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Molecular Mimicry as a Mechanism of Autoimmune Disease

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Abstract A variety of mechanisms have been suggested as the means by which infections can initiate and/or exacerbate autoimmune diseases. One mechanism is molecular mimicry, where a foreign antigen shares sequence or structural similarities with self-antigens. Molecular mimicry has typically been characterized on an antibody or T cell level. However, structural relatedness between pathogen and self does not account for T cell activation in a number of autoimmune diseases. A proposed mechanism that could have been misinterpreted for molecular mimicry is the expression of dual T cell receptors (TCR) on a single T cell. These T cells have dual reactivity to both foreign and self-antigens leaving the host vulnerable to foreign insults capable of triggering an autoimmune response. In this review, we briefly discuss what is known about molecular mimicry followed by a discussion of the current understanding of dual TCRs. Finally, we discuss three mechanisms, including molecular mimicry, dual TCRs, and chimeric TCRs, by which dual reactivity of the T cell may play a role in autoimmune diseases.

Keywords Molecular mimicry · Autoimmune diseases · Dual T cell receptor · Virus infection · Immunopathology

Chronic autoimmune diseases are the by-product of the immune system recognizing self-antigens as foreign, which can lead to inflammation and destruction of specific tissues and organs (immunopathology) [1]. The impact of these diseases is global and heterogeneous with over 100 million people afflicted with more than 80 different autoimmune diseases [2]. While the etiology of autoimmune diseases is not fully elucidated, the causes are likely based on a combination of hereditary and environmental factors [3]. Although host genetic background contributes to the induction of an immune response to self, epidemiological and molecular evidence implicates infectious agents (viral and bacterial) as the principal environmental insults responsible for the induction of autoimmune diseases (reviewed in [4–6]). Prolonged proinflammatory responses to infections have been associated with the initiation and exacerbation of autoimmune diseases (reviewed in [4, 7, 8]). Inflammation is facilitated by proinflammatory cytokines such as type I interferon (IFN), interleukin (IL)-1β, IL-12, IFN-γ, IL-17, and tumor necrosis factor (TNF)-α (reviewed in [7, 9, 10]). However, these proinflammatory cytokines are critical for clearance of pathogens, suggesting that environmental factors are able to divert the immune response towards immunopathogenesis. Although a number of immune cells are responsible for secreting proinflammatory cytokines, the primary cell types implicated in a vast majority of autoimmune disorders are autoreactive B and T cells, or antibody recognition of self [11]. Although a number of viruses and bacteria have been linked to the initiation of certain autoimmune diseases, identifying a particular virus or bacteria that is solely responsible for the induction of an autoimmune response is rare. This occurrence is due to the potential for multiple infections being involved in priming the immune system and other infections triggering disease, which could explain why no one viral infection has been conclusively linked to the development of immune-mediated autoimmune diseases [7]. However, there are a variety of examples of bacterial infections initiating and exacerbating autoimmune diseases. *Streptococcus pyogenes* is a gram-positive bacterium which

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causes group A streptococcal infection that is responsible for a number of diseases. The complications associated with *S. pyogenes* are rheumatic fever and glomerulonephritis. The infection causes the production of cross-reactive antibodies in response to the bacteria. Antibodies recognize the M protein (virulence factor) and the *N*-acetyl-β-D-glucosamine (GLcNAc) of *S. pyogenes* and cross-react with myosin leading to heart damage (reviewed in [8, 12, 13]). Further evidence of molecular mimicry due to the production of cross-reactive antibody includes infection with gram-negative bacteria, such as *Klebsiella pneumoniae* and *Campylobacter jejuni*. Infection with *K. pneumonia* or *C. jejuni* leads to the production of cross-reactive antibodies able to recognize the self-antigens histocompatibility leukocyte antigen (HLA)-B27 and gangliosides, which induce ankylosing spondylitis and Guillain–Barré syndrome, respectively (reviewed in [8, 14]). Examples of human autoimmune diseases with possible links with molecular mimicry are presented in Table 1.

The immune system has a number of mechanisms that are able to detect foreign pathogens by utilizing the major histocompatibility complex (MHC). This locus encodes the HLA genes and a variety of immune response (Ir) genes, thereby shaping the immune system that protects against pathogens. There are two main types of HLA antigens, HLA class I and class II. The function of HLA class I molecules is to present viral peptides at the surface of an infected cell to a T cell receptor (TCR) on a $CD8^+$ T cell. The activation of these $CD8^+$ T cells leads to the killing of the virally infected cell. This role of HLA class I, the identification of cells that are infected, explains why all nucleated cells have the capacity to express these MHC molecules. HLA class II molecules, in comparison, are expressed almost exclusively on the surface of dendritic cells, B lymphocytes, macrophages, endothelial cells, and activated T cells. Functionally, the HLA class II molecules present peptides to the TCR on $CD4^+$ helper T cells. The engagement of the TCR by the peptide–MHC complex is necessary for the activation of $CD4^+$ and $CD8^+$ T cells, thereby leading to an effective adaptive immune response against an invading pathogen [15]. $CD4^+$ T cells are central mediators of the adaptive immune response including cytokine secretion and cellular and humoral defenses against a pathogen. The HLA locus is extremely polymorphic leading to a heterogeneous population ensuring propagation of a species against novel pathogens. Unfortunately, this genetic heterogeneity adds to the complexity of identifying HLA genes implicated in autoimmune diseases.

In addition to its role in protection against pathogens, a second critical role of the MHC and Ir genes is to safeguard against self-reactivity by restriction of the immune response to self. In this regard, the immune system has developmental checkpoints for the maturation of a T cell. As a naïve T cell expressing a pre-TCR migrates from the bone marrow to the thymus, rearrangement of α and β TCR genes occurs and T cells that have either too high avidity or lack of recognition of self-antigens are selected against and subsequently programmed for cell death. This selection mechanism for generating mature αβ TCRs is named central tolerance. Further, peripheral mechanisms of tolerance are able to suppress autoreactive T cells through certain subsets of cells including regulatory T cells (Tregs) that are able to inhibit self-reactive immune cells in the periphery.

Unfortunately, there are a variety of mechanisms including molecular mimicry, bystander activation, exposure of cryptic antigens, and superantigens by which pathogens can aid in the expression of an autoimmune disease [16–21]. Inflammation induced by exposure to a foreign antigen can lead to autoimmune diseases from cross-reactive epitopes (molecular mimicry). These epitopes are segments of foreign antigens which, when presented to either T or B cells in the context of the MHC, can activate $CD4^+$ or $CD8^+$ T cells. The induction of the immune response and subsequent proinflammatory cytokine release is critical for clearance of a virus or bacteria. However, a sustained proinflammatory response against specific host tissues can occur when there is sequence or structural homology between foreign antigens and self-antigens, termed molecular mimicry [18]. Although this concept has been associated with autoimmunity, there are instances where mimicry (cross-reactivity) provides protection for the host, termed heterologous immunity [22]. Cross-reactivity or mimicry between various strains of viruses or bacteria could help explain how protective immunity arises in certain individuals even in the absence of prior exposure to an emerging pathogen. This example of sequence homology in which molecular mimicry between viruses leads to protective immunity is in contrast to a pathogen mimicking host epitopes (reviewed in [11]).

Brief History of Molecular Mimicry

Over 30 years ago, molecular mimicry by either a virus [18] or bacteria [23] was hypothesized to initiate and exacerbate an autoimmune response through sequence or structural similarities with self-antigens. Currently, molecular mimicry is the prevailing hypothesis as to how viral antigens initiate and maintain autoimmune responses which lead to specific tissue damage [18]. Initial work by Fujinami, Oldstone, and colleagues identified mouse antibodies to measles virus and herpes simplex virus (HSV-1) obtained from antibody-secreting B cell clones [18]. These antibodies were reactive to both intermediate filaments of normal cells and the proteins of measles virus and HSV-1,

Table 1 Examples of human autoimmune diseases with possible molecular mimicry as a mechanism

Human diseases	Target	T cells/Ab	Human antigen mimicked	Organism	Reference(s)
Spondyloarthropathies (SpAs), ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated SpA	Lumbar spine and sacroiliac joints	Abs	HLA-B27	*Klebsiella pneumoniae*, *Shigella*, *Chlamydia trachomatis*, and other gram-negative bacteria	[71–73]
Antiphospholipid syndrome	Fetal loss and thromboembolic phenomena	Abs	β2-glycoprotein I	Bacteria, viruses, yeast, and tetanus toxin	[74]
Autoimmune chronic gastritis (AIG) (gastric atrophy, hypochloridria and pernicious anemia)	Stomach epithelium cells or parietal cell canaliculi	T cell/Abs	H^+, K^+-ATPase, parietal cell canaliculi	*Helicobacter pylori*	[75]
Cogan's syndrome	Eye and ear	Abs	SSA/Ro; (DEP-1/CD148); connexin 26	Reovirus III major core protein lambda 1	[76]
Autoimmune thrombocytopenic purpura	Platelet	Abs	Platelet; platelet-associated immunoglobulin G (PAIgG)	*Helicobacter pylori*	[77]
Behçet's disease	Eyes, skin, oral cavity, joints, genital system, CNS and blood vessels	T cell	HSP60, HSP65, HSP70, alpha-tropomyosin, S-antigens	Mycobacterial HSP, *Plasmodium falciparum*	[78–82]
Cardiomyopathy (myocarditis)	Heart	T cell/Abs	Cardiac myosin	Coxsackie virus, group A streptococci, chlamydia, or *Trypanosoma cruzi*	[83]
Celiac sprue (celiac disease)	Small intestine	T cell	Transglutaminase	Gliadin (gluten), perinatal infections, adenovirus 12, hepatitis C virus (HCV)	[84, 85]
Chagas disease	Heart	T cell	Cardiac myosin	*Trypanosoma cruzi* B13 protein	[86, 87]
Chronic inflammatory demyelinating polyneuropathy	Schwann cells	Abs	Monosialoganglioside GM2	Melanoma, *Campylobacter jejuni*	[88, 89]
Crohn's disease	Gastrointestinal tract	T cell	Unknown	Gram-positive bacterial peptidoglycans	[90]
Dermatomyositis (juvenile)	Skin and muscle	T cell	Skeletal myosin	*Streptococcus pyogenes* M5 protein	[91]
Essential mixed cryoglobulinemia	B cell	Abs	IgG-Fc	HCV	[92]
Guillain-Barré syndrome	Gangliosides and peripheral nerve	Abs	Peripheral nerve	*Campylobacter jejuni*	[93]
Insulin dependent diabetes (type I)	Pancreas	T cell	Islet antigens (GAD 65, proinsulin carboxypeptidase H)	Coxsackie B virus, rubella, rotavirus, herpes, rhinovirus, hantavirus, flavivirus and retrovirus	[94–96], (reviewed in [97]); [98–100]
Systemic lupus erythematosus	Systemic	Abs	60 Kda Ro	Epstein–Barr virus (EBV nuclear antigen-1)	[101]
Multiple sclerosis	Myelin	T cell	Myelin basic protein	EBV, measles and HHV-6	[11, 35, 102]
Primary biliary cirrhosis	Liver (intrahepatic bile ducts)	Abs/B and T cell	PDE2, GP210, human pyruvate dehydrogenase complex-E2 (PDC-E2), HLA-DR	Gram-negative bacterium, *Escherichia coli*, *Helicobacter pylori*, *Pseudomonas aeruginosa*, cytomegalovirus, and *Haemophilus influenza*	[103–107]
Psoriasis	Skin	T cell	Epidermal keratins	*Streptococcus pyogenes* (streptococcal M protein)	[108]
Rheumatic fever	Heart	Abs/T cell	Cardiac myosin	M protein (major virulence factor of group A streptococci) and streptococcus carbohydrate epitope GlcNAc	[12, 109–111]
Rasmussen's encephalitis	CNS	Abs	Antiglutamate receptor (GLUR3)	Microorganisms	[112, 113]
Acute disseminating encephalomyelitis	CNS	T cell	Myelin basic protein	Measles virus, rabies vaccine, HHV-6, coronavirus, influenza virus hemagglutinin, EBV, Semliki Forest virus	[114, 115], reviewed in [116]

Table 1 (continued)

Human diseases	Target	T cells/Ab	Human antigen mimicked	Organism	Reference(s)
Myasthenia gravis	CNS	Abs	Acetylcholine receptor, neurofilaments	Herpes simplex virus type 1 gpD	[117]
Graft vs host disease	Solid organ transplant	Abs	HLA-DR, CD13 (aminopeptidase N)	Human cytomegalovirus (hCMV)	[118, 119]
Herpes stromal keratitis	Eye	T cell	Corneal tissue	Herpes simplex virus-type 1	[120]
Lyme arthritis	Joints	Abs	Human leukocyte function-associated antigen-1 (hLFA-1)	*Borrelia burgdorferi*	[121]
Sydenham's chorea	Brain	Abs	β-Tubulin, GlcNAc, calcium/calmodulin-dependent protein (CaM)	Goup A streptococcus	[122, 123]
Autoimmune uveitis	Eye and pineal gland in the brain	T cell	S-Antigen, interphotoreceptor binding protein (IRBP)	Viruses	[124]
Scleroderma	Endothelial cells	Abs	NAG-2 (tetraspan novel antigen-2)	hCMV UL94 protein	[125, 126]
Sjögren's syndrome	Systemic	Abs	Ro60 kD	Coxsackie virus	[127]
Stiff-person syndrome	Neurons and β cells	T cell/Abs	GAD65	hCMV (pUL57)	[128, 129]
Peptic/gastric ulcer	Gastric mucosa	Abs	Gastric mucosa antigens (Lewis antigens)	*Helicobacter pylori*	[130]

thereby demonstrating a relatedness between host and viral antigens [18]. Further work by Fujinami and Oldstone used myelin basic protein (MBP), a nerve sheath protein containing an encephalitogenic T cell epitope in rabbits. The hepatitis B virus polymerase (HBVP) protein was found through computer analysis to share six consecutive amino acids with the encephalitogenic MBP epitope [16], and when rabbits were sensitized with either MBP or HBV peptides, the rabbit's tissue serum reacted against MBP. Further, rabbits sensitized with the HBVP peptide developed central nervous system (CNS) pathology similar to rabbits sensitized with whole MBP protein or the MBP peptide [16]. Importantly, the rabbits sensitized with HBVP did not contract hepatitis but still developed encephalomyelitis and presented with a similar pathology as MBP-sensitized mice. These experiments were the first experimental demonstration of molecular mimicry, whereby a microbial peptide with similar amino acid sequences to the self-peptide was able to activate autoreactive T cells and subsequently cause specific tissue damage.

Relationship Between Molecular Mimicry and Autoimmune Diseases

Immune cells of the adaptive immune response are specifically activated, but the hallmark of autoimmunity is the dysregulation of the immune system, especially T and B cells recognizing self-antigens as foreign. The ability of T cells to evade central (thymic selection) and peripheral (Tregs) mechanisms of tolerance is evident by the large number of T cell-mediated human autoimmune diseases, such as type-1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis (MS) [24–28]. Molecular mimicry has been implicated in the pathogenesis of many of these autoimmune diseases including MS, spondyloarthropathies, Graves' disease, and diabetes mellitus [16, 29, 30]. In the case of MS, it has been hypothesized that certain viruses, such as Epstein–Barr virus (EBV), share sequence homology with antigenic structures in the CNS [31].

Activation of an autoimmune response could be enhanced by a variety of other, albeit, non-mutually exclusive non-specific mechanisms including bystander activation and superantigens. The difference between other non-specific mechanisms that initiate autoimmunity and molecular mimicry is that microbial mimics specifically direct the immune response towards a tissue and/or organ. Originally, T cell recognition was postulated to be highly specific and cross-reactivity was thought to be a rare phenomenon. However, the structural requirements for peptide binding by MHC class II molecules that are presented to T cells were found to be based on amino

acid properties, and amino acids sharing similar chemical features were able to bind at the same MHC peptide binding groove, thereby demonstrating that binding motifs were degenerate with only a small sequence needed for TCR recognition [32–34]. An illustration of TCR degeneracy was shown by Wucherpfennig and Strominger [35] using chemically related synthetic peptides mimicking the MBP(85–99) epitope that were incubated with human MBP(85–99)-specific T cell clones which were then tested for reactivity. Of the T cell clones that responded to the synthetic peptides, only eight of the 129 synthetic peptides were recognized by the T cell clones, and only one of the synthetic peptides that induced a response was clearly similar to MBP(85–99) [35, 36]. Therefore, these studies clearly demonstrate TCRs binding to a spectrum of specific peptides that is based upon structural relatedness, termed poly-specificity [37]. This flexibility exhibited by TCR binding and the existence of pathogens that share sequence or structural similarities with self-antigens could be one reason why investigators have been unable to conclusively associate a specific virus with autoimmune diseases, such as MS (reviewed in [4]).

Linear sequence matches in amino acid motifs is not the only criteria for mimicry [32]. It has been hypothesized that self-reactive immune cells are primed by molecular mimicry and bystander activation, thereby sensitizing the immune cells and leading to a "fertile field" but no apparent disease. Subsequent environmental insults could induce these sensitized autoreactive cells to cause an autoimmune disease. Work from our laboratory demonstrated that recombinant viruses having molecular mimicry with self-CNS antigens were unable to initiate an autoimmune disease individually [38]. However, infected mice that were subsequently challenged, after viral clearance, with a non-specific immunologic insult developed disease [38]. Further, subsequent experiments showed that conventional inflammatory responses to specific pathogens were able to induce disease in animals primed with a molecular mimic to a CNS antigen [39]. Therefore, not only is the priming of the immune system necessary for an autoimmune disease but the milieu to which the primed immune cells are exposed is an important factor in initiating an autoimmune disease. Animal models of various autoimmune diseases have explored the role of molecular mimicry as a contributing factor (Table 2).

The use of transgenic (tg) mice expressing virus proteins as transgenes in specific organs has been an important model for providing evidence for molecular mimicry. The expression of lymphocytic choriomeningitis virus (LCMV) viral antigens in pancreatic islet cells and the subsequent cross of this tg mouse with a TCR-tg mouse specific for LCMV glycoprotein resulted in an animal that only developed autoimmune disease if virally infected [40, 41]. These results demonstrated that "self"-reactive T cells are present in the periphery and the immune cells appear to remain quiescent until an appropriate signal (viral infection) triggers the T cells to respond.

Dual TCR and How This Impacts Our Interpretation of Molecular Mimicry

There are a variety of non-mutually exclusive factors that lead to a fully activated T cell, such as the quantity of peptide–MHC presented on the surface of antigen-presenting cells and TCR avidity. The interaction between the peptide–MHC and TCR is critical for the initiation of an adaptive immune response and clearance of a pathogen [15]. In order for T cells to reach maturity, the T cell goes through a number of developmental checkpoints leading to somatic recombination of various gene segments. The TCR α- and β-chains are generated by V-D-J recombination, which leads to αβ TCRs expressed on the surface of T cells [42, 43]. Although it was believed that T cell signaling was mediated by a single antigen receptor, recent evidence demonstrates that T cells are capable of expressing functional dual Vα TCRs at a frequency of approximately 30% in humans and 15% in mice; however, an accurate number of dual specific TCRs is lacking due to the limited availability of anti-Vα monoclonal antibodies (mAbs) [44–46]. Interestingly, in contrast to the high frequency of dual expressing Vα T cells, only 1% of humans and 5–7% of mice express two β-chains due to allelic exclusion mechanisms, but the frequencies of dual Vβ TCRs have been found to be higher with age and in TCR-tg mice [47–49]. Expression of multiple TCR Vαs on the surface of a T cell is the result of simultaneous rearrangement of both TCRα loci during thymocyte development [50–52]. Further, TCR Vβ-chains preferentially bind to certain Vα-chains leading to differential expression of chimeric TCRs on the surface of T cells [51, 53, 54].

Due to the heterogeneity of TCRs normally expressed in the periphery of humans and mice, TCR-tg mice have been used to track and determine the fate of T cells expressing dual TCRs. The use of TCR-tg mice has led to the identification of a potential role for dual TCRs in a variety of conditions including graft-versus-host disease, human immunodeficiency virus infection, inflammatory bowel disease, T cell leukemia, T cell lymphoma, and MS [55–61].

The expression of dual TCRs by the same T cell has been proposed to be a potential mechanism for autoimmune disease. Normally, high avidity self-reactive T cells are thymically depleted, but it has been hypothesized that the expression of a self-TCR on a T cell is lower when presented in the context of a second TCR, thereby providing a cover for high avidity self-TCRs from both central and peripheral tolerance. Blichfeldt et al. [62]

Table 2 Examples of murine models of autoimmune diseases where molecular mimicry is proposed as a mechanism

Human autoimmune disease	Mouse strain	Initiating agent(s)	Reference(s)
Behçet's disease	ICR mice	HSV type 1 (F strain) inoculation in ear lobe	[131]
Myocarditis	BALB/c	Mouse cytomegalovirus (MCMV)	[132]
Insulin-dependent diabetes (type I)	Tg mice expressing LCMV protein in pancreas	Pichinde virus infection of mice	[133]
Guillain–Barré syndrome	BALB/c	lipooligosaccharide of *Brucella melitensis*	[134]
Autoimmune hepatitis type 2	FVB	infection with recombinant adenovirus encoding human cytochome CYP2D6	[135, 136]
Herpes stromal keratitis	C.AL-20	HSV-1	[120, 137]
Autoimmune uveitis	C3H/HeN	*Salmonella typhimurium*	[138, 139]
Sjögren's syndrome	C57BL/6; [B6]+/+; Fas-deficient B6-lpr/lpr; TNFR1-deficient B6; and TNFR1-deficient lpr/lpr)	MCMV	[140]
Multiple sclerosis	SJL/J	Theiler's murine encephalomyelitis virus	[141]
	C57BL/6	Semliki Forest virus infection	[142]

demonstrated that dual tg-TCRs, which have lower expression of each TCR on the surface of a T cell, needed higher concentrations of peptide, presented by MHC, to induce a similar T cell proliferative response compared to a single receptor T cell.

A potential role of dual TCRs in autoimmunity is in the rescue of autoreactive T cells from thymic selection. For example, the double tg mouse for autoimmune diabetes, in which the mice express a TCR specific for peptide 111–119 of hemagglutinin (HA) (TCR-HA) under the control of the rat insulin promoter and develop spontaneous diabetes and insulitis [63], were used to determine how T cells could escape tolerance mechanisms even if the antigen was ubiquitously expressed [64]. Low expressing TCR-HA co-expressing T cells were more effective at transferring diabetes than TCR-HA high dual TCRs, suggesting that the surface level expression of a dual TCR can be modulated by a second TCR expressed on the same T cell, thus "escape" of autoreactive T cells could be the first step in an autoimmune disease.

The "trigger" of an autoimmune disease could be linked to environmental insults, such as viruses. A T cell co-expressing TCRs specific for a self-antigen and a foreign antigen could potentially allow for autoreactive T cells to be activated if the host is exposed to that foreign antigen. The activation of a subset of T cells could than lead to tolerance being broken and the initiation of an autoimmune disease if these T cells experienced a particular organ or tissue that expressed the self-antigen for the other TCR expressed at the surface of the T cell. In support of a role for dual TCRs in autoimmune diseases, work performed in our laboratory characterized autoreactive $CD8^+$ T cells isolated from the spleens of Theiler's murine encephalomyelitis virus (TMEV)-infected SJL/J mice [65]. In vitro assays testing $CD8^+$ T cell killing activity found a population of $CD8^+$ T cells that killed uninfected syngeneic cells [65]. Adoptively transferring these TMEV-specific autoreactive $CD8^+$ T cells into non-infected SJL/J mice caused CNS pathology [65]. Further support for the importance of the mechanism by which viral infection could induce an autoimmune disease through dual TCR-expressing T cells was performed by Ji et al. [61] using MBP(79–87) TCR-tg mice [66]. Cytometric phenotyping, in vitro $CD8^+$ T cell killing assays, and adoptive transfer experiments were used to track the expansion and killing capacity of Vα8Vβ8 MBP (79–87)-specific TCR and Vα8Vβ6-vaccinia virus-specific TCR. Infection of these tg mice with vaccinia virus induced autoimmune disease, thus demonstrating a virus triggering an autoimmune disease through dual TCR expressing T cells [61]. Although several tg TCR β-chains have been described on peripheral T cell [61, 67–70], there is no evidence that co-expression of dual TCRs leads to autoimmunity without the use of TCR-tg mice. As described above, current work in our laboratory has characterized TMEV-specific autoreactive $CD8^+$ T cell clones derived from a wild-type animal, and these autoreactive TMEV-specific T cell clones express dual TCRs (manuscript in preparation). Importantly, we were able to induce CNS pathology in naïve SJL/J mice by adoptively transferring the TMEV-specific clones. Although further work is needed in order to identify the self-antigen that activates these $CD8^+$ T cells, to our knowledge these results are the first demonstration of an autoimmune disease initiated by a dual expressing TCR characterized in the virus' natural host.

Taken together, three possible mechanisms could explain how the dual reactivity of the TCR may play a role in autoimmune diseases (manuscript in preparation). The first mechanism is molecular mimicry, whereby the induction of

an autoimmune response to self is due to a single TCR recognizing both a virus and a self-antigen. The second mechanism is the expression of dual TCRs on a single T cell, where one TCR is able to recognize a microbial antigen and the other TCR recognizes self. The third mechanism involves a T cell expressing chimeric TCRs generated from either a single Vα combining with two different Vβs or a single Vβ combining with two different Vαs, resulting in a T cell with the potential of expressing two different chimeric TCRs specific for a self-antigen and a foreign antigen.

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