41. Mokhtarian F, Huan CM, Roman C, Raine CS. Semliki Forest virus-induced demyelination and remyelination–involvement of B cells and anti-myelin antibodies. J Neuroimmunol. 2003; 137:19–31. [PubMed: 12667644]
42. Subak-Sharpe I, Dyson H, Fazakerley J. In vivo depletion of CD8+ T cells prevents lesions of demyelination in Semliki Forest virus infection. J Virol. 1993; 67:7629–7633. [PubMed: 7901429]
43. Tseng YF, Wang CC, Liao SK, Chuang CK, Chen WJ. Autoimmunity-related demyelination in infection by Japanese encephalitis virus. J Biomed Sci. 2011; 18:20. [PubMed: 21356046]
44. Liu TH, Liang LC, Wang CC, Liu HC, Chen WJ. The blood-brain barrier in the cerebrum is the initial site for the Japanese encephalitis virus entering the central nervous system. J Neurovirol. 2008; 14:514–521. [PubMed: 19023687]
45. Horner PJ, Gage FH. Regenerating the damaged central nervous system. Nature. 2000; 407:963–970. [PubMed: 11069169]
46. Chaudhuri A, Kennedy PG. Diagnosis and treatment of viral encephalitis. Postgrad Med J. 2002; 78:575–583. [PubMed: 12415078]
47. Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. Lancet. 2002; 359:507–513. [PubMed: 11853816]

48. Engelhardt B, Sorokin L. The blood-brain and the blood-cerebrospinal fluid barriers: function and dysfunction. Semin Immunopathol. 2009; 31:497–511. [PubMed: 19779720]
49. Muldoon LL, et al. Immunologic privilege in the central nervous system and the blood-brain barrier. J Cereb Blood Flow Metab. 2013; 33:13–21. [PubMed: 23072749]
50. Zhang JR, Tuomanen E. Molecular and cellular mechanisms for microbial entry into the CNS. J Neurovirol. 1999; 5:591–603. [PubMed: 10602400]
51. German AC, et al. A preliminary neuropathological study of Japanese encephalitis in humans and a mouse model. Trans R Soc Trop Med Hyg. 2006; 100:1135–1145. [PubMed: 16814333]
52. Soilu-Hanninen M, Eralinna JP, Hukkanen V, Roytta M, Salmi AA, Salonen R. Semliki Forest virus infects mouse brain endothelial cells and causes blood-brain barrier damage. J Virol. 1994; 68:6291–6298. [PubMed: 7916058]
53. Ho DD, Rota TR, Hirsch MS. Infection of human endothelial cells by human T-lymphotropic virus type I. Proc Natl Acad Sci USA. 1984; 81:7588–7590. [PubMed: 6095308]
54. Hoxie JA, Matthews DM, Cines DB. Infection of human endothelial cells by human T-cell leukemia virus type I. Proc Natl Acad Sci USA. 1984; 81:7591–7595. [PubMed: 6095309]
55. Romero IA, et al. Interactions between brain endothelial cells and human T-cell leukemia virus type 1-infected lymphocytes: mechanisms of viral entry into the central nervous system. J Virol. 2000; 74:6021–6030. [PubMed: 10846084]
56. Serafini B, et al. Dysregulated Epstein-Barr virus infection in the multiple sclerosis brain. J Exp Med. 2007; 204:2899–2912. [PubMed: 17984305]
57. King NJ, Getts DR, Getts MT, Rana S, Shrestha B, Kesson AM. Immunopathology of flavivirus infections. Immunol Cell Biol. 2007; 85:33–42. [PubMed: 17146465]
58. Ehrengruber MU, Ehler E, Billeter MA, Naim HY. Measles virus spreads in rat hippocampal neurons by cell-to-cell contact and in a polarized fashion. J Virol. 2002; 76:5720–5728. [PubMed: 11992000]
59. Martinat C, Jarousse N, Prevost MC, Brahic M. The GDVII strain of Theiler's virus spreads via axonal transport. J Virol. 1999; 73:6093–6098. [PubMed: 10364364]
60. Hsieh MJ, White PJ, Pouton CW. Interaction of viruses with host cell molecular motors. Curr Opin Biotechnol. 2010; 21:633–639. [PubMed: 20638267]
61. Getts DR, et al. Ly6c+ "inflammatory monocytes" are microglial precursors recruited in a pathogenic manner in West Nile virus encephalitis. J Exp Med. 2008; 205:2319–2337. [PubMed: 18779347]
62. Wada Y, Pierce ML, Fujinami RS. Importance of amino acid 101 within capsid protein VP1 for modulation of Theiler's virus-induced disease. J Virol. 1994; 68:1219–1223. [PubMed: 8289355]
63. Oldstone MB, et al. Measles virus infection in a transgenic model: virus-induced immunosuppression and central nervous system disease. Cell. 1999; 98:629–640. [PubMed: 10490102]
64. Villarreal D, Young CR, Storts R, Ting JW, Welsh CJ. A comparison of the neurotropism of Theiler's virus and poliovirus in CBA mice. Microb Pathog. 2006; 41:149–156. [PubMed: 16935465]
65. Burkala EJ, He J, West JT, Wood C, Petito CK. Compartmentalization of HIV-1 in the central nervous system: role of the choroid plexus. AIDS. 2005; 19:675–684. [PubMed: 15821393]
66. Falangola MF, Hanly A, Galvao-Castro B, Petito CK. HIV infection of human choroid plexus: a possible mechanism of viral entry into the CNS. J Neuropathol Exp Neurol. 1995; 54:497–503. [PubMed: 7602324]
67. Petito CK, Chen H, Mastri AR, Torres-Munoz J, Roberts B, Wood C. HIV infection of choroid plexus in AIDS and asymptomatic HIV-infected patients suggests that the choroid plexus may be a reservoir of productive infection. J Neurovirol. 1999; 5:670–677. [PubMed: 10602407]
68. Herndon RM, Johnson RT, Davis LE, Descalzi LR. Ependymitis in mumps virus meningitis. Electron microscopical studies of cerebrospinal fluid. Arch Neurol. 1974; 30:475–479. [PubMed: 4827064]
69. Coscoy L, Gonzalez-Dunia D, Brahic M, Ozden S. Infection of choroid plexus cells by human T cell leukaemia virus type I. J Gen Virol. 1997; 78:143–146. [PubMed: 9010297]

70. Lawrence DM, Patterson CE, Gales TL, D'Orazio JL, Vaughn MM, Rall GF. Measles virus spread between neurons requires cell contact but not CD46 expression, syncytium formation, or extracellular virus production. J Virol. 2000; 74:1908–1918. [PubMed: 10644364]
71. Terry RL, Getts DR, Deffrasnes C, van Vreden C, Campbell IL, King NJ. Inflammatory monocytes and the pathogenesis of viral encephalitis. J Neuroinflammation. 2012; 9:270. [PubMed: 23244217]
72. Teodoro JG, Branton PE. Regulation of apoptosis by viral gene products. J Virol. 1997; 71:1739–1746. [PubMed: 9032302]
73. Fujinami RS, von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clin Microbiol Rev. 2006; 19:80–94. [PubMed: 16418524]
74. Clarke P, Tyler KL. Apoptosis in animal models of virus-induced disease. Nat Rev Microbiol. 2009; 7:144–155. [PubMed: 19148180]
75. Zong WX, Thompson CB. Necrotic death as a cell fate. Genes Dev. 2006; 20:1–15. [PubMed: 16391229]
76. Hood C, Cunningham AL, Slobedman B, Boadle RA, Abendroth A. Varicella-zoster virus-infected human sensory neurons are resistant to apoptosis, yet human foreskin fibroblasts are susceptible: evidence for a cell-type-specific apoptotic response. J Virol. 2003; 77:12852–12864. [PubMed: 14610206]
77. Konig A, Homme C, Hauroder B, Dietrich A, Wolff MH. The varicella-zoster virus induces apoptosis in vitro in subpopulations of primary human peripheral blood mononuclear cells. Microbes Infect. 2003; 5:879–889. [PubMed: 12919856]
78. Baiker A, et al. Varicella-zoster virus infection of human neural cells in vivo. Proc Natl Acad Sci USA. 2004; 101:10792–10797. [PubMed: 15247414]
79. Nargi-Aizenman JL, Griffin DE. Sindbis virus-induced neuronal death is both necrotic and apoptotic and is ameliorated by N-methyl-D-aspartate receptor antagonists. J Virol. 2001; 75:7114–7121. [PubMed: 11435592]
80. Levine B, Huang Q, Isaacs JT, Reed JC, Griffin DE, Hardwick JM. Conversion of lytic to persistent alphavirus infection by the bcl-2 cellular oncogene. Nature. 1993; 361:739–742. [PubMed: 8441470]
81. Lewis J, Wesselingh SL, Griffin DE, Hardwick JM. Alphavirus-induced apoptosis in mouse brains correlates with neurovirulence. J Virol. 1996; 70:1828–1835. [PubMed: 8627707]
82. Irusta PM, Hardwick JM. Neuronal apoptosis pathways in Sindbis virus encephalitis. Prog Mol Subcell Biol. 2004; 36:71–93. [PubMed: 15171608]
83. Griffin DE. Neuronal cell death in alphavirus encephalomyelitis. Curr Top Microbiol Immunol. 2005; 289:57–77. [PubMed: 15791951]
84. Anderson R, Harting E, Frey MS, Leibowitz JL, Miranda RC. Theiler's murine encephalomyelitis virus induces rapid necrosis and delayed apoptosis in myelinated mouse cerebellar explant cultures. Brain Res. 2000; 868:259–267. [PubMed: 10854578]
85. Havert MB, Schofield B, Griffin DE, Irani DN. Activation of divergent neuronal cell death pathways in different target cell populations during neuroadapted sindbis virus infection of mice. J Virol. 2000; 74:5352–5356. [PubMed: 10799613]
86. Ishii KJ, Koyama S, Nakagawa A, Coban C, Akira S. Host innate immune receptors and beyond: making sense of microbial infections. Cell Host Microbe. 2008; 3:352–363. [PubMed: 18541212]
87. Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. Int Rev Immunol. 2011; 30:16–34. [PubMed: 21235323]
88. Liang XH, Goldman JE, Jiang HH, Levine B. Resistance of interleukin-1beta-deficient mice to fatal Sindbis virus encephalitis. J Virol. 1999; 73:2563–2567. [PubMed: 9971844]
89. Libbey JE, Kennett NJ, Wilcox KS, White HS, Fujinami RS. Interleukin-6, produced by resident cells of the central nervous system and infiltrating cells, contributes to the development of seizures following viral infection. J Virol. 2011; 85:6913–6922. [PubMed: 21543484]
90. Kapil P, Atkinson R, Ramakrishna C, Cua DJ, Bergmann CC, Stohlman SA. Interleukin-12 (IL-12), but not IL-23, deficiency ameliorates viral encephalitis without affecting viral control. J Virol. 2009; 83:5978–5986. [PubMed: 19339350]

91. Chen BP, Lane TE. Lack of nitric oxide synthase type 2 (NOS2) results in reduced neuronal apoptosis and mortality following mouse hepatitis virus infection of the central nervous system. J Neurovirol. 2002; 8:58–63. [PubMed: 11847593]
92. Getts DR, et al. Targeted blockade in lethal West Nile virus encephalitis indicates a crucial role for very late antigen (VLA)-4-dependent recruitment of nitric oxide-producing macrophages. J Neuroinflammation. 2012; 9:246. [PubMed: 23111065]
93. Getts MT, Kim BS, Miller SD. Differential outcome of tolerance induction in naive versus activated Theiler's virus epitope-specific CD8+ cytotoxic T cells. J Virol. 2007; 81:6584–6593. [PubMed: 17428853]
94. Bennett JL, Elhofy A, Charo I, Miller SD, Dal Canto MC, Karpus WJ. CCR2 regulates development of Theiler's murine encephalomyelitis virus-induced demyelinating disease. Viral Immunol. 2007; 20:19–33. [PubMed: 17425418]
95. Glass WG, Liu MT, Kuziel WA, Lane TE. Reduced macrophage infiltration and demyelination in mice lacking the chemokine receptor CCR5 following infection with a neurotropic coronavirus. Virology. 2001; 288:8–17. [PubMed: 11543653]
96. Wu GF, Dandekar AA, Pewe L, Perlman S. CD4 and CD8 T cells have redundant but not identical roles in virus-induced demyelination. J Immunol. 2000; 165:2278–2286. [PubMed: 10925317]
97. Fujinami RS, Oldstone MB. Molecular mimicry as a mechanism for virus-induced autoimmunity. Immunol Res. 1989; 8:3–15. [PubMed: 2647867]
98. Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science. 1985; 230:1043–1045. [PubMed: 2414848]
99. Hammer J, Sturniolo T, Sinigaglia F. HLA class II peptide binding specificity and autoimmunity. Adv Immunol. 1997; 66:67–100. [PubMed: 9328640]
100. Gautam AM, Lock CB, Smilek DE, Pearson CI, Steinman L, McDevitt HO. Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules: implications in induction of autoimmunity. Proc Natl Acad Sci USA. 1994; 91:767–771. [PubMed: 7507253]
101. Wucherpfennig KW, et al. Structural requirements for binding of an immunodominant myelin basic protein peptide to DR2 isotypes and for its recognition by human T cell clones. J Exp Med. 1994; 179:279–290. [PubMed: 7505801]
102. Hemmer B, et al. Identification of candidate T-cell epitopes and molecular mimics in chronic Lyme disease. Nat Med. 1999; 5:1375–1382. [PubMed: 10581079]
103. Lang HL, et al. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. Nat Immunol. 2002; 3:940–943. [PubMed: 12244309]
104. Croxford JL, Olson JK, Miller SD. Epitope spreading and molecular mimicry as triggers of autoimmunity in the Theiler's virus-induced demyelinating disease model of multiple sclerosis. Autoimmun Rev. 2002; 1:251–260. [PubMed: 12848977]
105. Massilamany C, Asojo OA, Gangaplara A, Steffen D, Reddy J. Identification of a second mimicry epitope from Acanthamoeba castellanii that induces CNS autoimmunity by generating cross-reactive T cells for MBP 89-101 in SJL mice. Int Immunol. 2011; 23:729–739. [PubMed: 22058327]
106. Massilamany C, Steffen D, Reddy J. An epitope from Acanthamoeba castellanii that cross-react with proteolipid protein 139-151-reactive T cells induces autoimmune encephalomyelitis in SJL mice. J Neuroimmunol. 2010; 219:17–24. [PubMed: 20005578]
107. Zhao ZS, Granucci F, Yeh L, Schaffer PA, Cantor H. Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection. Science. 1998; 279:1344–1347. [PubMed: 9478893]
108. Coppieters KT, Wiberg A, von Herrath MG. Viral infections and molecular mimicry in type 1 diabetes. APMIS. 2012; 120:941–949. [PubMed: 23051179]
109. Mokhtarian F, Zhang Z, Shi Y, Gonzales E, Sobel RA. Molecular mimicry between a viral peptide and a myelin oligodendrocyte glycoprotein peptide induces autoimmune demyelinating disease in mice. J Neuroimmunol. 1999; 95:43–54. [PubMed: 10229114]

110. Gauntt CJ, et al. Molecular mimicry, anti-coxsackievirus B3 neutralizing monoclonal antibodies, and myocarditis. J Immunol. 1995; 154:2983–2995. [PubMed: 7533190]
111. Lawson CM. Evidence for mimicry by viral antigens in animal models of autoimmune disease including myocarditis. Cell Mol Life Sci. 2000; 57:552–560. [PubMed: 11130455]
112. Oldstone MB, Nerenberg M, Southern P, Price J, Lewicki H. Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. Cell. 1991; 65:319–331. [PubMed: 1901765]
113. Ohashi PS, et al. Ablation of “tolerance” and induction of diabetes by virus infection in viral antigen transgenic mice. Cell. 1991; 65:305–317. [PubMed: 1901764]
114. von Herrath MG, Dockter J, Oldstone MB. How virus induces a rapid or slow onset insulin-dependent diabetes mellitus in a transgenic model. Immunity. 1994; 1:231–242. [PubMed: 7889411]
115. Evans CF, Horwitz MS, Hobbs MV, Oldstone MB. Viral infection of transgenic mice expressing a viral protein in oligodendrocytes leads to chronic central nervous system autoimmune disease. J Exp Med. 1996; 184:2371–2384. [PubMed: 8976191]
116. Olson JK, Croxford JL, Calenoff M, Dal Canto MC, Miller SD. A virus-induced molecular mimicry model of multiple sclerosis. J Clin Invest. 2001; 108:311–318. [PubMed: 11457884]
117. Carrizosa AM, et al. Expansion by self antigen is necessary for the induction of experimental autoimmune encephalomyelitis by T cells primed with a cross-reactive environmental antigen. J Immunol. 1998; 161:3307–3314. [PubMed: 9759846]
118. Croxford JL, Ercolini AM, Degutes M, Miller SD. Structural requirements for initiation of cross-reactivity and CNS autoimmunity with a PLP139-151 mimic peptide derived from murine hepatitis virus. Eur J Immunol. 2006; 36:2671–2680. [PubMed: 16981179]
119. Greene MT, Ercolini AM, Degutes M, Miller SD. Differential induction of experimental autoimmune encephalomyelitis by myelin basic protein molecular mimics in mice humanized for HLA-DR2 and an MBP(85-99)-specific T cell receptor. J Autoimmun. 2008; 31:399–407. [PubMed: 19008075]
120. Christen U, et al. A viral epitope that mimics a self antigen can accelerate but not initiate autoimmune diabetes. J Clin Invest. 2004; 114:1290–1298. [PubMed: 15520861]
121. Yurasov S, et al. Defective B cell tolerance checkpoints in systemic lupus erythematosus. J Exp Med. 2005; 201:703–711. [PubMed: 15738055]
122. Samuels J, Ng YS, Coupillaud C, Paget D, Meffre E. Impaired early B cell tolerance in patients with rheumatoid arthritis. J Exp Med. 2005; 201:1659–1667. [PubMed: 15897279]
123. Lovett-Racke AE, Trotter JL, Lauber J, Perrin PJ, June CH, Racke MK. Decreased dependence of myelin basic protein-reactive T cells on CD28-mediated costimulation in multiple sclerosis patients. A marker of activated/memory T cells. J Clin Invest. 1998; 101:725–730. [PubMed: 9466965]
124. Markovic-Plese S, Cortese I, Wandinger KP, McFarland HF, Martin R. CD4+CD28-costimulation-independent T cells in multiple sclerosis. J Clin Invest. 2001; 108:1185–1194. [PubMed: 11602626]
125. Bielekova B, Sung MH, Kadom N, Simon R, McFarland H, Martin R. Expansion and functional relevance of high-avidity myelin-specific CD4+ T cells in multiple sclerosis. J Immunol. 2004; 172:3893–3904. [PubMed: 15004197]
126. Baranzini SE, Jeong MC, Butunoi C, Murray RS, Bernard CC, Oksenberg JR. B cell repertoire diversity and clonal expansion in multiple sclerosis brain lesions. J Immunol. 1999; 163:5133–5144. [PubMed: 10528220]
127. Babbe H, et al. Clonal expansions of CD8(+) T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. J Exp Med. 2000; 192:393–404. [PubMed: 10934227]
128. Skulina C, et al. Multiple sclerosis: brain-infiltrating CD8+ T cells persist as clonal expansions in the cerebrospinal fluid and blood. Proc Natl Acad Sci USA. 2004; 101:2428–2433. [PubMed: 14983026]

129. Meinl E, et al. Myelin basic protein-specific T lymphocyte repertoire in multiple sclerosis. Complexity of the response and dominance of nested epitopes due to recruitment of multiple T cell clones. J Clin Invest. 1993; 92:2633–2643. [PubMed: 7504690]
130. Goebels N, Hofstetter H, Schmidt S, Brunner C, Wekerle H, Hohlfeld R. Repertoire dynamics of autoreactive T cells in multiple sclerosis patients and healthy subjects: epitope spreading versus clonal persistence. Brain. 2000; 123:508–518. [PubMed: 10686174]
131. Muraro PA, et al. Molecular tracking of antigen-specific T cell clones in neurological immune-mediated disorders. Brain. 2003; 126:20–31. [PubMed: 12477694]
132. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. Ann Neurol. 2006; 59:499–503. [PubMed: 16502434]
133. Nielsen TR, et al. Multiple sclerosis after infectious mononucleosis. Arch Neurol. 2007; 64:72–75. [PubMed: 17210811]
134. Lunemann JD, et al. Increased frequency and broadened specificity of latent EBV nuclear antigen-1-specific T cells in multiple sclerosis. Brain. 2006; 129:1493–1506. [PubMed: 16569670]
135. Lunemann JD, et al. EBNA1-specific T cells from patients with multiple sclerosis cross react with myelin antigens and co-produce IFN-gamma and IL-2. J Exp Med. 2008; 205:1763–1773. [PubMed: 18663124]
136. Harari A, et al. Skewed association of polyfunctional antigen-specific CD8 T cell populations with HLA-B genotype. Proc Nat Acad Sci USA. 2007; 104:16233–16238. [PubMed: 17911249]
137. Zipris D, Lien E, Xie JX, Greiner DL, Mordes JP, Rossini AA. TLR activation synergizes with Kilham rat virus infection to induce diabetes in BBDR rats. J Immunol. 2005; 174:131–142. [PubMed: 15611235]
138. Walker LS, Abbas AK. The enemy within: keeping self-reactive T cells at bay in the periphery. Nat Rev Immunol. 2002; 2:11–19. [PubMed: 11908514]
139. Enouz S, Carrie L, Merkler D, Bevan MJ, Zehn D. Autoreactive T cells bypass negative selection and respond to self-antigen stimulation during infection. J Exp Med. 2012; 209:1769–1779. [PubMed: 22987800]
140. D'Agostino PM, et al. Viral-induced encephalitis initiates distinct and functional CD103+ CD11b + brain dendritic cell populations within the olfactory bulb. Proc Natl Acad Sci USA. 2012; 109:6175–6180. [PubMed: 22474352]
141. McRae BL, Vanderlugt CL, Dal Canto MC, Miller SD. Functional evidence for epitope spreading in the relapsing pathology of experimental autoimmune encephalomyelitis. J Exp Med. 1995; 182:75–85. [PubMed: 7540658]
142. Yu M, Johnson JM, Tuohy VK. A predictable sequential determinant spreading cascade invariably accompanies progression of experimental autoimmune encephalomyelitis: A basis for peptide-specific therapy after onset of clinical disease. J Exp Med. 1996; 183:1777–1788. [PubMed: 8666934]
143. Miller SD, et al. Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. Nat Med. 1997; 3:1133–1136. [PubMed: 9334726]
144. Katz-Levy Y, et al. Endogenous presentation of self myelin epitopes by CNS-resident APCs in Theiler's virus-infected mice. J Clin Invest. 1999; 104:599–610. [PubMed: 10487774]
145. Katz-Levy Y, et al. Temporal development of autoreactive Th1 responses and endogenous antigen presentation of self myelin epitopes by CNS-resident APCs in Theiler's virus-infected mice. J Immunol. 2000; 165:5304–5314. [PubMed: 11046065]
146. Borrow P, Welsh CJ, Tonks P, Dean D, Blakemore WF, Nash AA. Investigation of the role of delayed-type-hypersensitivity responses to myelin in the pathogenesis of Theiler's virus-induced demyelinating disease. Immunology. 1998; 93:478–484. [PubMed: 9659218]
147. Kaufman DL, et al. Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. Nature. 1993; 366:69–72. [PubMed: 7694152]
148. Prasad S, Kohm AP, McMahon JS, Luo X, Miller SD. Pathogenesis of NOD diabetes is initiated by reactivity to the insulin B chain 9-23 epitope and involves functional epitope spreading. J Autoimm. 2012; 39:347–353.

149. Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. J Clin Invest. 2001; 108:1097–1104. [PubMed: 11602615]

150. Brocke S, et al. Induction of relapsing paralysis in experimental autoimmune encephalomyelitis by bacterial superantigen. Nature. 1993; 365:642–644. [PubMed: 7692305]

151. Cole BC, Griffiths MM. Triggering and exacerbation of autoimmune arthritis by the Mycoplasma arthritidis superantigen MAM. Arth Rheum. 1993; 36:994–1002. [PubMed: 8318046]

152. Dalwadi H, Wei B, Kronenberg M, Sutton CL, Braun J. The Crohn's disease-associated bacterial protein I2 is a novel enteric T cell superantigen. Immunity. 2001; 15:149–158. [PubMed: 11485746]

153. Pender MP. Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases. Trends Immunol. 2003; 24:584–588. [PubMed: 14596882]

154. Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. N Engl J Med. 2004; 350:1328–1337. [PubMed: 15044644]

155. Nanbo A, Inoue K, Adachi-Takasawa K, Takada K. Epstein-Barr virus RNA confers resistance to interferon-alpha-induced apoptosis in Burkitt's lymphoma. EMBO J. 2002; 21:954–965. [PubMed: 11867523]

156. Mullbacher A, Hill AB, Blanden RV, Cowden WB, King NJ, Hla RT. Alloreactive cytotoxic T cells recognize MHC class I antigen without peptide specificity. J Immunol. 1991; 147:1765–1772. [PubMed: 1890303]

157. King NJ, Maxwell LE, Kesson AM. Induction of class I major histocompatibility complex antigen expression by West Nile virus on gamma interferon-refractory early murine trophoblast cells. Proc Nat Acad Sci USA. 1989; 86:911–915. [PubMed: 2492666]

158. Leis AA, Szatmary G, Ross MA, Stokic DS. West nile virus infection and myasthenia gravis. Muscle Nerve. 2013 Epub ahead of print. 10.1002/mus.23869

159. Olson JK, Miller SD. Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. J Immunol. 2004; 173:3916–3924. [PubMed: 15356140]

160. Hamilton-Williams EE, Lang A, Benke D, Davey GM, Wiesmuller KH, Kurts C. Cutting edge: TLR ligands are not sufficient to break cross-tolerance to self-antigens. J Immunol. 2005; 174:1159–1163. [PubMed: 15661868]

161. Gronski MA, et al. TCR affinity and negative regulation limit autoimmunity. Nat Med. 2004; 10:1234–1239. [PubMed: 15467726]

162. Lang KS, et al. Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease. Nat Med. 2005; 11:138–145. [PubMed: 15654326]

163. Mokhtarian F, Grob D, Griffin DE. Role of the immune response in Sindbis virus-induced paralysis of SJL/J mice. J Immunol. 1989; 143:633–637. [PubMed: 2472447]

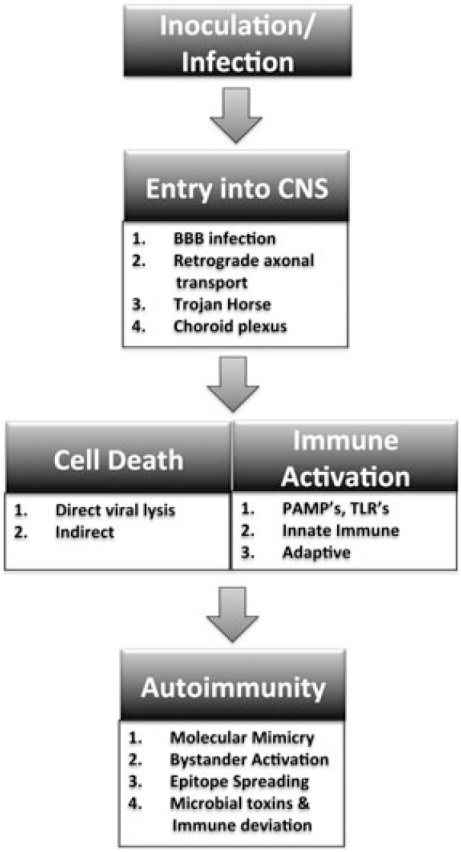

Fig. 1.
Schematic outlining the potential pathway(s) through which infection may trigger autoimmunity.

Table 1

Select viruses associated with central nervous system autoimmune diseases

Virus	Species	Family	Associated with autoimmune disease	Mechanism	Reference(s)
Measles virus	Human	Paramyxoviridae	Yes – multiple sclerosis (MS)	Bystander activation* Molecular mimicry*	(11, 31)
Epstein–Barr virus	Human	Herpesviridae	Yes – MS	Bystander activation* Molecular mimicry*	(56, 134)
HTLV-1	Human	Retroviridae	Yes – HTLV-1-associated myelopathy/tropical spastic paraparesis	Bystander activation* Molecular mimicry*	(20)
Theiler's murine encephalomyelitis virus (TMEV)	Mouse	Picornoviridae	Yes – TMEV-induced demyelinating disease	Molecular mimicry Epitope spreading bystander activation	(35, 37, 116)
Japenese encephalitis virus (JEV)	Mouse	Flaviviridae	Yes	Molecular mimicry	(43)
Sindbis virus	Mouse	Flaviviridae	Yes	Molecular mimicry	(163)
Semliki Forest virus	Mouse	Flaviviridae	Yes	Molecular mimicry	(41, 42)
WNV	Human/Mouse	Flaviviridae	Yes	Immune decoy* Bystander activation*	(57, 158)

*Suggested or proposed mechanism.