Molecular Mimicry as a Mechanism of Autoimmune Disease

Matthew F. Cusick · Jane E. Libbey · Robert S. Fujinami

Published online: 19 November 2011 © Springer Science+Business Media, LLC 2011

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...
causes group A streptococcal infection that is responsible for a number of diseases. The complications associated with \textit{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 \textit{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 \textit{Klebsiella pneumoniae} and \textit{Campylobacter jejuni}. Infection with \textit{K. pneumonia} or \textit{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,
| Human diseases | Target | Human antigen mimicked | 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 thrombembolic phenomena | Abs | β2-glycoprotein I | Bacteria, viruses, yeast, and toxoplasmosis | [74] |
| Autoimmune chronic gastritis (AIG) | 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, mouth, 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 | Coxsvirus, group A streptococci, enteroviruses, adenovirus 12, hepatitis C virus (HCV), Trypanosoma cruzi, B13 protein | [83] |
| Celiac sprue (celiac disease) | Small intestine | T cell | Transglutaminase | Gliadin (gluten), perinatal infections, adenovirus 12, hepatitis C virus (HCV), E. coli O157:H7, C. jejuni, M. avium, L. monocytogenes, S. typhimurium, S. enteritidis, S. typhi | [84, 85] |
| Chagas disease | Heart | T cell | Cardiac myosin | Trypanosoma cruzi B13 protein | [86, 87] |
| Chronic inflammatory demyelinating polyneuropathy | Schwann cells | Abs | Monosialoganglioside GM1 | Melanoma, Campylobacter jejuni | [88, 89] |
| Crohn’s disease | Gastrointestinal tract | T cell | Unknown | Alpha-tropomyosin, S-antigens | [90] |
| Dermatomyositis (juvenile) | Skin and muscle | T cell | Skeletal myosin | Streptococcus pyogenes | [91] |
| Essential mixed cryoglobulinemia | B cells | Abs | IgG-Fc | HCV | [92] |
| Guillain-Barré syndrome | Peripheral nerve | Abs | Campylobacter jejuni | Campylobacter jejuni | [93] |
| Insulin dependent diabetes (type I) | Pancreas | T cell | Myelin basic protein | EBV, measles, and HHV-6 | [94–96], reviewed in [97] |
| Systemic lupus erythematosus | Systemic | Abs | 60 Kda Ro | Epstein-Barr virus, cytomegalovirus, and EBV nuclear antigen-1 | [101] |
| Multiple sclerosis | Myelin | Abs | PDE2, GP210, human pyruvate dehydrogenase complex-E2 | Myelin basic protein, myelin basic protein | [102] |
| Rheumatoid arthritis | Primary biliary cirrhosis | Abs | Mycetogenous (GAD 65, prionin, carbonic anhydrase H) | Epithelial keratin | [103] |
| Psoriasis | Skin | Abs | Mycetogenous (GAD 65, prionin, carbonic anhydrase H) | Epidermal keratin | [104–106] |
| Rasmussen’s encephalitis | CNS | Abs | Antigliutamate receptor (GLUR3) | Mycetogenous (GAD 65, prionin, carbonic anhydrase H) | [108] |
| Acute disseminating encephalomyelitis | CNS | Abs | Mycetogenous (GAD 65, prionin, carbonic anhydrase H) | Mycetogenous (GAD 65, prionin, carbonic anhydrase H) | [109–111] |
thereby demonstrating a relatedness between host and viral antigens. 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, 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. 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). Molecular mimicry has been implicated in the pathogenesis of many of these autoimmune diseases including MS, spondyloarthropathies, Graves' disease, and diabetes mellitus. 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.

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 sequences.
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]...
demonstrated that dual 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 then 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 autoimmunity, work performed in our laboratory characterized autoreactive CD8⁺ T cells isolated from the spleens of Thélier’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

---

**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 1) | Tg mice expressing LCMV protein in pancreas | Pichinde virus infection of mice | [133] |
| Guillain–Barré syndrome           | BALB/c      | lipo polysaccharide of Brucella melitensis                  | [134]        |
| Autoimmune hepatitis type 2       | FVB         | infection with recombinant adenovirus encoding human cytochrome 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]        |

---

 автоиммунная болезнь | ICR мышь | HSV типа 1 (F штамм) инокуляция в уши | [131] |
|-------------------|----------|-------------------------------------|-------|
| Миокардит         | BALB/c   | Мышь вируса цитомегаловирус (MCMV)  | [132] |
| Диабет на основе инсулина (тип 1) | Tg мышь, выражающая LCMV белок в поджелудочной железе | Вирус Пичинда инфекция мышей | [133] |
| Болезнь Гиллан-Барре | BALB/c | липополисахарид Бруцелла мелинис | [134] |
| Аутоиммунный хепатит типа 2 | FVB | инфицирование рекомбинантным адено вирусом, кодирующим человеческий цитохром CYP2D6 | [135, 136] |
| Герпетическая стоматокератит | C.AL-20 | HSV-1 | [120, 137] |
| Аутоиммунная увеит | C3H/HeN | Б. тифимуриум | [138, 139] |
| Синдром Сёэгrena | C57BL/6; [B6]+/+; Fas-дефицитный B6-Lpr/lpr; TNFR1-дефицитный B6; и TNFR1-дефицитный lpr/lpr | МCMV | [140] |
| Множественная склероз | SJL/J | Вирус Thélier’s encephalomyelitis virus | [141] |
| | C57BL/6 | Вирус Semliki Forest virus инфекция мышей | [142] |
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 or a single Vβ 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.

Acknowledgments We wish to thank Ms. Kathleen Borick for her excellent preparation of the manuscript. This work was supported by NIH 1R01NS065714.

References

1. Abou-Raya A, Abou-Raya S (2006) Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmun Rev 5:331–337
2. Selgrade MK, Cooper GS, Germolec DR, Heindel JJ (1999) Linking environmental agents and autoimmune disease: an agenda for future research. Environ Health Perspect 107(Suppl 5):811–813
3. von Herrath MG, Fujinami RS, Whitley JL (2003) Microorganisms and autoimmunity: making the barren field fertile? Nat Rev Microbiol 1:151–157
4. Libbey JE, Fujinami RS (2010) Potential triggers of MS. Results Probl Cell Differ 51:21–42
5. Fujinami RS (2001) Viruses and autoimmune disease—two sides of the same coin? Trends Microbiol 9:377–381
6. Ascherio A, Munger KL (2007) Environmental risk factors for multiple sclerosis. Part II: noninfectious factors. Ann Neurol 61:504–513
7. McCoy L, Tsunoda I, Fujinami RS (2006) Multiple sclerosis and autoimmunity: the multifaceted relationship. J Leukoc Biol 87:385–395
8. Sfriso P, Ghirardello A, Botsios C et al (2010) Infections and autoimmunity: the multifaceted relationship. J Leukoc Biol 87:385–395
9. Trinchieri G (2010) Type I interferon: friend or foe? J Exp Med 207:2053–2062
10. Iwakura Y, Ishigame H, Saijo S, Nakae S (2011) Functional specialization of interleukin-17 family members. Immunity 34:149–162
11. Libbey JE, McCoy LL, Fujinami RS (2007) Molecular mimicry in multiple sclerosis. Int Rev Neurobiol 79:127–147
12. Whitten JL, Feuer R (2004) Myocarditis, microbes and autoimmunity. Autoimmunity 37:375–386
13. Libbey JE, Fujinami RS (2010) Role for antibodies in altering behavior and movement. Autism Res 3:147–152
14. Shahrizaila N, Yuki N (2011) Guillain–Barré syndrome animal model: the first proof of molecular mimicry in human autoimmune disorder. J Biomed Biotechnol 2011:829129
15. Ahmed R (1992) Immunological memory against viruses. Semin Immunol 4:105–109
16. Fujinami RS, Oldstone MBA (1985) Amino acid homology between the encephalitogenic site of myelin basic protein and virus: Mechanism for autoimmunity. Science 230:1043–1045
17. Oldstone MBA (1987) Molecular mimicry and autoimmune disease. Cell 50:819–820
18. Fujinami RS, Oldstone MBA, Wroblewska Z, Frankel ME, Koprowski H (1983) Molecular mimicry in virus infection: crossreaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments. Proc Natl Acad Sci USA 80:2346–2350
19. McRae BL, Vanderlugt CL, Dal Canto MC, Miller SD (1995) Functional evidence for epitope spreading in the relapsing pathology of experimental autoimmune encephalomyelitis. J Exp Med 182:75–85
20. Vanderlugt CL, Begolka WS, Neville KL et al (1998) The functional significance of epitope spreading and its regulation by co-stimulatory molecules. Immunol Rev 164:63–72
21. Scherer MT, Ignatowicz L, Winslow GM, Kapppler JW, Marrack P (1993) Superantigens: Bacterial and viral proteins that manipulate the immune system. Annu Rev Cell Biol 9:101–128
22. Chen HD, Fraire AE, Joris I, Brehm MA, Welsh RM, Selin LK (2001) Memory CD8+ T cells in heterologous antiviral immunity and immunopathology in the lung. Nat Immunol 2:1067–1076
23. Zabriskie JB, Freimer EH (1966) An immunological relationship between the group A streptococcus and mammalian muscle. J Exp Med 124:661–678
24. Gregersen PK, Silver J, Winchester RJ (1987) The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 30:1205–1213
25. Burns J, Rosenzweig A, Zweiman B, Lisak RP (1983) Isolation of myelin basic protein-reactive T-cell lines from normal human blood. Cell Immunol 81:335–440
26. Mathis D, Vence L, Benoist C (2001) β-Cell death during progression to diabetes. Nature 414:792–798
27. Tisch R, McDevitt H (1996) Insulin-dependent diabetes mellitus. Cell 85:291–297
28. Bertsias GK, Salmon JE, Boumpas DT (2010) Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade. Ann Rheum Dis 69:1603–1611
29. Ebringer A, Baines M, Ptaszynska T (1985) Spondyloarthropathy, uveitis, HLA-B27 and Kliedessierta. Immunol Rev 86:1–116
30. Quarantino S, Thorpe CJ, Travers PJ, Londei M (1995) Similar antigenic surfaces, rather than sequence homology, dictate T-cell epitope molecular mimicry. Proc Natl Acad Sci USA 92:10398–10402
31. Wucherpfennig KW, Southwood S et al (1994) Association of myelin basic protein-reactive T-cell lines from normal human blood. Cell Immunol 81:335–440
32. Sinigaglia F, Hammer J (1994) Defining rules for the peptide–MHC class II interaction. Curr Opin Immunol 6:52–56
33. Wucherpfennig KW, Strominger JL (1995) Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 80:695–705
34. Hausmann S, Martin M, Gauthier L, Wucherpfennig KW (1999) Structural features of autoreactive TCR that determine the degree of degeneracy in peptide recognition. J Immunol 162:3946–3957
35. Wucherpfennig KW, Allen PM, Celada F et al (2007) Polyspecificity of T cell and B cell receptor recognition. Semin Immunol 19:216–224
51. Marolleau J-P, Fondell JD, Malissen M et al (1988) The joining of

50. Alam SM, Crispe IN, Gascoigne NR (1995) Allelic exclusion of

47. Davodeau F, Peyrat M-A, Romagné F et al (1995) Dual T cell

45. Padovan E, Casorati G, Dellabona P, Meyer S, Brockhaus M,

40. Ohashi PS, Oehen S, Buerki K et al (1991) Ablation of

39. Tsunoda I, Libbey JE, Fujinami RS (2007) Sequential poly-

36. Taupin J-L, Halary F, Dechanet J et al (1999) An enlarged

35. Oldstone MBA, Nerenberg M, Southern P, Price J, Lewicki H (1991) Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. Cell 65:319–331.

34. Petrie HT, Livak F, Schatz DG, Strasser A, Crispe IN, Shortman K (1993) Multiple rearrangements in T cell receptor α chain genes maximize the production of useful thymocytes. J Exp Med 178:615–622.

33. Pang SS, Berry R, Chen Z et al (2010) The structural basis for autonomous dimerization of the pre-T-cell antigen receptor. Nature 467:844–848.

32. Casanova J-L, Romero P, Widmann C, Kourilsky P, Maryanski JL (1991) T cell receptor genes in a series of I major histocompatibility complex-restricted cytotoxic T lymphocyte clones specific for a Plasmodium berghei nonapeptide: implications for T cell allelic exclusion and antigen-specific repertoire. J Exp Med 174:1371–1383.

31. Padovan E, Casorati G, Dellabona P, Meyer S, Brockhaus M, Lanzavecchia A (1993) Expression of two T cell receptor α chains: dual receptor T cells. Science 262:422–424.

30. Corlay H, Nandakumar KS, Holmdahl R (2001) Evaluation of the percentage of peripheral T cells with two different T cell receptor α-chains and of their potential role in autoimmunity. J Autoimmun 16:423–429.

29. Davodeau F, Peyrat M-A, Romagné F et al (1995) Dual T cell receptor β chain expression on human T lymphocytes. J Exp Med 181:1391–1398.

28. Padovan E, Giachino C, Cellà M, Valitutti S, Acuto O, Lanzavecchia A (1995) Normal T lymphocytes can express two different T cell receptor β chains: implications for the mechanism of allelic exclusion. J Exp Med 181:1587–1591.

27. Munthe I, Blachfeldt E, Sollien A, Dembic Z, Bogen B (1996) T cells with two TcR chains and reactivity to both MHC/idiotype peptide and superantigen. Cell Immunol 170:283–290.

26. Alam SM, Crispe IN, Gascoigne NR (1995) Allelic exclusion of mouse T cell receptor α-chains occurs at the time of thymocyte TCR up-regulation. Immunity 3:449–458.

25. Marolleau J-P, Fondell JD, Malissen M et al (1988) The joining of germ-line Vα to Jα genes replaces the preexisting Vα-Jα complexes in a T cell receptor α, β positive T cell line. Cell 55:291–300.

24. Malissen M, Trucy J, Letourneur F et al (1988) A T cell clone expresses two T cell receptor α genes but uses one αβ heterodimer for allorecognition and self MHC-restricted antigen recognition. Cell 55:49–59.

23. Saito T, Sussman JL, Ashwell JD, Germain RN (1989) Marked differences in the efficiency of expression of distinct αβ T cell receptor heterodimers. J Immunol 143:3379–3384.

22. Vacchio MS, Granger L, Kanagawa O et al (1993) T cell receptor Vα-Vβ combinatorial selection in the expressed T cell repertoire. J Immunol 151:1322–1327.

21. Morris GP, Allen PM (2009) Cutting edge: highly alloreactive dual TCR T cells play a dominant role in graft-versus-host disease. J Immunol 182:6639–6643.

20. Taupin J-L, Halary F, Dechanet J et al (1999) An enlarged subpopulation of T lymphocytes bearing two distinct γδ TCR in an HIV-positive patient. Int Immunol 11:545–552.

19. Söderström K, Bucht A, Halapi E, Grönberg A, Magnusson I, Kiessling R (1996) Increased frequency of abnormal γδ T cells in blood of patients with inflammatory bowel diseases. J Immunol 156:2331–2339.

18. Hinz T, Marx S, Nerl C, Kabelitz D (1996) Clonal expansion of γδ T cells expressing two distinct T-cell receptor. Br J Haematol 94:62–64.

17. Boehrer S, Hinz T, Schui D et al (2001) T-large granular lymphocyte leukaemia with natural killer cell-like cytotoxicity and expression of two different α- and β-T-cell receptor chains. Br J Haematol 112:201–203.

16. Weidmann E, Hinz T, Klein S et al (2000) Cytotoxic hepatosplenic γδ T-cell lymphoma following acute myeloid leukemia bearing two distinct γ chains of the T-cell receptor. Biologic and clinical features. Haematologica 85:1024–1031.

15. Ji Q, Perchellet A, Governors JM (2010) Viral infection triggers central nervous system autoimmunity via activation of CD8+ T cells expressing dual TCRs. Nat Immunol 11:628–634.

14. Blichfeldt E, Munthe LA, Rotnes JS, Bogen B (1996) Dual T cell receptor T cells have a decreased sensitivity to physiological ligands due to reduced density of each T cell receptor. Eur J Immunol 26:2876–2884.

13. Sarukhan A, Lanoue A, Franzke A, Brousse N, Buer J, von Boehmer H (1998) Changes in function of antigen-specific lymphocytes correlating with progression towards diabetes in a transgenic model. EMBO J 17:71–80.

12. Sarukhan A, García C, Lanoue A, von Boehmer H (1998) Allelic inclusion of T cell receptor α genes poses an autoimmune hazard due to low-level expression of autoreactive receptors. Immunity 8:563–570.

11. Tsunoda I, Kuang L-Q, Kobayashi-Warren M, Fujinami RS (2005) Central nervous system pathology caused by autoreactive CD8+ T cell clones following virus infection. J Virol 79:14640–14646.

10. Perchellet A, Storones I, Pang JM, Governors J (2004) CD8+ T cells maintain tolerance to myelin basic protein by ‘epitope theft’. Nat Immunol 5:606–614.

9. Borgulya P, Kishi H, Uematsu Y, von Boehmer H (1992) Exclusion and inclusion of α and β T cell receptor alleles. Cell 69:529–537.

8. Balomenos D, Balderas RS, Mulvany KP, Kaye J, Kono DH, Theofilopoulos AN (1995) Complete T cell receptor Vβ repertoire and Vβ-expressing cells. J Immunol 155:3308–3312.

7. Hurst SD, Sitterding SM, Ji S, Barrett TA (1997) Functional differentiation of T cells in the intestine of T cell receptor transgenic mice. Proc Natl Acad Sci USA 94:3920–3925.

6. Heath WR, Miller JFAP (1993) Expression of two α chains on the surface of T cells in T cell receptor transgenic mice. J Exp Med 178:1807–1811.

5. Stagg AJ, Breban M, Hammer RE, Knight SC, Taurog JD (1995) Defective dendritic cell (DC) function in a HLA-B27 transgenic rat model of spondyloarthropathy (SpA). Adv Exp Med Biol 378:557–559.

4. Ebringer R, Cawdell D, Ebringer A (1979) Klebsiella pneumoniae and acute anterior uveitis in ankylosing spondylitis. Br Med J 1:383.

3. Schwimmbeck PL, Yu DTY, Oldstone MBA (1987) Autointothebodies to HLA B27 in the sera of HLA B27 patients with ankylosing spondylitis and Reiter’s syndrome. Molecular mimicry with Klebsiella pneumoniae as potential mechanism of autoimmune disease. J Exp Med 166:173–181.

2. Shoenfeld Y, Blank M, Cervera R, Font J, Raschi E, Meroni PL (2006) Infectious origin of the antiphospholipid syndrome. Ann Rheum Dis 65:2–6.

1. Amedei A, Bergman MP, Appelmelk BJ et al (2003) Molecular mimicry between Helicobacter pylori antigens and H+, K+-...
adenosine triphosphatase in human gastric autoimmunity. J Exp Med 198:1147–1156
76. Lunardi C, Bason C, Leandri M et al (2002) Autoantibodies to inner ear and endothelial antigens in Cogan’s syndrome. Lancet 360:915–921
77. Takahashi T, Yujiri T, Shinohara K et al (2004) Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. Br J Haematol 124:91–96
78. DiRuskeneli H, Hasan A, Shinnick T et al (1996) Recognition of B-cell epitopes of the 65 kDa HSP in Behçet’s disease. Scand J Immunol 43:464–471
79. de Smet MD, Ramadan A (2001) Circulating antibodies to inducible heat shock protein 70 in patients with uveitis. Ocul Immunol Inflamm 9:85–92
80. Suzuki Y, Hoshi K, Matsuda T, Mizushima Y (1992) Increased peripheral blood yδ+ T cells and natural killer cells in Behçet’s disease. J Rheumatol 19:588–592
81. Mahesh SP, Li Z, Buggage R et al (2005) Alpha tropomyosin as a self-antigen in patients with Behçet’s disease. Clin Exp Immunol 140:368–375
82. de Smet MD, Dayan M (2000) Prospective determination of T-cell responses to S-antigen in Behçet’s disease patients and controls. Invest Ophthalmol Vis Sci 41:3480–3484
83. Cunningham MW (2004) T cell mimicry in inflammatory heart disease. Mol Immunol 40:1121–1127
84. Dieterich W, Ehnis T, Bauer M et al (1997) Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 3:797–801
85. Plot L, Amital H (2009) Infectious associations of Celiac disease. Autoimmun Rev 8:316
86. Iwai LK, Juliano MA, Juliano L, Kalil J, Cunha-Neto E (2005) Peripheral blood T cell mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. Br J Haematol 124:91–96
87. Cunha-Neto E, Bilate AM, Hyland KV, Fonseca SG, Kalil J, Cunha-Neto E (2005) Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clin Microbiol Rev 18:90–94
88. Koller H, Kieseier BC, Jander S, Hartung H-P (2005) Chronic inflammatory demyelinating polyneuropathy and melanoma. Neurology 64:360–364
89. Köller H, Kieseier BC, Jander S, Hartung H-P (2005) Chronic inflammatory demyelinating polyneuropathy and melanoma. Neurology 64:360–364
90. Clift K, Yarwood PJ, McMillan DJ et al (2001) Antibody responses to S-antigen in Behçet’s disease. Autoimmun Rev 8:316
91. Massa M, Costouros N, Mazzoli F et al (2002) Self epitopes shared between human skeletal myosin and Streptococcus pyogenes M5 protein are targets of immune responses in active juvenile dermatomyositis. Arthritis Rheum 46:3015–3025
92. De Re V, Sansonno D, Simula MP et al (2006) HCV-NS3 and IgG-Fc crossreactive IgM in patients with type II mixed cryoglobulinemia and B-cell clonal proliferations. Leukemia 20:1145–1154
93. Hemachudha T, Griffin DE, Giiffels JJ, Johnson RT, Moser AB, Phanuphak P (1987) Myelin basic protein as an antigen in encephalitis in encephalomyelitis and polyneuritis following rabies vaccination. N Engl J Med 316:369–374
115. Johnson RT, Griffin DE, Hirsch RL et al (1984) Measles
encephalomyelitis—clinical and immunologic studies. N Engl J Med 310:134–141

116. Tenenbaum S, Chitnis T, Ness J, Hahn JS (2007) Acute
disseminated encephalomyelitis. Neurology 68(Suppl 2):S23–S36

117. Schwimmbeck PL, Dybridge T, Drachman DB, Oldstone MBA
(1989) Molecular mimicry and myasthenia gravis. An autoimmune
genic site of the acetylcholine receptor α-subunit that has bio-
logic activity and reacts immunologically with herpes
simplex virus. J Clin Invest 84:1174–1180

118. Fujinami RS, Nelson JA, Walker L, Oldstone MBA (1988)
Sequence homology and immunologic cross-reactivity of human
cytomegalovirus with HLA-DR β chain: a means for graft
rejection and immunosuppression. J Virol 62:100–105

119. Nauclér CS, Larsson S, Möller E (1996) A novel mechanism
for an autoimmune disease: oral treatment of uveitis-patients
with an MHC-peptide crossreactive with autoantigen
lysate. Immunol Lett 57:193–201

120. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW (2003)
Molecular mimicry by herpes simplex virus-type 1: autoim-
une disease after viral infection. Science 297:1344–1347

121. Gross DM, Forsthuber T, Tary-Lehmann M et al (1998)
Identification of LFA-1 as a candidate autoantigen in treatment-
resistant Lyme arthritis. Science 281:703–706

122. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW (2002)
Mimicry and autoantibody-mediated neuronal cell signaling in
Sydenham chorea. Nat Med 9:194–920

123. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW (2007)
Tubulin is a neuronal target of autoantibodies in Sydenham’s
chorea. J Immunol 178:7412–7421

124. Thurauf SR, Diedrichs-Möhring M, Fricke H, Schäffer PA, Cantor H (1998)
Molecular mimicry by herpes simplex virus—role of molecular mimicry
in the pathogenesis of viral myocardiitis. Immunology 75:513–519

125. Christen U, Edelmann KH, McGavern DB et al (2004) A viral
epitope that mimics a self antigen can accelerate but not initiate
autoimmune diabetes. J Clin Invest 114:1290–1298

126. Watanabe K, Kim S, Nishiguchi M, Suzuki H, Watarai M (2005)
Brucella melitensis infection associated with Guillain-Barré
syndrome through molecular mimicry of host structures. FEMS
Immunol Med Microbiol 45:121–127

127. Hintermann E, Holdener M, Bayer M et al (2011) Epitope
spreading of the anti-CYP2D6 antibody response in patients
with autoimmune hepatitis and in the CYP2D6 mouse model. J
Autoimmun 37:242–253

128. Holdener M, Hintermann E, Bayer M et al (2008) Breaking
tolerance to the natural human liver autoantigen cytochrome
P450 2D6 by virus infection. J Exp Med 205:1409–1422

129. Avery AC, Zhao Z-S, Rodriguez A et al (1995) Resistance to
polymerase and host Lewis blood group antigens in autoim-
515
mmunity. Infect Immun 64:2031–2040

130. Sohn S, Lee ES, Bang D, Lee S (1998) Behcet’s disease-like
symptoms induced by the Herpes simplex virus in ICR mice. Eur
J Dermatol 8:21–23

131. Johnson RT, Griffin DE, Hirsch RL et al (1984) Measles
encephalomyelitis—clinical and immunologic studies. N Engl J Med 310:134–141

132. Appelmelk BJ, Simoons-Smit I, Negri R et al (1996) Potential
role of molecular mimicry between Helicobacter pylori lipo-
poly saccharide and host Lewis blood group antigens in autoim-
munity. Infect Immun 64:2031–2040

133. Johnson RT, Griffin DE, Hirsch RL et al (1984) Measles
encephalomyelitis—clinical and immunologic studies. N Engl J Med 310:134–141

134. Watanabe K, Kim S, Nishiguchi M, Suzuki H, Watarai M (2005)
Brucella melitensis infection associated with Guillain-Barré
syndrome through molecular mimicry of host structures. FEMS
Immunol Med Microbiol 45:121–127

135. Hintermann E, Holdener M, Bayer M et al (2011) Epitope
spreading of the anti-CYP2D6 antibody response in patients
with autoimmune hepatitis and in the CYP2D6 mouse model. J
Autoimmun 37:242–253

136. Holdener M, Hintermann E, Bayer M et al (2008) Breaking
tolerance to the natural human liver autoantigen cytochrome
P450 2D6 by virus infection. J Exp Med 205:1409–1422

137. Avery AC, Zhao Z-S, Rodriguez A et al (1995) Resistance to
herpes stromal keratitis conferred by an IgG2a-derived peptide.
Nature 376:431–434

138. de Smet MD, Chan CC (2000) Biphasic ocular inflammatory
response to endotoxin-induced uveitis in the mouse. Arch Ophthal-
mosc 45:121–127

139. Shen DF, Chang MA, Matteson DM, Buggage R, Koizich AT,
Chan CC (2000) Biphasic ocular inflammatory response to
endothxin-induced uveitis in the mouse. Arch Ophthalm-
mosc 45:121–127

140. Fleck M, Kern ER, Zhou T, Lang B, Mountz JD (1998) Murine
cytomegalovirus induces a Sjögren’s syndrome-like disease in
C57Bl/6-lpr/lpr mice. Arthritis Rheum 41:2175–2184

141. Yamada M, Zurbriggen A, Fujinami RS (1990) Monoclonal
antibody to Thelier’s murine encephalomyelitis virus defines a
determinant on myelin and oligodendrocytes, and augments
demyelination in experimental allergic encephalomyelitis. J Exp
Med 171:1893–1907

142. Mokhtarian F, Zhang Z, Shi Y , Gonzales E, Sobel RA (1999)
Molecular mimicry between a viral peptide and a myelin
oligodendrocyte glycoprotein peptide induces autoimmune demy-
elinating disease in mice. J Neuroimmunol 95:43–54

154