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Autoimmunity in picornavirus infections

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Abstract

Enteroviruses are small, non-enveloped, positive-sense single-strand RNA viruses, and are ubiquitously found throughout the world. These viruses usually cause asymptomatic or mild febrile illnesses, but have a propensity to induce severe diseases including type 1 diabetes and pancreatitis, paralysis and neuroinflammatory disease, myocarditis, or hepatitis. This pathogenicity may result from induction of autoimmunity to organ-specific antigens. While enterovirus-triggered autoimmunity can arise from multiple mechanisms including antigenic mimicry and release of sequestered antigens, the recent demonstration of T cells expressing dual T cell receptors arising as a natural consequence of Theiler's virus infection is the first demonstration of this autoimmune mechanism.

Picornaviruses are non-enveloped, small, single-stranded positive-sense RNA genome viruses. The genome consists of approximately 7500 nucleotides containing an open reading frame flanked by a 5' and 3' untranslated region (UTR), and the 5' UTR equipped with a highly conserved internal ribosome entry site [1]. The open reading frame is translated into a single polypeptide which is subsequently processed by viral proteases into 11–12 individual viral proteins. The family comprises enteroviruses (EVs), hepatoviruses, parechoviruses, rhinoviruses, aphthoviruses, and cardioviruses [2]. Although aphthoviruses and cardioviruses have been historically deemed animal pathogens, a recently isolated human cardiovirus — scaffold virus — in a child with febrile illness, indicates human pathogenesis is possible, can occur worldwide, and can primarily infect children under six years of age [3]. Other new picornavirus genera include *Cosavirus* and *Kobuvirus*, but little is known about them [4]. Human EVs are subgrouped into polioviruses (PVs; 3 serotypes), coxsackievirus A (CVAs; 23 serotypes), coxsackievirus B (CVBs; 6 serotypes), echoviruses (28 serotypes), and EVs 68–72. EV infections in humans are predominantly asymptomatic or cause minor respiratory illnesses. However, more severe outcomes, including type 1 diabetes, paralysis, myocarditis, and menin-

goencephalitis, are often associated with various EV infections [4–7,8*].

EV infections are relatively common and confirmed cases are voluntarily documented in the Centers for Disease Control Morbidity and Mortality Weekly Report. During surveillance between 1970 and 2005 [9], 52,812 detections of EV were reported to the Centers for Disease Control in the United States, but the dominant forms of EV varied from year to year. The total number of EV infections decreased after 1990 but increased again in 2000. Of all reported EV infections during that time frame, infection with CVB4 (9.8%), CVB2 (5.9%), and CVB3 (5.4%) resulted in the highest fatal outcomes. CVBs are distributed throughout the world based on antibody seroprevalence and the lowest numbers reported were 6.7–21.6% in Greece with the highest being over 50% in China [10,11]. EV-D68 recurred seasonally in the Netherlands between 2011 and 2014, primarily affecting individuals who were less than 20 years old and between the ages of 50 and 59. In 2014, an EV-D68 outbreak in the United States resulted in 1152 confirmed cases; interestingly, mainly children were affected and disease was associated with flaccid myelitis [12,13]. Although EVs occur everywhere in the world, enteroviral pathogenesis may be more pronounced in certain geographic regions than others. For instance, there are recurrent outbreaks of EV-71 in the Asia-Pacific region. The outbreaks predominantly afflict children with hand-foot-and-mouth disease and occasionally more serious complications, such as aseptic meningitis, acute flaccid paralysis, and brainstem encephalitis and/or severe pulmonary edema and shock [14]. Generally, outbreaks of EV-71 have been sporadic or small-clustered in Africa, Europe, and North America and only rarely accompanied by severe complications [14]. The incidence and severity of EV-71's pathogenicity in the Asia-Pacific region is not completely understood, but a genetic link between human leukocyte antigen (HLA)-A33 and EV pathogenesis has been reported [15]. It should be noted that HLA-A33 is frequently found in Asian populations but rarely occurs in non-Asians.

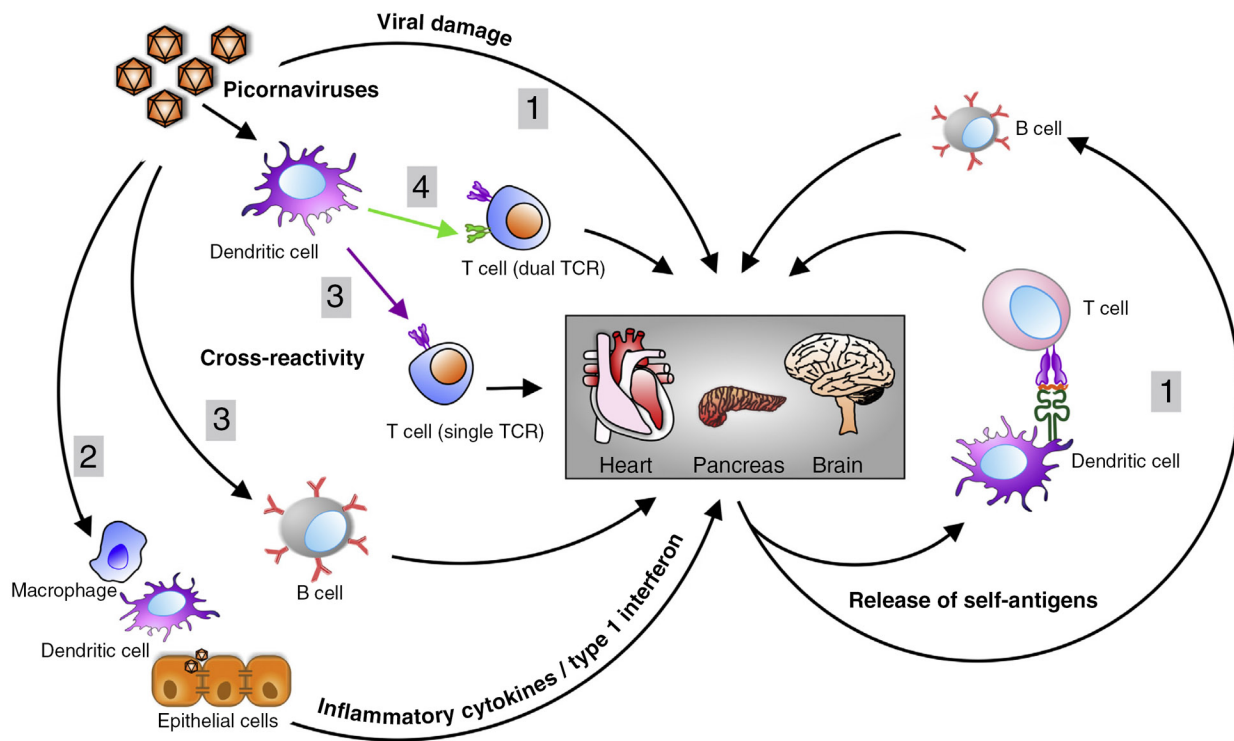


Figure 1. Proposed autoimmune mechanisms in picornaviral infections. (1) Viruses, depending on their tropism for various organ systems, such as cardiovascular, digestive, and central nervous system, can directly damage target organs, leading to the release of self-antigens, including those located within the cells. The newly released antigens are then taken up by dendritic cells, and after processing, self-peptides presented by dendritic cells may trigger induction of potentially pathogenic self-reactive T cells. Alternatively, autoreactive B cells can also take up these antigens and produce autoantibodies that then contribute to tissue damage by activating immune complex-mediated complements. (2) Acute damage can also result when innate immune cells such as macrophages and dendritic cells engage in excessive inflammatory cytokine production. Likewise, IFN-I, when produced in excess by virus-infected cells, can contribute to tissue damage. (3) Exposure to viruses carrying mimicry sequences for self-antigens can lead to the generation of cross-reactive T-cell and antibody responses. Whereas T cells can induce damage through delayed-type hypersensitivity reaction (CD4 T-cell-dependent) and cytotoxicity (CD8 T-cell-dependent), autoantibodies mediate tissue damage via complement activation. (4) Alternatively, if T cells bearing dual receptors (presumably one receptor specific for the foreign antigen and the other for self-antigen) are responsive to viral infections, by virtue of their response to viruses, they could also potentially attack self-tissues in the context of mistaken identity. In all of these scenarios, once self-tissues are damaged, *de novo* generation of self-reactive T and B cells precipitate the disease process, leading to chronicity as observed in many organ-specific autoimmune diseases.

One of the major features of severe pathogenic diseases as a result of several picornavirus infections (type 1 diabetes, myocarditis, or paralysis) is a strong association with autoimmunity. This is especially true in type 1 diabetes [16] and myocarditis [17,18]. Although PV-induced paralysis does not appear to be the result of an immunopathogenic mechanism (resulting instead from direct viral infection and neuronal destruction), another member of the picornavirus family, Theiler's murine encephalomyelitis virus (TMEV), is often used as a murine model of virus-induced multiple sclerosis to induce T-cell-mediated autoimmune demyelinating disease [19,20]. Although the link between autoimmunity and microbial infections is not novel, what remains highly controversial is the role infection may play in autoimmunity. The simplest explanation may be that infection with cytopathic infectious agents results in cell death or injury,

thus releasing either sequestered or cellular autoantigens which are present at low concentrations before infection, thus preventing auto-sensitization (Figure 1). Self-reactive T-cell clones should be deleted in the thymus during T-cell ontogeny when thymic epithelial cells present autoantigens (central tolerance) but this process requires the autoantigen to be available to the epithelial cells. Thus, it follows that T cells reactive to cardiac myosin, myelin basic protein, or islet beta cells would most probably escape central tolerance as these antigens are not present in the thymus during T cell ontogeny (Figure 1). Also, T cells with low affinity self-reactive TCR could escape clonal deletion within the thymus. When organs such as the heart, islets or CNS undergo substantial damage and release of normally sequestered antigens; breakdown of the blood brain barrier; or chemokine induced infiltration of the damaged tissue with leukocytes;

the low-affinity self-reactive T cells or T cells reactive to sequestered antigens may encounter appropriately presented self-antigens by professional antigen presenting cells at adequate MHC-peptide threshold levels and with appropriate accessory molecule stimulation and cytokines necessary for their activation and proliferation. This process, designated bystander activation, may initially lack vigor as the T cells would be low affinity. However, since TCR have the potential to undergo somatic mutations during replication, there is the potential to evolve higher affinity and a broadening of reactivity (epitope spreading) self-reactivity over time. Thus, autoimmunity may evolve for months or even longer before pathogenic disease becomes evidence [21].

EVs activate the RIG-I-like helicase melanoma differentiation gene 5 (MDA5) [22], which in turn stimulates the activation of interferon regulatory transcription factors (IRFs) 3 and 7 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) via the common adaptor mitochondrial antiviral-signaling protein. Activation of IRF3/7 results in type 1 interferon (IFN-I) expression, whereas nuclear translocation of NF- κ B leads to the upregulation of many cytokine, chemokine, and accessory molecules involved in host defense [23,24]. MDA5 activation may directly result in autoimmunity post picornaviral infection because (a) gain-of-function mutations in MDA5 are associated with spontaneous lupus-like autoimmunity induction in mice [25]; (b) chronic, high-level expression of IFN-I results in lupus-like conditions [26]; and (c) transgenic mice expressing multiple copies of the MDA5 gene (*Iflh1*) are more prone to autoimmunity [27*]. The results of these animal studies have been corroborated in patients having naturally occurring gain-of-function mutations in *Iflh1* which resulted in neuroimmunological disease, and MDA5 showing increased RNA binding avidity and IFN signature [28*]. Because several picornaviruses, including PV [29], CVB [30], and foot-and-mouth disease [31], can induce persistent viral infections, chronic activation of MDA5 and upregulation of IFN-I could produce the adjuvant effect attributed by some investigators as the major contributing factor in picornavirus infections to induce autoimmunity [32]. While MDA5 activation and an IFN-I signature are implicated in autoimmunity induction, other potential mechanisms should be considered as well. With the increased use of IFN-I in chronic hepatitis C treatment, there are now more reports of side effects leading to dilated cardiomyopathies [33–38] and prolonged treatment with PEGylated IFN-I was associated with cardiomyopathies with poor prognosis [33]. The mechanism underlying IFN-I-induced cardiomyopathy is unknown, but it has been suggested that cardiomyopathy could be the result of impaired myocyte metabolism rather than histological damage [38]. High IFN-I levels resulting from picornavirus infections could also result in impaired myocyte metabolism which itself could be pathologic or could lead to myocyte

necrosis/apoptosis and release of autoantigens. This would explain why picornaviruses can effectively result in the manifestation of a range of autoimmune diseases: since the infection specifically produces an environment that attracts and promotes activation of T cells and antigen-presenting cells to damaged tissues or self-antigens released as a consequence of infection. This hypothesis differs from another current major theory for virus-induced autoimmunity — antigenic mimicry — that assumes the sharing of peptide epitopes between the infectious agent and self-molecules, thus necessitating proteins or peptides from viruses such as CVB to mimic multiple autoantigens.

Antigenic mimicry, the shared sequence or tertiary structure between foreign and self-antigens, has long been considered the most popular and well-established theory [39]. Pathogenic mimicry between specific pathogens (group A streptococcus and *Campylobacter jejuni*, respectively) and tissues is well documented [40–42] in rheumatic heart disease and Guillain-Barré syndrome. Strong evidence suggests that picornavirus infections induce experimental autoimmunity at both T-lymphocyte and B-lymphocyte levels. Cardiac myosin autoantibodies occur in CVB3-infected mice with developing myocarditis, and passive administration of autoantibodies can transfer disease [43,44]. At least a portion of these antimyosin antibodies are cross-reactive to CVB3 as well as group A streptococcus [45]. These antibodies react to alpha helical sequences, thus possibly explaining the broad cross-reactivity of cross-reactive anti-streptococcal antibodies to cardiac myosin and many other tissue antigens, including tropomyosin, laminin, vimentin, and keratin [41]. Similarly, CVB3-infected mice can generate CD4⁺ T cells capable of transferring myocarditis to naïve mice [46]. Other studies have found cross-reactivity between NT4 peptides in group A streptococcus, cardiac myosin, and CVB3 and have shown that mice tolerized to this cross-reactive peptide abrogated induction of CVB3-myocarditis, indicating that the mimicking epitope was a major pathogenic factor in the experimental disease [47].

The mimicry hypothesis has also been tested in the context of type 1 diabetes, but little evidence exists to support this mechanism [48]. For example, glutamate decarboxylase (GAD) 247–279, and a peptide fragment derived from CVB protein (P2-C, amino acids 32–47), have been shown to induce T cell responses in type 1 diabetes patients [49]. Conversely, T cell clones specific to GAD 247–280 generated from type 1 diabetes patients failed to react with its mimicry epitope, P2C 28–50, a derivative of P2-C protein from CVB [50]. Paradoxically however, infection of BDC2.5 T-cell receptor (TCR) transgenic mice with CVB4 led to the development of diabetes rapidly, probably due to the release of autoantigens, leading to bystander activation of autoreactive T cells [51]. Thus, the relevance of molecular mimicry to the immune

pathogenesis of type I diabetes continues to be uncertain. Similarly, although, upregulation of costimulatory molecules in the inflammatory microenvironment is believed to break the self-tolerance by activating the bystander T cells, targeted expression of IL-2 or IL-12 in the pancreatic β cells to promote continuous proliferation of T cells and/or induction of Th1 cytokines failed to initiate the disease [52,53]. Likewise, induction of type 1 interferon response did not trigger diabetes in TCR transgenic mice [54]. Thus, bystander activation as an underlying immune mechanism of diabetes lacks a good experimental evidence. However, it may be possible that the release of sequestered antigens secondary to primary damage, if any, can possibly act as putative target auto-antigens, as BDC2.5 TCR transgenic mice treated with subdiabetogenic doses of streptozotocin that causes damage to the pancreatic islets, developed diabetes spontaneously [54].

Although humoral cross-reactivity is commonly understood as antibodies that typically react to tertiary structures such as alpha helices (which are common among proteins), cross-reactivity between T-cell epitopes might initially seem less probably, since, primary amino acid sequences must be loaded onto major histocompatibility complex (MHC) antigens and presented to the TCR. However, it is now accepted that there is substantial TCR degeneracy in epitope recognition because, amino acids are recognized by the chemical properties they share rather than the need for a specific amino acid at a specific location within the peptide sequence [55,56]. Indeed, one investigator concluded that the sharing of just one amino acid between two peptides may be sufficient for T-cell cross-reactivity to occur [57]. Such flexibility in the recognition of peptides by T cells may make singling out antigenic mimicry as a cause of autoimmunity in viral infection difficult. A second point of note is that antigenic mimicry alone may not adequately support autoimmune disease, despite sensitizing autoreactive T or B cells. von Herrath and colleagues proposed a "fertile-field hypothesis" [58] in that, encounter with a virus or microbe bearing mimicry epitope for self-antigens may not always necessarily results in disease [59]. Instead, exposure to infectious pathogens may lead to the generation of auto-reactive cells as a result of their multiplication within the target tissues (heart, brain or pancreas). Once such repertoires are formed, future encounters with unrelated microbes could possibly trigger pathogenic autoimmune responses non-specifically through the adjuvant effects of microbes or bystander activation. Similarly, serial infection or exposing individuals with cross-reactive epitopes to self-antigens such as cardiac myosin and a multitude of different microbes/agents could reactivate autoimmune responses, leading to ever-more potent memory T cells until a substantial or chronic degenerative condition is achieved. Studies by Massilamany *et al.* [60] demonstrated that epitopes in *Bacillus sp.* NRRL B-14911, *Magnetospirillum gryphiswaldense*, *Cryptococcus neoformans*, and *Zea mays* have

a shared sequence identity with the myocarditic epitope in cardiac myosin heavy chain- α and have varying capacities to induce myocarditis when injected into mice. As indicated above, CVB3 and group A streptococcus NT4 peptide share a mimicking epitope with cardiac myosin, and tolerization of mice to the NT4 peptide, abrogated subsequent induction of myocarditis via CVB3.

Another potential mechanism for picornaviral induction of autoimmunity is T-cell expression of dual TCRs (Figure 1). Although, it was originally thought that T cells generated a single V-(D)-J rearrangement during T-cell ontogeny in the thymus, it is now known that approximately 30% of T cells in humans and 15% in mice express TCR with two different V α rearrangements and therefore different antigen specificities [61–63]. By contrast, considerably fewer T cells express dual V β TCR (15% in humans and 5–7% in mice) [61,64,65]. Because the total space available for TCRs on a plasma membrane must be divided between the two types TCRs, when one of them is autoimmune, the level of stimulation dual TCR-bearing T cells receive in the thymus may be insufficient to result in clonal deletion. Furthermore, when the TCR that is reactive to foreign antigen activates the T cell, the cell will subsequently be primed to respond to self-antigens through self-reactive TCR, thus breaking self-tolerance. This hypothesis is supported by studies in a KRN autoimmune arthritis mouse model using transgenically produced dual TCR-bearing T cells with a capacity to avoid clonal deletion in the thymus and drive spontaneous late-onset autoimmune arthritis [66**]. Although this model depended on transgenic T cells, studies by Libbey and colleagues [67] using TMEV provide strong evidence that dual TCR-bearing T cells may drive autoimmunity in picornaviral infections [61]. Both V β 3 and V β 6, as well as multiple V α proteins, have been detected in TMEV-induced CD8⁺ T cells capable of adoptively transferring flaccid paralysis. However, the authors were not able to determine the individual TCR antigen specificities in the TMEV model, although the investigation appears to be ongoing. Should future studies reveal the natural coexistence of self-reactive and virus-specific TCR on the same T cell, this would be the first demonstration of a virus-induced autoimmunity through this mechanism.

In summary, autoimmunity has been shown to occur as a consequence in three experimental picornavirus infection models: CVB3-induced myocarditis, CVB4-induced type 1 diabetes and TMEV-induced demyelinating central nervous system disease. In all the three models, viruses damage target organs (heart and pancreas in CVB and brain and spinal cord in TMEV), leading to the secondary generation of autoimmune responses. The exact mechanism or mechanisms inducing this autoimmunity remain controversial, although evidence supporting several proposals exists: adjuvants and release of sequestered self-antigens from virally

damaged cells, antigenic mimicry, or dual TCR expression. Distinct methods for induction of autoimmunity could potentially dominate either under different conditions or in different individuals. Additionally, self-reactive immune responses may not necessarily be pathogenic in all conditions [68,69,70**,71]. The challenge lies in proving causal links between the infectious agent, the physiological response induced by the host (which might persist subclinically for weeks or months), and the ultimate clinical outcome. Finally, not all individuals infected with picornaviral infection show equivalent disease susceptibility. As indicated above, EV-71-induced pathology may be more severe in individuals with HLA-A33 [72]. Similarly, HLA-A3, HLA-B40, and HLA-Cw2 may increase susceptibility to CVB-induced myocarditis [73]. In an experimental model, host genetics clearly determined viral pathogenesis, as the same virus that infected inbred mouse strains resulted in either no autoimmunity and no disease or produced severe autoimmunity with accompanying pathology [74]. Thus, it would be erroneous to assume that anyone infected with potential pathogens will develop autoimmune diseases. It is unclear whether well-controlled epidemiological studies can determine if this supposed relationship between various genetic markers and infections even exists. The uncertainty lies in the time lag between initial infection and the clinical appearance of symptoms, the latter possibly taking weeks or months to manifest. Until this kind of epidemiological study can identify cause-and-effect relationships in a human setting, experimental models remain the only tool available to systematically research autoimmune events.

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