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Review

Molecular mimicry in neurological disease: what is the evidence?

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Abstract. Autoimmune diseases are a leading cause of disability and are increasing in incidence in industrialized countries. How people develop autoimmune diseases is not completely understood, but is related to an interaction between genetic background, environmental agents, autoantigens and the immune response. Molecular mimicry continues to be an important hypothesis that explains how an infection with an environmental agent results in autoimmune disease of the nervous system and other target organs. Although molecular mimicry has yet to be unequivocally proven, in the past several years there has been a sharpening of its definition with better experimental data implicating it as a cause of neurological disease in humans.

Keywords. Molecular mimicry, neurological, autoimmune, antibody, T lymphocyte, virus, bacteria, disease.

Overview and definition

The purpose of this review is to examine the contribution of molecular mimicry to the pathogenesis of immune-mediated diseases of the nervous system in humans. Animal models will be examined only as they relate to human neurological diseases. There are several general reviews on molecular mimicry involving almost every target organ, and readers are directed to these articles [1–7]. Molecular mimicry is immunological cross-reactivity in which patients develop an immune response to an environmental agent that cross-reacts with a host antigen resulting in autoimmune disease of the nervous system [1, 8–10]. To implicate molecular mimicry in the pathogenesis of disease, the following traditional criteria are generally accepted: (1) there is linear or conformational homology of a peptide between an environmental agent and self-antigen, (2) there is a cellular and/or antibody-mediated immune response directed to the homologous peptide, (3) the immune response is present in patients with disease and absent or reduced in patients

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without disease, (4) the immune response to the homologous peptide results in organ-specific damage and (5) the organ specific damage results in disease. Other corollaries that support the existence of molecular mimicry include: epidemiological data linking infection exposure to the neurological disease [3, 11, 12], evidence that the immune response contributes to the pathology of the disease process [11, 12], data showing mimicking epitopes are not random but include functionally significant regions of a molecule [4, 8, 13], data showing that the phenotype of the T cell reaction directed at the infecting agent is identical to that directed at the autoantigen [7] and animal models that closely mimic human disease [2, 5, 12, 14–16]. Although there is a vast amount of data showing cross-reactivity between infectious agents and host antigens, only recently have experiments been performed that strongly suggest that these cross-reactive immune reactions damage nervous system targets. Important scientific themes have evolved over time. These include data that indicate that structural mimicry, rather than sequence identity of protein or peptides, is more common when studying biologically relevant and potentially pathologic molecular mimics [1, 9, 17–25]. Furthermore, studies show that a cross-reactive immune response may not be limited to proteins, but may include interactions between proteins, lipids, nucleic acids, carbohydrates or post-translational modification of target antigens [12, 26–30]. In addition, original studies focused on cross-reactivity of cellular immune responses, however, current data indicate that antibody-mediated immune reactions are equally important [9, 13, 26, 27, 30, 31]. Thus, we will cite examples of human neurological diseases in which there is growing evidence that molecular mimicry contributes to their pathogenesis.

Examples of human neurological diseases associated with molecular mimicry

Table 1 provides an overview about our knowledge concerning the involvement of molecular mimicry in neurological diseases.

Sydenham's Chorea (SC)

Movement disorders are typically the result of damage to the basal ganglia or its connections in the human brain. Sydenham's Chorea (SC) is a neurological movement disorder characterized by involuntary choreoform movements and neuropsychiatric changes associated with infection by *Streptococcus pyogenes* [32, 33]. Clinical, pathological and imaging data show basal ganglia damage in these patients [27, 28, 34–36]. Following a sore ('strep') throat, patients, typically children, develop these neurological abnormalities as a consequence of acute rheumatic fever [32, 33]. In addition to SC, the sequalae of acute rheumatic fever include carditis, which can lead to permanent heart valve damage [27, 32]. For years, there has been solid evidence that molecular mimicry exists between streptococcal and human heart valve antigens that contribute to the pathogenesis of rheumatic heart disease [37, 38]. More recently, scientific data have accumulated showing that cross-reactive antibodies between specific group A streptococcal and human neural antigens contribute to the pathogenesis of SC via molecular mimicry [27–29]. Specifically, human monoclonal antibodies derived from an SC patient were shown to react with N-acetyl-β-D-glucosamine (GlcNAc), the immunodominant epitope of group A streptococcal carbohydrate, which is a major constituent of the bacterial cell wall [27]. Lysoganglioside GM1 (lyso-GM1), a glycolipid localized to the central nervous system (CNS), inhibited the monoclonal antibody binding to GlcNAc, implicating it as a molecular mimic of the GlcNAc of the group A streptococcal carbohydrate [27]. Remarkably, there was significantly less cross-reactivity with monosialogangliosides or disialogangliosides, which have similar carbohydrates structures to lyso-GM1 [27]. Importantly, lyso-GM1 is a CNS ganglioside that plays a role in neuronal signal transduction. The cerebrospinal fluid (CSF) and serum of patients with SC showed elevated antibody titers to lyso-GM1 compared to control populations [27]. In addition, both the human monoclonal antibody (mAb) (designated 24.3.1) and serum from an SC patient immunoreacted with the caudate nucleus of human brain and were inhibited by incubation with lyso-GM1 [27]. With cross-reactivity established between GlcNAc of group A streptococcal carbohydrate and lyso-GM1, as well as specificity of the immune reaction for CNS tissue, the next series of experiments were designed to test if this cross-reactive immune response was biologically active and potentially pathogenic. Like the CNS tissue, the human mAb was found to react with the human neuroblastoma cell line SK-N-SH [27]. The authors hypothesized that the mAb-lysoganglioside interaction would lead to a change in calcium/calmodulin-dependent protein kinase II (CaM kinase II activity) in these cells. This was found to be the case, as application of the mAb as well as serum from SC patients to the SK-N-SH cells resulted in an increase in CaM kinase II activity [27]. Given that CaM kinase II plays a

Table 1. Evidence for molecular mimicry in neurological diseases.

	Sydenham's chorea (SC)	CNS lupus	Guillain-Barré syndrome	Multiple sclerosis	Chronic neuro-borreliosis	HAM/TSP
Non-self antigen	N-acetyl-β-D-glucosamine (GlcNAc) group A *Streptococcus*	dsDNA	*Campylobacter jejuni* lipooligosaccharide	EBV DNA polymerase (627-641) – DRB5*0101 TCR-DR2a complex	multiple *Borrelia burgdorferi* proteins	HTLV-1-tax (immunodominant epitope)
Self-antigen	lysoganglioside GM1 (extracellular) β-tubulin (intracellular)	NR2 A/B subunits of NMDA receptor (D/E-W-D/E-Y-S/G)	human GM1, GD1a, GQ1b gangliosides	myelin basic protein (MBP) (85-99) DRB1*1501 TCR-DR2b complex	myelin-associated oligodendrocyte basic protein and other proteins	hnRNP A1 (M9 sequence: required for nuclear-cytoplasmic transport)
Cross-reactive antibodies or T cell clones	human mab 24.3.1 serum and CSF from SC patients	anti-dsDNA Ab (R4A murine Ab) serum and CSF Abs from SLE patients	IgG from GBS patients mab to LOS reacts with GM1 and peripheral nerves	human T cell clone Hy.2E11 isolated from an MS patient	T cell clone from the CSF of a chronic neuroborreliosis patient	serum and CSF IgG from HAM/TSP patients tax mab affinity-purified hnRNP A1 antibody
Biological effect on nervous system targets	induction of CaM kinase II and dopamine release in neurons	apoptosis of hippocampal neurons immunization of mice with D/E-W-D/E-Y-S/G causes neuronal loss and neuropsychiatric dysfunction	immunization of rabbits with LOS causes limb weakness and GBS pathology mab to LOS and IgG from GBS patients blocks action potentials in muscle spinal cord cultures	DRB*1501-MBP(85-99) complex present in human MS lesions Hy.2E11 recognizes both MBP and EBV	direct experiments not done – pathology shows CNS vasculitis and lymphocytic infiltrates	inhibition of neuronal firing
Primary references	27–29	26, 41, 42	12, 31, 45, 52, 54, 62	20, 21	19	9, 13, 150

CNS, central nervous system; NMDA N-methyl-D-aspartate; CSF, cerebrospinal fluid; SLE, systemic lupus erythematosus; mab, monoclonal antibody; LOS, lipooligosaccharide; GBS, Guillain-Barré syndrome; MS, multiple sclerosis; EBV, Epstein-Barr virus; MBP, myelin basic protein; HTLV-1, human T-lymphotropic virus type 1; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis.

role in a number of CNS processes including behavior, learning and neurotransmitter release, these data suggest that cross-reactive antibodies generated via molecular mimicry result in antibody-induced signal transduction that contributes to the clinical symptoms seen in SC. Interestingly, using the same system, the mAb also altered dopamine levels in this cell line [28]. Dopamine is a neurotransmitter that plays a major role in control of movement, thus these data further implicated an antibody-mediated mechanism as playing a role in SC and implied that antibody binding to extracellular targets (in this case, lyso-GM1) results in changes in intracellular pathways (CaM kinase II and dopamine) [27, 28]. In a follow-up study, human mAbs derived from SC patients were tested for immunoreactivity with intracellular antigens [29]. This led to the identification of β-tubulin as an autoantigen [29]. Furthermore, incubation with lyso-GM1 blocked mAb immunoreactivity with β-tubulin, confirming the specificity of the mAb for both lyso-GM1 and β-tubulin [29].

These data broaden our understanding of molecular mimicry in a number of ways. First, they emphasize the importance of studying antibody reactions. Second, they show the significance of immunologic cross-reactivity involving dissimilar antigens (GlcNAc of group A streptococcal cell wall, human lyso- GM1 and β-tubulin). Third, they show that antibodies due to molecular mimicry not only cross-react with environmental and human antigens, but are also biologically active and potentially pathogenic. Fourth, they show that more than one auto-antigen can be involved in molecular mimicry.

Neuropsychiatric complications of systemic lupus erythematosus

Systemic lupus erythematosus (SLE, 'lupus') is an autoimmune connective tissue disease that affects almost every organ system in the human body. Thus, its clinical presentation is highly variable and may include a broad range of signs and symptoms including rash, arthritis, heart disease, kidney disease (nephritis) and nervous system dysfunction [26, 39]. SLE complications of nervous system function are also variable and include stroke, encephalopathy, psychosis, dementia, progressive cognitive dysfunction, confusional states and coma [26, 39]. SLE patients produce a number of autoantibodies to intra- and extra-cellular autoantigens, many of which have been associated with specific clinical manifestations of the disease [30, 39].

Importantly, recent data indicate that the initial development of lupus is associated with infection with Epstein-Barr virus (EBV) via molecular mimicry [30]. Specifically, the immunodominant epitopes of autoantibodies to the autoantigen Ro (one of the earliest antibodies to be detected in lupus patients) and EBV were analyzed. Of the 29 lupus patients analyzed, 26 showed immunoreactivity to Ro amino acids 169–180 (TKYKQRNGWSHK). In addition, other epitopes were also recognized. Affinity-purified anti-Ro 169–180 antibodies were tested for immunoreactivity to an EBV infected cell line and were found to react with amino acids 58–72 (GGSGSGPRHRDGVRR) of EBV nuclear antigen-1 (EBNA-1), but not other viral antigens [30]. Interestingly, there was no sequence identity between the peptides, indicating that molecular mimicry is related to the structure of the antigens, rather than their sequence. Rabbits immunized with either of these peptides developed lupus-like organ damage as well as autoantibodies to other autoantigens, including nuclear ribonucleoprotein (nRNP) and dsDNA by epitope spreading [30].

Antibodies to dsDNA are present in the majority of lupus patients and are most commonly associated with renal disease where they cause damage by cross-reactivity with glomerular antigens [26, 39]. To determine potential autoantigens recognized by dsDNA antibodies, a murine mAb to dsDNA named R4A was used to screen a phage library [40]. This antibody bound the sequence Asp/Glu-Trp-Asp/Glu-Tyr-Ser/Gly (D/E-W-D/E-Y-S/G) and was found to be a molecular mimic of dsDNA [26, 40]. Subsequent studies showed that the D/E-W-D/E-Y-S/G sequence is present in the extracellular domain of the murine and human glutamate N-methyl-D-aspartate receptor (NMDAR) subunits NR2A and NR2B [26]. There is a high concentration of NMDARs on hippocampal neurons, and infusion of murine mAbs, human dsDNA antibodies and antibodies isolated from the CSF of lupus patients with neuropsychiatric disease into the hippocampus of C57BL/6 mice resulted in neuronal loss [26]. Importantly, this occurred without local complement fixation or inflammation and was abrogated by treatment with MK-801, an NMDAR-NR2 blocker [26]. In addition, primary fetal neuronal cultures exposed to similar experimental paradigms showed neuronal damage and death that was mediated by apoptosis [26].

A number of follow-up studies confirmed and extended these observations showing the contribution of molecular mimicry between dsDNA and NDMARs in the pathogenesis of SLE [41–43]. BALB/c mice immunized with a multimeric form of the D/E-W-D/E-Y-S/G pentapeptide ('MAP peptide') along with lipopolysaccharide [LPS, which causes blood-brain barrier (BBB) disruption] developed antibodies to dsDNA and the pentapeptide, which localized to hippocampal neurons [41]. The hippocampus plays a critical role in memory and learning. Concurrently, there was evidence of neuronal loss in the hippocampi of these animals (by both histology and magnetic resonance spectroscopy) as well as poor memory function as tested by a number of tasks directly related to intact hippocampal neurons [41]. In a second study, similar experiments were performed, using epinephrine instead of LPS to promote BBB breakdown in MAP-peptide immunized mice [42]. Epinephrine was chosen because increased levels are associated with stress. In these animals, antibodies developed to both dsDNA and D/E-W-D/E-Y-S/G, localized to neurons of the amygdale and caused neuronal loss and behavioral abnormalities directly related to amygdala dysfunction [42]. Neuronal loss was prevented with memantine (an NMDAR antagonist) as well as the D-isoform of the pentapeptide, thus confirming that neuronal damage was directly related to NMDAR dysfunction [42]. Finally, when human IgG isolated from an SLE patient that was cross-reactive to anti-dsDNA and anti-NMDAR was infused into mice, it was found to specifically bind hippocampal neurons, and was associated with apoptosis and impaired cognitive testing related to hippocampal function [43]. Furthermore, IgG eluted directly from an SLE patient brain with neuropsychiatric disease bound dsDNA and the NMDAR peptide (D/E-W-D/E-Y-S/G) and caused hippocampal neuron damage when injected directly into mouse brain [43]. In situ IgG in the brains of four SLE patients with neuropsychiatric disease co-localized with rabbit anti-NR2A and anti-NR2B antibodies, confirming that at least a fraction of the IgG deposition in SLE brain specific for NMDAR in the hippocampus of human brain [43].

Although the initiation of anti-dsDNA antibodies may be via epitope spreading following infection with EBV [30], molecular mimicry in SLE patients with neuropsychiatric syndromes was identified not between two proteins or an identical peptide, but between a peptide sequence and dsDNA, emphasizing the importance of very dissimilar structures resulting in immunological cross-reactivity, related to the three-dimensional structure of the cross reactive epitopes.

Guillain-Barré syndrome

There is also evidence that molecular mimicry plays a significant role in the pathogenesis of Guillain-Barré Syndrome (GBS); the most common cause of immune-mediated paralysis of the peripheral nervous system in humans [31, 44, 45]. These patients develop the acute onset of flaccid paralysis with variable amounts of sensory and autonomic dysfunction associated with antecedent infection [12, 31, 44, 45]. Immune attack of the peripheral nervous system targets, either Schwann cells (myelin-producing cells) or axons thought to cause GBS [12, 44–46]. There are several subtypes of the disease, each with a unique clinical presentation, prognosis and neurophysiological signature (as determined by nerve conduction studies) [12, 44–46]. One subtype, known as acute inflammatory demyelinating polyneuropathy (AIDP) is associated with T lymphocytes, antibody formation and macrophages directed toward Schwann cells or myelin, resulting in demyelination and peripheral nervous system dysfunction [44]. AIDP is the most frequent clinical presentation of GBS, particularly in the western hemisphere [12, 45, 47]. Cytomegalovirus (CMV), EBV or *Mycoplasma pneumoniae* infection precedes the development of disease in a proportion of these patients [44, 47, 48]. The acute motor axonal neuropathy (AMAN) form (which is more common in Japan and Asia) [12, 44, 47, 48] and the Fisher syndrome ('FS,' which is clinically characterized by ophthalmoplegia, ataxia and areflexia) are associated with infection with *Campylobacter jejuni* (*C. jejuni*) and antibody attack directed at peripheral nervous system axons at several sites, including the axolemma, nodes of Ranvier or pre-synaptic nerve terminal of the neuromuscular junction (NMJ) [12, 31, 45, 49–52].

There are data to support the hypothesis that molecular mimicry contributes to the pathogenesis of all forms of GBS particularly those related to *C. jejuni* infection [12, 31, 44–46, 49]. A significant proportion of patients with GBS were found to have *C. jejuni* enteritis prior to the development of neurological symptoms [53]. These patients were found to have titers directed against *C. jejuni* and concurrently towards GM1 ganglioside [12, 31, 44, 46, 49]. *C. jejuni* isolated from a patient with AMAN who had antibodies to GM1 expressed a specific oligosaccharide structure [Galβ1–3 GalNAcβ1–4(NeuAcα2–3)Galβ] which protrudes from the lipo-oligosaccharide (LOS) core [54]. An almost identical oligosaccharide epitope is present on GM1, indicating the existence of molecular mimicry between the two molecules [31, 44, 54].

Initial studies showed that immunization of rabbits with a mixture of brain-derived gangliosides resulted in acute paralysis caused by antibody-mediated attack of axons, confirming the significance of the immune response to GM1 [55]. Subsequent studies, using a more sophisticated paradigm to test for molecular mimicry, found that Japanese white rabbits immunized with the *C. jejuni* LOS developed limb weakness [31]. Importantly, control animals immunized with LOS from *Escherichia Coli* or *S. minnesota*, or adjuvant alone, did not develop disease. Furthermore, the animals immunized with *C. jejuni* LOS, who developed disease made antibodies to both *C. jejuni*-LOS and GM1 [31]. Pathologically, there was axonal degeneration of the proximal nerve roots and peripheral nerves of these animals, with protein G deposition on axons, indicating that bound IgG contributed to the axonal degeneration [31]. In separate experiments, a monoclonal antibody to GM1 was tested for biological activity [31]. This antibody stained both the myelin sheaths and axons in human spinal nerve roots, which was confirmed by immunoelectron microscopy. Specifically, electron microscopy showed staining of the myelin lamellae of Schwann cell processes, the basal lamina, the axolemmas of axons as well as vesicles and mitochondria within the axoplasm [31]. When applied to an *in-vitro* muscle-spinal cord co-culture system, the anti-GM1 Ab (in contrast to control antibodies) caused asynchronous contractions of individual muscle fibers and prolonged muscle action potential intervals [31]. Importantly, sera from GBS patients associated with anti-GM1 antibodies following *C. jejuni* enteritis replicated the data. Interestingly, passive transfer of the human or mouse anti-GM1 antibodies did not result in limb weakness, although this may be due to an intact blood-nerve barrier in this model (analogous to the BBB of the CNS) [31].

Next, the biosynthetic glycosylation pathways of the *C. jejuni* LOS were evaluated to determine if specific *C. jejuni* genes were required to synthesize the oligosaccharide epitope that cross-reacts with gangliosides. These studies suggest that specific *C. jejuni* LOS synthetic genes isolated from GBS patients compared to *C. jejuni* LOS genes from patients infected with *C. jejuni* without neurological disease, are present, result in the expression of the cross-reactive LOS epitope and are associated with antibodies to gangliosides. In addition, LOS sialylation appears to be essential for

the induction of the anti-ganglioside antibodies [56–60]. Finally, *C. jejuni* gene polymorphisms of specific glycosylation enzymatic pathways may contribute to the development of specific subtypes of GBS [61].

Interestingly, similar results have been obtained for the FS subtype in GBS. In contrast to AMAN patients who develop antibodies to GM1 (and/or GD1a) and present with predominantly pure motor weakness [12, 44], FS patients develop antibodies to GQ1b and clinically present with ophthalmoparesis and ataxia [12, 44, 45]. Importantly, GM1 is expressed on motor nerves and GQ1b on oculomotor nerves and primary sensory neurons, thus there is a strong correlation between immunoreactivity to gangliosides and clinical disease [12]. In FS patients, specific *C. jejuni* strains (different than those with the AMAN subtype of GBS) develop antibodies to an LOS epitope that cross-reacts with GQ1b as well as to GT1a, GD3 and GD1b [12, 45, 62]. The anti-GQ1b immunoreaction has been the most extensively studied. Specifically, with an in vitro mouse model that utilizes hemidiaphragm preparations, anti-GQ1b antibodies associated with FS were found to bind the motor nerve terminal, indicating that the pre-synaptic nerve terminal of the NMJ is a target for the FS form of GBS [50–52, 63]. In this model, the antibodies activate and fix complement which results in influx of calcium into the nerve terminal via the membrane attack complex and degradation of the terminal axon [50–52, 63].

In addition to single gangliosides, recent data indicate that 'ganglioside complexes' are also targets for molecular mimicry in GBS [64–68]. Specifically, serum from 8 of 100 patients with GBS was found to react with a ganglioside complex of GD1a and GD1b as well as to other ganglioside complexes, but not with individual gangliosides [64]. In a separate study of 21 GBS patients associated with *C. jejuni* infection, two showed immunoreaction to a GM1/GD1a gangloiside complex and two others to GQ1b/GD1a complex [65]. Remarkably, the GM1/GD1a patients had predominantly motor involvement and the GQ1b/GD1a presented with ophthalmoplegia [65].

Thus, patients with the AMAN and FS sub-types of GBS show evidence of molecular mimicry due to the three-dimensional carbohydrate structure of cross-reactive antigens (in this case, glycolipids and glycolipid complexes) – data that could not have been predicted at either the nucleic acid or protein level, again emphasizing the importance of immunological cross-reactivity in determining molecular mimics in human diseases. Interestingly, recent experiments suggest that the breaking of tolerance to ganglioside targets contributes to the development of GBS associated with *C. jejuni* infection [69].

Multiple sclerosis

In contrast to the previous examples, the difficulty in analyzing the data related to multiple sclerosis (MS) is that no single infectious agent or group of agents has unequivocally been shown to cause MS. Although not unequivocally proven, molecular mimicry is, nevertheless, still a leading hypothesis being tested to explain its pathogenesis [1, 16, 22, 23, 70–74]. In addition, there are data that other hypotheses such as epitope spreading [75] and non-specific immunologic stimulation of the immune response following molecular mimicry priming by an environmental agent [16] also contribute to the pathogenesis of MS.

MS is the most common autoimmune disease of the nervous system in humans [76]. Clinically, patients present with a number of neurological syndromes including optic neuritis, transverse myelitis, diplopia, spasticity, paraparesis and urinary incontinence [76, 77]. The most common type of MS is relapsing remitting multiple sclerosis (RRMS), in which neurological symptoms appear over a time frame of hours to days, and then resolve spontaneously or with the use of steroids [76, 78]. The CNS lesion, known as the MS plaque, consists of areas of demyelination and axonal damage associated with an intense inflammatory response including B lymphocytes and antibody-producing plasma cells, T lymphocytes (both CD4+ and CD8+), and macrophages [76–83]. A number of studies have shown that immune responses to myelin antigens such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP) contribute to the pathogenesis of MS [1, 16, 20, 22, 23, 70–74]. MS relapses are associated with the development of MS plaques that can be viewed *in vivo* by magnetic resonance imaging (MRI) of the brain and spinal cord [82, 84–86]. Over time, patients with RRMS develop progressive neurological symptoms independent of the number of relapses [87]. This type of MS is known as secondary progressive MS and is associated with worsening neurological function and increasing numbers of plaques on MRI scans [87]. In contrast, a subset of patients develop progressive neurological disease without relapses, known as primary progressive MS (PPMS). Recent studies indicate that populations of these patients have a worse prognosis than those with RRMS [88]. A minority of patients have progressive symptoms at onset, and then years later develop relapses – this is termed progressive relapsing MS [89].

In original studies designed to test for molecular mimicry in MS, the animal model experimental allergic encephalomyelitis (EAE) was used. These experiments compared primary sequences of viral proteins with encephalogenic regions of myelin basic protein (MBP) [14]. Injecting MBP into mice causes

EAE, which, like MS, is characterized by immune-mediated demyelination of the CNS [77]. Fujinami et al. [14] showed that MBP shared a six-amino-acid sequence with hepatitis B virus polymerase (HBVP). Injection of the HBVP peptide into rabbits resulted in antibody production and lymphocyte proliferation to both proteins and infiltration of the CNS with lymphocytes. Although there was no clinical disease, these experiments were the first to show that an environmental agent could stimulate a cross-reactive cellular and humoral immune response to a host antigen, and that immune cells homed to the target organ [14]. In separate experiments, T lymphocytes from mice immunized with a herpes virus saimiri peptide that was homologous to only 5 of 11 amino acids of an immunodominant MBP peptide caused EAE in naïve recipients [90]. This suggests that identical sequences between an infectious and host antigen are not required to cause disease due to molecular mimicry.

Although these were very important studies, neither hepatitis B nor herpes virus saimiri was associated with MS in humans. Over the past 20 years, multiple infectious agents have been associated with the development of MS [16]. Recent data have implicated a potential role of *Chlamydia pneumoniae*, human herpes virus six (HHV-6) and EBV in the pathogenesis of MS [91–97]. Currently, the data related to EBV have the strongest association with MS. This is due to recent studies showing an extremely low risk for MS in individuals seronegative for EBV, as well as a significantly increased risk of MS in individuals who develop infectious mononucleosis (clinical evidence of primary EBV infection) after childhood [95–97]. MS patients develop antibodies predominantly to EBNA-1, the same antigen associated with lupus [30, 95–97].

A number of human studies, mostly involving immunodominant T-lymphocyte responses to myelin antigens (particularly MBP), have demonstrated a role for molecular mimicry in the pathogenesis of MS. [20, 70, 74, 98, 99]. Since the development of MS is associated with human leukocyte antigen DR2 (HLA-DR2), one study performed a data base search of potential mimics of MBP based on structural requirements of DR2 binding and T cell receptor (TCR) recognition of MBP [20]. Six hundred pathogens were identified and 72 were tested for cellular activity using T cell clones (TCCs) specific for immunodominant MBP (amino acids 85–99). Seven viral and one bacterial peptide activated the TCCs. Only one of the peptides showed molecular mimicry by sequence alignment. Since the other six environmental agents activated MBP specific TCCs, it was concluded that conformational molecular mimicry existed between these environmental agents and MBP [20]. Subsequently, DR2 and TCR binding studies showed that amino acid substitutions, even at primary binding sites, still allowed for binding [98]. These data suggest that immunologic or conformational binding, not primary sequence homology, is critical in the pathogenesis of autoimmune disease via molecular mimicry. Other studies have confirmed and extended these observations. Using synthetic peptide combinatorial libraries (SPCLs) along with peptide database searches, systematic amino acid substitutions of immunodominant MBP (83–99) were tested by their ability to stimulate TCCs. These studies showed that peptides that shared no sequence identity with MBP (83–99) can be molecular mimics [74, 100]. Taken together, these data indicate that in MS there is considerable degeneracy of T cell recognition, such that viral peptides with limited or no sequence homology to self antigens can stimulate autoreactive TCCs [70, 74, 99, 100]. Remarkably, autoantibodies purified from brains of MS patients cross-reacted with the identical immunodominant MBP epitope, suggesting a potential role of antibodies in the pathogenesis of MS [101, 102].

From these original studies, one particular TCC derived from the blood of an RRMS patient, designated Hy.2E11, has been used in a number of experimental models that suggest a continuing role for molecular mimicry in the pathogenesis of MS [20]. This DR2 (DR2b = DRB1*1501, DR2a = DRB5*0101) restricted TCC that recognizes MBP 85–99 (ENPVVHFFKNIVTPR) was stimulated by EBV DNA polymerase peptide 627–641 (TGGVYHFVKKHVHES), implicating structural molecular mimicry between the two antigens [20]. Because DRB1*1501 and DRB5*0101 are in linkage disequilibrium, their contribution to the immune response in MS had not been evaluated independently [21, 71–73]. Using cells that express DRA*0101 along with either DR2a (DRB5*0101) or DR2b (DRB1*1501) (but not both), Hy.2E11 TCR transfectants recognized MBP 85–99 in the context of HLA-DR2b (DRB*1501) and EBV DNA polymerase 627–641 in the context of HLA-DR2a (DRB5*0101) [21, 71]. Similar data were generated using transgenic mice. Importantly, even though the Hy.2E11 TCRs recognized MBP in the context of HLA-DR2b and EBV in the context of HLA-DR2a, the crystal structure of the two was remarkably similar [21, 71]. Thus, molecular mimicry is the result of structural mimicry, not sequence homology, as shown by different peptide interactions with two different HLAs, [21, 71]. Importantly, this same Hy.2E11 clone was used to test the influence of HLA-DR2a on HLA-DR2b [72, 73]. In this study, humanized transgenic mice expressing the Hy.2E11 TCR and HLA-DR2b were gener-

ated and found to develop spontaneous EAE that was very severe and showed a relentlessly progressive course. Remarkably, the addition of HLA-DR2a significantly reduced the severity of the disease and in some animals showed a more relapsing remitting course [72, 73]. Thus, the HLA-DR2a allele significantly influenced the DR2b allele [72, 73]. Although the EBV peptide was not used in this paradigm, its role as a molecular mimic in this setting would certainly yield interesting results. Furthermore, targets other than MBP may be involved in molecular mimicry. For example, one study showed that autoantibodies from MS patients cross reacted with transaldolase (a major component of oligodendrocytes) and capsid antigens derived from EBV and herpes virus type 1 [103, 104]. In addition to these as well as the original animal studies designed to test molecular mimicry, other animal models have also given insight into the role played by molecular mimicry in MS. For example, intracerebral inoculation with Theiler's murine encephalomyelitis virus (TMEV) into SJL mice results in a progressive, demyelinating neurological disease that mimics some of the pathology seen in MS [22, 105–107]. In a series of studies, Miller and colleagues showed that when a *non-pathogenic* strain of TMEV was engineered to encode a 30-mer peptide that included the immunodominant encephalitogenic epitope of the myelin antigen PLP, animals developed neurological disease [22, 105–107]. Importantly, when the same virus was engineered with a *Haemophilus influenzae* protease peptide that mimicked the PLP peptide (6 of 13 amino acids were identical, including the primary TCR contact for PLP), the animals showed cross-reactivity to PLP (139–151) and became ill [105]. Follow-up studies showed that tolerance can be induced by pre-treatment with PLP (139–151) and exacerbated by repeat injections of the *H. influenzae*-TMEV construct [106, 107]. These data indicate molecular mimicry between *H. Influenzae* and PLP in the pathogenesis of immune mediated demyelinating disease [22, 105–107]. Interestingly, in humans, the Hy.2E11 TCC as well as TCCs derived from other MS patients also showed reactivity to *H. influenzae*, although to different proteins [20, 100].

Other infectious agents have also been implicated as playing a role in the pathogenesis of MS via molecular mimicry [91–94, 108]. For example, HHV-6, which is tropic for CD4+ lymphocytes, has been localized to oligodendrocytes in the brain of MS patients, and increased HHV-6 DNA levels have been associated with MS [91, 92, 108]. The HHV-6 protein U24 (amino acids 1–13) contains a seven-amino-acid sequence that is identical to that of MBP (93–105). T-lymphocyte and antibody responses to this cross-reactive peptide are present in MS patients, suggesting that molecular mimicry between the two contributes to the pathogenesis of the disease [92]. Other studies refute these data. For example, Cirone et al. [109], showed that there was little difference in either T lymphocyte or humoral responses to HHV-6 in MS patients (n=22) compared to controls (n=16). Similarly, elevated antibodies to and bacterial DNA levels of *C. pneumoniae* were found in the spinal fluid of MS patients [93]. Follow-up studies using the *C. pneumoniae* Cpn0483 protein, which has significant homology to rat MBP (68–86), were found to induce EAE in Lewis rats, again implicating molecular mimicry between an environmental and myelin antigen in the pathogenesis of MS [94].

Chronic neuroborreliosis

Lyme disease is caused by infection with *Borrelia burgdorferi* transmitted to humans by the bite of an ixodid tick [11, 110]. Acutely, patients develop a characteristic skin rash called erythema migrans [11, 110]. The acute phase may also be complicated by meningitis, neuritis and encephalitis [110]. The complications of chronic lyme disease may include arthritis as well as chronic neuroborreliosis – a constellation of neurological symptoms that may include pain, poor concentration, difficulty with memory and fatigue [11, 19, 110]. The cause of these chronic complications of *B. burgdorferi* are largely unknown, however data indicate autoimmune responses, including molecular mimicry, as contributing factors to the pathogenesis [19, 110]. In fact, there are data to suggest that molecular mimicry – in this case using TCCs – exists between the outer surface protein A (OspA) of *Borrelia* and human leukocyte functional-associated antigen-1 (hLFA-1) in patients with chronic, treatment-resistant lyme arthritis [111]. In addition, a TCC derived from the CSF of a patient with chronic lyme disease associated with recurrent attacks of meningoencephalitis was tested for its ability to proliferate following testing with a number of *Borrelia* and human antigens [19]. Similar to the studies in MS, positional scanning of SPCLs and biometric data analysis were used to test the TCC for reactivity to *Borrelia* and human antigens. Using this unbiased approach, a search of the GenPept database of the *Borrelia* and human genome, identified a number of antigens from both the infectious [such as the *Borrelia* outer surface protein C (OspC), p22 lipoprotein and others] and host targets [myelin-associated oligodendrocyte basic protein (MOBP) and others] that stimulated the TCC [19]. Thus, previously unknown human target antigens – potential molecular mimics – were identified. Importantly, as suggested in previous studies [20], the host antigens did not contain amino acid sequence homology, and thus direct sequence

homology between the environmental agent and host target antigen are not required for molecular mimicry to occur. Pathologically, these patients show vasculitis and meningoencephalitis of the CNS. However, beyond proliferative responses and cytokine production, evidence for T cell immunoreactivities causing changes in neural function in vitro or in vivo have yet to be performed. In addition, a recent study evaluating antibody responses in the CSF of a patient with neuroborreliosis suggested that mechanisms other than molecular mimicry may be contributing to its pathogenesis [112]. In this study, monoclonal antibodies were prepared by reverse transcription of immunoglobulin genes derived from single plasma cells and used to test for immunoreactivity to *B. burgdorferi* antigens and human CNS tissues [112]. These experiments showed that different antibodies immunoreacted with *B. burgdorferi* antigens than human CNS tissue, and that there was no cross-reactivity between the antibodies that reacted with either antigen [112]. Although western blot analyses of CNS antigens were not performed, these data suggest that an autoimmune process other than molecular mimicry contributes to the pathogenesis of neuroborreliosis.

Human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis

Human T-lymphotropic virus type 1 (HTLV-1) was the first human retrovirus discovered and soon thereafter was found to cause both adult T cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a chronic, progressive neurological disease [113–116]. HTLV-1 may infect up to 10 million people worldwide; however, only 1–5% will develop ATL or HAM/TSP, the remainder being asymptomatic carriers of the virus [117, 118]. Why this occurs is largely unknown; however, similar to other infectious diseases that result in chronic human disease, there are data to suggest that viral strain, HLA, viral load and the immune response all contribute [119–128]. Clinically, people with HAM/TSP develop progressive spastic paraparesis associated with early onset of bladder dysfunction and sensory symptoms [120, 129–132]. This clinical presentation mimics PPMS, and in fact, many of these patients were diagnosed with PPMS prior to the discovery of HTLV-1 and its association with HAM/TSP [129]. Pathologically, CNS structures that are preferentially damaged include the corticospinal and sensory pathways, which correlate strongly with the clinical presentation in these patients. Also, like MS, there is a robust inflammatory response in the CNS including infiltration of T lymphocytes (CD4+ and CD8+), B lymphocytes, macrophages and elevated levels of antibodies associated with demyelination and axonal dystrophy [130, 133–140]. There is little evidence that direct infection of neural elements with HTLV-1 causes HAM/TSP [120, 121, 123, 131]. Instead, data indicate that immune-mediated mechanisms, including molecular mimicry, play a significant role [9, 10, 13, 120, 121, 123, 127, 131, 141]. HAM/TSP patients make immune responses to a number of viral targets including HTLV-1-tax, -env and –gag, which separates them from control populations [121, 142–145]. Specifically, HAM/TSP patients develop CD8+, HLA-2-restricted cytotoxic lymphocytes (CTLs) specific for tax and $CD4^+$ responses to both *tax* and *env* that are thought to contribute to disease [121, 142, 145]. In contrast, other studies suggest that these same tax-specific CTLs are protective rather than pathogenic [119, 121, 146]. Interestingly, the HLA class 2 gene, HLA-DRB1*0101, increased HTLV-1 viral load and elevated HTLV-1 antibody titers were found to increase the risk of HAM/TSP [119–121, 126, 146–148]. It is the antibody responses that have been tested experimentally and found to contribute to molecular mimicry in HAM/TSP [9, 10, 13, 149–151]. Specifically, IgG isolated from HAM/TSP patients, in contrast to control populations, was found to stain uninfected human CNS neurons [9, 149]. *tax* mAbs also stained these neurons [9, 149, 151]. CNS neurons were isolated from human brain at autopsy, proteins purified, separated by two-dimensional gel electrophoresis and used for Western blotting with HAM/TSP IgG. Using this technique, HAM/TSP IgG was found to immunoreact with heterogeneous nuclear ribonuclear protein A1 (hnRNP A1), an RNA-binding protein that transports mature mRNA out of the nucleus [9, 152–154]. IgG isolated from the CSF of a HAM/TSP patient also immunoreacted with hnRNP A1 [9]. The tax mAbs immunoreacted with hnRNP A1 suggesting molecular mimicry between it and HTLV-1-tax [9, 151]. The following series of experiments were performed that indicate that molecular mimicry between HTLV-1-tax and hnRNP A1 contributes to the pathogenesis of HAM/TSP.

First, the epitope of the tax mAb was defined as tax 346–353, which coincides with the immunodominant epitope of HTLV-1-infected patients [151, 155]. Preincubation of the tax mAbs with tax 346–353 (KHFRETEV) abolished immunoreactivity with hnRNP A1 and uninfected CNS neurons [151]. The hnRNP A1 epitope recognized by HAM/TSP IgG has also been experimentally defined and was found to include M9 (293-GQYFAKPRNQGG-304), a region of hnRNP A1 required for its transport in and out of the nucleus [13, 152–154]. The tax mAb also immunoreacted with this epitope. There is little sequence identity between the two epitopes, thus, like the

cellular and antibody responses described previously, this indicates that molecular mimicry is the result of structural rather than sequence identity [13]. In addition, preliminary data from our laboratory show that glycosylated antigens may also contribute to molecular mimicry (unpublished observation).

Next, experiments were designed to determine if HAM/TSP IgG correlated with the CNS dysfunction in HAM/TSP patients. We hypothesized that HAM/TSP IgG immunoreactivity would preferentially react with the corticospinal system, whose damage results in spastic paraparesis, the major source of disability in these patients. Experiments were performed using both HTLV-1-seronegative and HAM/TSP brain tissue. In HTLV-1-seronegative human brain, neurons were purified from the precentral gyrus (motor cortex), which contains Betz cells (the major contributor of the corticospinal tract) and compared to neurons of other brain regions [9]. These experiments showed that HAM/TSP IgG preferentially reacted with hnRNP A1 in neurons of the motor cortex by both Western blot and immunohistochemistry. Next, we determined the *in situ* IgG deposition in the brains of HAM/TSP patients. These experiments showed that IgG deposition preferentially reacted with cells and axons of the corticospinal pathway [134]. Thus, there is a strong correlation between HAM/TSP IgG immunoreactivity and neurons that are preferentially damaged in HAM/TSP patients.

Finally, we used HAM/TSP IgG and the tax mAbs in a series of experiments designed to test whether this cross-reactive immune response was biologically active and potentially pathogenic to neurons [9, 150]. In these experiments, patch clamp techniques using rat brain slices containing motor cortex were exposed to HAM/TSP IgG, the tax mAbs and hnRNP A1 affinity-purified antibodies from HAM/TSP patients. In contrast to control antibodies, all three antibodies inhibited neuronal firing in a concentration-dependent manner.

In summary, these data indicate that HAM/TSP IgG contributes to the pathogenesis of HAM/TSP via molecular mimicry. First, HAM/TSP IgG was used to identify the autoantigen hnRNP A1, which showed cross-reactivity with HTLV-1-tax. Second, both HAM/TSP IgG and the tax mAbs immunoreacted with the same immunodominant epitopes of the cross-reactive proteins. Third, the immune reaction to both the environmental agent (the tax epitope correlates with the immunodominant epitope of HTLV-1-infected patients) and the autoantigen (M9 of hnRNP A1) are not random, but include functionally important regions of the proteins. Fourth, molecular mimicry is based on structural rather than sequence identity. Fifth, there is a strong correlation between HAM/TSP IgG immunoreactivity and damaged neurons in the CNS and, finally, cross-reactive antibodies inhibited neuronal firing, suggesting that the immune reaction is biologically active and potentially pathogenic [9, 10, 13, 134, 149–151].

Other diseases

Molecular mimicry may also contribute to the pathogenesis of myasthenia gravis (MG), epilepsy, celiac disease and the antiphospholipid syndrome (APS). In the 1980s, an association between MG and herpes simplex virus (HSV) was reported [156]. MG is caused by an autoimmune attack of the acetylcholine receptor (AChR) resulting in progressive weakness. These data showed a cross-reactive epitope between HSV glycoprotein D (amino acids 286–293) and the AChR alpha subunit (amino acids 160–167). Serum from MG patients reacted with the cross-reactive peptides and the HSV peptide inhibited rabbit anti-AChR binding. Recent data indicate some cross-reactivity between several microbial antigens and four of the AChR alpha subunit immunodominant determinants (amino acids 12–27, 111–126, 122–138, 182–200) [157].

Recently, there have been increasing data that certain epilepsy syndromes are associated with autoimmune reactions to neurons [158–161]. These include autoimmunity to the B peptide (amino acids 372–395) of the glutamate/AMPA (α-3-hydroxy-5-methyl-4-isoxazolepropionic acid) subtype 3 receptor which may be associated with cross-reactivity to dsDNA or influenza A vaccination in patients with Rasmussen's encephalitis. In addition, there are preliminary data showing cross-reactivity between gliadin and neuronal synapsin I in patients with celiac disease (which can be complicated by neurological syndromes such as neuropathy, seizures and behavioral changes) [157, 162]. Finally, molecular mimicry may contribute to the pathogenesis of patients with APS that develop chorea [6, 163]. APS is characterized by recurrent fetal loss, thrombocytopenia and thromboembolic disease [6, 163]. These patients develop autoantibodies to β-2-glycoprotein-I (β2GPI), which may be induced by molecular mimicry [6, 163]. In a subset of patients with APS and chorea, serum reacted with streptococcal GlcNAc, and the interaction was inhibited with β2GPI, suggesting molecular mimicry between two antigens [164].

Conclusions and future directions

For over 20 years, experimental evidence has accumulated indicating that molecular mimicry makes major contributions to the pathogenesis of neuro-

logical diseases in humans. Initial studies evaluated molecular mimicry by searching for exact nucleic acid or amino acid matches in the infecting agent and host antigen. Over time, it became clear that this limited the number of molecular mimics that theoretically existed and that structural mimicry was more biologically relevant. This has been shown in experimental systems evaluating both cellular and antibody-mediated responses. Importantly, although initial studies focused mostly on T lymphocyte responses, data now show that antibody-mediated responses (even in the absence of nervous system inflammation) make major contributions to the pathogenesis of neurological diseases via molecular mimicry. This is particularly important clinically, since many of these diseases are associated with elevated levels of antibodies in the serum, CSF or CNS. Finally, it has become clear that it is unlikely that a single antibody:antigen interaction results in molecular mimicry but, instead, a number of target antigens (both infectious and host) are relevant to the pathogenesis of immune-mediated neurological diseases in humans. Future experiments will continue to evaluate which immune target responses are relevant as well as the biological consequences of molecular mimicry in neurological diseases.

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