

# Molecular Mimicry, Microbial Infection, and Autoimmune Disease: Evolution of the Concept

M. B. A. Oldstone (✉)

Division of Virology, Departments of Neuropharmacology and Infectology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA  
*mbaobo@scripps.edu*

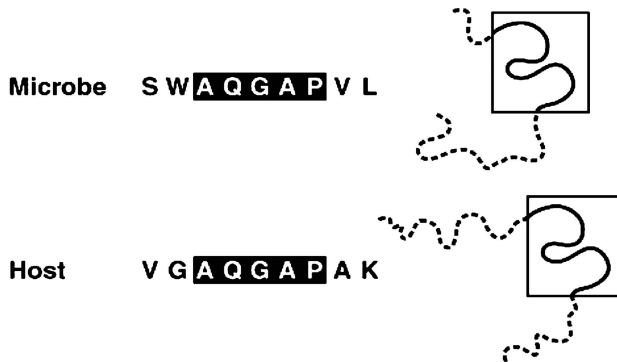
1	Definition of Molecular Mimicry and Development of the Concept . . . . .	2
2	Occurrence of Molecular Mimicry at the Antibody and T Cell Level . . . . .	4
3	Searches for Molecular Mimics . . . . .	5
4	Experimental Animal Models of Molecular Mimicry and Autoimmune Disease . . . . .	5
5	Equating Human Autoimmune Disease with Molecular Mimicry . . . . .	10
6	Overview of Autoimmune Responses and Infections . . . . .	11
7	Summary . . . . .	13
	References . . . . .	14

**Abstract** Molecular mimicry is defined as similar structures shared by molecules from dissimilar genes or by their protein products. Either several linear amino acids or their conformational fit may be shared, even though their origins are separate. Hence, during a viral or microbe infection, if that organism shares cross-reactive epitopes for B or T cells with the host, then the response to the infecting agent will also attack the host, causing autoimmune disease. A variation on this theme is when a second, third, or repeated infection(s) shares cross-reactive B or T cell epitopes with the first (initiating) virus but not necessarily the host. In this instance, the secondary infectious agents increase the number of antiviral/antihost effector antibodies or T cells that potentiate or precipitate the autoimmune assault. The formation of this concept initially via study of monoclonal antibody or clone T cell cross-recognition in vitro through its evolution to in vivo animal models and to selected human diseases is explored in this mini-review.

## 1

**Definition of Molecular Mimicry and Development of the Concept**

We initially defined molecular mimicry as similar structures shared by molecules from dissimilar genes or by their protein products (Fujinami et al. 1983; Oldstone 1987; reviewed in Oldstone 1998). Either the molecules' linear amino acid sequences or their conformational fit (Fig. 1) may be shared, even though their origins are separate. Examples would be self-determinants from a virus and a normal host or from two kinds of viruses, one that persists in a selected tissue with little or no injury until the second virus infects the same host and generates an immune response that cross-reacts with tissue expressing peptides from the first virus.

**Molecular Mimicry**

- Close enough in homology (between self and microbe) to share determinants.
- Distant enough from homology to be recognized as foreign by the immune system.
- Homology at self determinants (epitope) having important biologic activity.

**Fig. 1** Cartoon of a shared linear amino acid sequence or of a conformational fit between a microbe and a host “self” determinant. This is the basis for the first phase of molecular mimicry. Autoimmunity can occur if: (1) a host immune response raised against the sequence from the microbe cross-reacts with the host “self” sequence, and (2) the host sequence is a biologically important domain, e.g., encephalitogenic site of myelin basic protein, the site on the acetylcholine receptor that is important for gating membrane changes needed for a synapse. A similar scenario might occur when, early in life, a virus or microbe initiates a persistent infection in a specific tissue, and a second cross-reactive infectious agent later induces an antiviral or antimicrobial immune response

The sequence homology between the infected host's self-components and those of the microbe must be close enough to share immunogenic determinants, yet sufficiently distant to be recognized as nonself by the host's immune system. Further, such homology must involve a self-determinant having important biological activity so that the immune assault injures tissue and causes disease (Fig. 1). For instance, we know that immune attack on the encephalitogenic peptide of myelin can injure oligodendrocytes and that similar violence to islet or myocardial surface-expressed peptides harms the pancreas or heart, respectively. Such homologies between proteins have been detected either by use of immunologic agents, humoral or cellular, that cross-react with two protein structures (virus–host, virus–virus) or by computer searches to match proteins described in storage banks. Because guanine-cytosine (GC) sequences and introns designed to be spliced away may provide false hybridization signals and nonsense homologies, respectively, focus on molecular mimicry is necessary at the protein level. Regardless of the methods used for identification, it is now abundantly clear that molecular mimicry occurs between proteins encoded by numerous microbes and host self-proteins and is rather common [reviewed in Cunningham and Fujinami 2000; Oldstone 1989, 1998; with over 500 published papers on this subject listed in PubMed from 2003 to the present (October 2004)]. This information is useful not only for research in autoimmunity but also to those seeking a likely mechanism by which viral proteins are processed inside cells (Dales et al. 1983a, 1983b; Oldstone 1998).

The conceptual basis for molecular mimicry was first defined in the early 1980s when monoclonal antibodies against viruses were also shown to react with nonviral host protein; in this case, measles virus phosphoprotein cross-reacted with host cell cytokeratin (Fujinami et al. 1983), herpes simplex virus type 1 with host cell vimentin (Fujinami et al. 1983) and vaccinia virus with host cell intermediate filaments (Dales et al. 1983b). After this discovery, others emerged, again at the clonal level, that T cell clones against proteins from a variety of infectious agents also reacted with host antigenic determinants (Cunningham 2004; Wucherpfennig and Strominger 1995). The clonal distinction was imperative for the initial definition of mimicry. At least 30 years before our initial description of molecular mimicry involving cross-reactions between numerous microbes, on the polyclonal antibody level, streptococcus was believed to react with renal glomeruli, heart, and basal ganglia to account for glomerulonephritis, heart and valvular disease, and chorea, respectively (reviewed in Froude et al. 1989; Kaplan 1963). However, subsequent research showed that the nephritis was caused by immune complex deposits and the tissue damage they produced (Dixon 1963). Later, in 1990, the cross-reactivity of streptococcal antigen with myocardial antigens on a clonal level was un-

covered (Dell et al. 1991). Hence, for both historical reasons and mechanistic understanding, it is best to provide evidence for cross-reactivity at the clonal level to prove that molecular mimicry exists.

## 2

### **Occurrence of Molecular Mimicry at the Antibody and T Cell Level**

Critical analysis has revealed that molecular mimicry during the infectious process is not rare. For example, multiple monoclonal antibodies against a battery of DNA and RNA viruses were noted to be cross-reactive with host determinants (reviewed in Oldstone et al. 1998). Frequency of cross-reactivity between viral proteins and host self-antigens analyzed with more than 800 monoclonal antibodies revealed that nearly 5% of the monoclonal antibodies against 15 different viruses cross-reacted with host cell determinants expressed on or in uninfected tissues (Lane and Hoeffler 1980; Oldstone 1998; Shrinivasappa et al. 1986). The viruses studied were among the most common that afflict humans, including those of the herpesvirus group, vaccinia virus, myxoviruses, paramyxoviruses, arenaviruses, flaviviruses, alphaviruses, rhabdoviruses, coronaviruses, and human retroviruses. Considering that five to six amino acids are needed to induce a monoclonal antibody response, the probability that 20 amino acids will occur in six identical residues between two proteins is  $20^6$  or 1 in 128,000,000. Similarly, a variety of T lymphocytes sensitized to cellular proteins such as myelin basic protein, proteolipid protein of myelin, and glutamic decarboxylase (GAD) were also noted to cross-react when added to proteins or peptides from selected viruses. Biological/chemical analyses used to document these effects were amino acid sequencing, immunochemistry, cell proliferation, lysis, and the release or display of cytokines (reviewed in Cunningham and Fujinami 2000; reviewed in Oldstone 1989, 1998; Wucherpfennig and Strominger 1995). The reverse was also noted, in that T lymphocytes sensitized specifically to a virus would cross-react with a host protein or peptide (Oldstone et al. 1999). The permissivity of the T cell receptor to numerous peptides (Mason 1998) indicated that the problem was not the probability of multiple recognition but rather how the host limited/controlled such cross-recognition.

Computer searches revealed interesting sequence homologies that might explain a variety of diseases; for example, the amino acids shared between specific coagulation proteins and dengue virus or between human immunodeficiency virus and brain proteins could indicate part of the pathogenic mechanism underlying dengue hemorrhagic shock syndrome and AIDS dementia complex, respectively. Clinical studies have shown a high degree of

correlation between the immune response to GAD and other islet antigens in patients who progress to or who have insulin-dependent diabetes. Sequences obtained by computer search revealed identity between a component of GAD amino acids 247 to 279 and other auto-antigens with several viruses (Atkinson et al. 1994; Honeyman et al. 1998). Similarly, evidence has linked chlamydia protein with heart disease, herpes simplex virus with corneal antigens, herpes viruses with myasthenia gravis (Bachmaier et al. 1999; Schwimbeck et al. 1989; Zhao et al. 1997), the bacteria *Campylobacter jejuni* with Guillain-Barré disease (Hafer-Macko et al. 1996; Yuki et al. 2004) and certain strains of *Yersinia*, *Shigella*, and *Klebsiella* with ankylosing spondylitis (AS) (Oldstone 1998; Schwimbeck et al. 1987). In these instances, the protein and antigen of the microbe acting as mimics and inducers of antibodies and/or T lymphocytes were implicated as likely causes of the respective diseases.

### 3

#### Searches for Molecular Mimics

As experimental knowledge increased about the T cell epitopes and their flanking sequences that were necessary for T cell recognition, it became possible to change a single amino acid and, thereby, convert a poorly binding T cell epitope to one that bound with high affinity and, vice versa, convert a strongly binding peptide to one of mediocre affinity (Table 1). Armed with this information, better designs for computer searches are now possible to identify molecular mimics. These data, coupled with interesting sequence similarities to evaluate, provide a list of microbial and host proteins worthy of investigation (Table 2). However, immunochemical analysis of cross-reactive epitopes has revealed that reactivity can be dependent on a single amino acid (Dyrberg and Oldstone 1986; Dyrberg et al. 1990; Hudrisier et al. 2001) (Table 1), so experimental evidence is required to support computerized identification of a sequence fit.

### 4

#### Experimental Animal Models of Molecular Mimicry and Autoimmune Disease

An essential step in validation of the molecular mimicry concept was obtaining proof of principle from animal models to establish molecular mimicry as more than an epiphenomenon. The initial observation utilized myelin basic protein and the model of experimental autoimmune encephalomyelitis (EAE)

**Table 1** Effect of mutation at non-anchor position P2 on the H-2D<sup>b</sup> binding properties of H-2D<sup>b</sup>-restricted viral peptides

Peptide	Binding affinity	
	Competition (IC <sub>50</sub> , nM)	Stabilization (SC <sub>50</sub> , nM)
<i>Influenza</i>		
NP366-374	7 ± 1	10 ± 1
Ala Ser Asn Glu Asn Met Glu Thr Met		
[Glu] <sup>2</sup> -NP366-374	1,939 ± 109	12,350 ± 350
Ala Glu Asn Glu Asn Met Glu Thr Met		
<i>LCMV</i>		
GP33-41	21 ± 4	470 ± 63
Lys Ala Val Tyr Asn Phe Ala Thr Cys Gly Ile		
[Glu] <sup>2</sup> -GP33-41	13000 ± 3790	53000 ± 8460
Lys Glu Val Tyr Asn Phe Ala Thr Cys Gly Ile		
GP276-286	13 ± 2	23 ± 3
Ser Gly Val Glu Asn Pro Gly Gly Tyr Cys Leu		
[Glu] <sup>2</sup> -GP276-286	15067 ± 5715	43000 ± 5650
Ser Glu Val Glu Asn Pro Gly Gly Tyr Cys Leu		
<i>LCMV</i>		
GP16-24	>100000	>100000
Asp Glu Val Ile Asn Ile Val Ile Ile		
[Ser] <sup>2</sup> -GP16-24	1400 ± 450	2050 ± 390
Asp Ser Val Ile Asn Ile Val Ile Ile		
[Gly] <sup>2</sup> -GP16-24	2033 ± 887	4930 ± 721
Asp Gly Val Ile Asn Ile Val Ile Ile		

Substitution of a single amino acid can reverse a good binder to a poor binder or enhance a poor binder to become a better binder. IC<sub>50</sub> of <100 nM indicates a good binder, whereas <50 nM indicates an excellent binder. These data are from study of binding of virus-specific MHC-restricted peptides to the appropriate MHC class I-D<sup>b</sup> glycoprotein. See Hudrisier et al. 2001 for details.

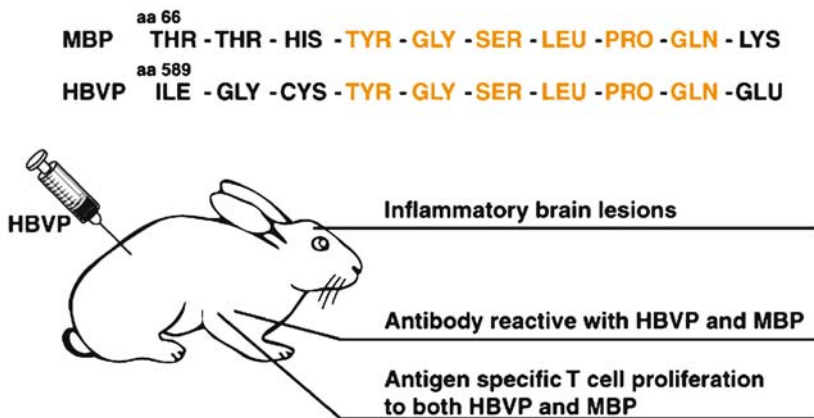
(Fujinami and Oldstone 1985) (Fig. 2). Several myelin basic protein sequences that cause EAE are known, and the encephalitogenic site of 8 to 10 amino acids has been mapped for multiple animal species. The first step was computer analysis to match the myelin proteins (peptides) known to cause EAE to viral proteins for homologies. That search uncovered several such viral proteins, including a hemagglutinin nucleoprotein of influenza virus, the core protein

**Table 2** Interesting sequence similarities between microbial proteins and human host proteins

Protein	Residue	Sequence
Measles virus P3	219	<u>EISDNLGQEGRASTSGTP</u>
Myelin basic protein	158	EISFKLGQEGRDSRSGTP
Measles virus P3	13	<u>LECIRALK</u>
Corticotropin	18	LECIRACK
Adenovirus 12 E1B	384	<u>LRRGMFRPSQCN</u>
A-gliadin	206	LGQGSFRPSQQN
<i>Klebsiella pneumoniae</i> nitrogenase	186	SRQTDREDE
Human lymphocyte antigen B27	70	KAZTDREDL
Rabies virus glycoprotein	147	<u>TKESLVIIS</u>
Insulin receptor	764	NKESLVISE
Papillomavirus E2	76	SLH <u>LES</u> LKDS
Insulin receptor	66	VYGLESLKDL
Poliovirus VP2	70	STTKESRGTT
Acetylcholine receptor	176	TVIKESRGTK
Coxsackie B3	2152	<u>YEA FIRKIRSV</u>
Myosin	138	YEA FVKHIMSV
Dengue	269	<u>IKKSKAL</u>
Coagulation factor x1	68	IKKSKAL
HIV Pol	222	<u>DSTKWRKVD</u>
Brain protein	156	DSTKNRKT D
HCMV IE-2	79	PDPLGRPDED
HLA DR	50	VTELGRPDAE

of adenovirus, the EC-LF2 protein of Epstein-Barr virus, the hepatitis B virus polymerase (HBVP), and several other viral proteins. The best fit was between the myelin basic protein encephalitogenic site in the rabbit and HBVP. Subsequently, inoculation of the HBVP peptide peripherally into rabbits caused perivascular infiltration localized to the central nervous system, reminiscent of the disease induced by inoculating whole myelin basic protein or the peptide component of the encephalitogenic site of myelin basic protein (Fujinami and Oldstone 1985) (Fig. 2). Furthermore, a specific immune response, both cellular and humoral, to myelin basic protein occurred. However this model was artificial, because there was no epidemiological evidence associating hepatitis

## Biological Consequences of Mimicry Between Rabbit Myelin Basic Protein (MBP) and Hepatitis B Virus Polymerase (HBVP)



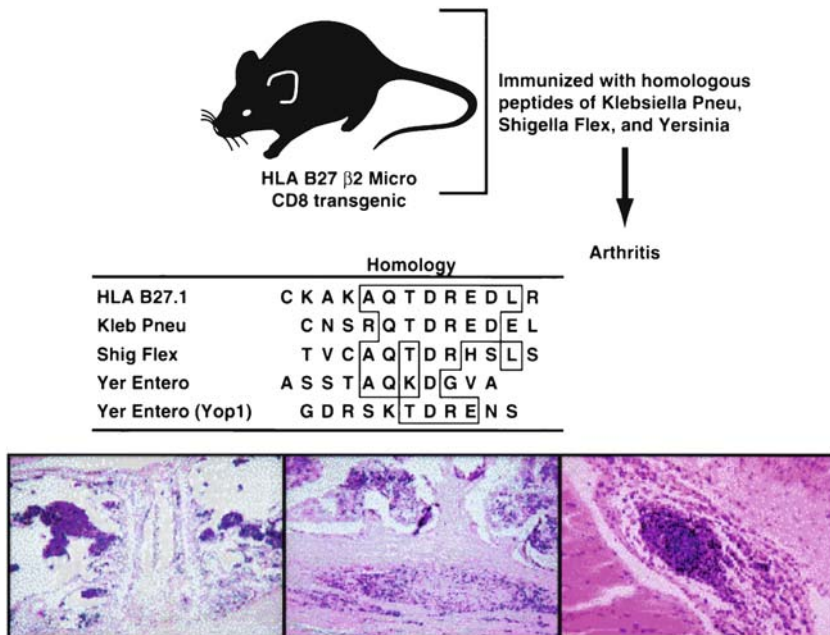
**Fig. 2** First demonstration that molecular mimicry could cause disease. When New Zealand rabbits were inoculated with the 10-amino acid peptide from hepatitis B virus polymerase (*HBVP*), they generated specific T (proliferation) and B (antibody) lymphocyte responses. Most significant, inoculated rabbits developed histopathologic criteria for lesions of EAE. In contrast, studies with over 10 different peptides in multiple rabbits failed to elicit EAE. (See Fujinami and Oldstone 1985 for experimental details)

B with an EAE-like disease. Nevertheless, the importance of the observation was in providing proof of the molecular mimicry concept in vivo. A more meaningful model followed with our observations correlating several bacteria with HLA B27-associated ankylosing spondylitis (AS), an arthritic disease of humans. Epidemiological, bacteriologic, and immunologic evidence is firm for a strong relationship between AS, the hypervariable region of HLA B27, and several bacterial infections including those of *Shigella flexneri*, *Yersinia enterocolitica*, and *Klebsiella pneumoniae* (Brewerton et al. 1973; Gilliland and Mannik 1986; Khare et al. 1996; Schwimmbeck and Oldstone 1989). Over 90% of patients who develop AS have the HLA B27 haplotype, but this haplotype occurs in only about 10% of the general population. Further, monozygotic twins show a discordance for AS (Eastmond and Woodrow 1977), indicating a role for environmental factors, which epidemiological evidence suggests is associated with infections by selective bacteria. For example, in a *S. flexneri* epidemic of about 150,000 cases in Finland during the 1940s, 344 infected



individuals developed Reiter's syndrome; of these 82 went on to develop AS. We observed amino acid sequence homology between enteric bacteria known to cause Reiter's syndrome and thus associated with AS and with the hypervariable region of HLA B27 (Table 2, Fig. 3).

To mimic AS, we humanized mice through transgenic technology to express human HLA (LaFace et al. 1995). For HLA B27-restricted T cell function, it was necessary to create a triple transgenic mouse that not only expressed human HLA B27 but also human  $\beta_2$ -microglobulin and human CD8 (Tishon et al. 2000). Challenge of such humanized transgenic mice with cross-reactive peptides derived from the bacteria (Fig. 3) led to immune responses with inflammatory cells located in the joints and vertebral columns of approximately



**Fig. 3** Sequence sharing between the hypervariable region of HLA B27 molecule and sequences from bacteria epidemiologically associated with causing Reiter's syndrome, a disease that often precedes HLA B27-associated ankylosing spondylitis. Inoculation of the *Shigella flexneri* peptide (center panel) or *Klebsiella pneumoniae* peptide (right panel) into transgenic mice expressing HLA B27 human  $\beta_2$ -microglobulin and human CD8 leads to inflammatory responses in joints and the vertebral column. Monoclonal antibodies to HLA B27 are also found in these mice, but not in other mice given cross-reactive bacterial peptides. The control mice also fail to demonstrate inflammatory lesions (left panel)

40% of the inoculated, triple transgenic mice but not of control mice (Oldstone 1998). Interestingly, a transgenic rat model was developed by Hammer et al. (1990) in which HLA B27 expression was associated with a clinical and histopathologic picture reminiscent of AS. AS-like disease occurred in rats housed in a normal vivarium but not when such rats were quartered under germ-free conditions (Taurog et al. 1994). Yet, when the germ-free rats were later colonized by bacteria, they developed arthritis (Rath et al. 1996). In addition to the molecular mimicry mechanism, HLA B27 may be associated with a delayed or disordered clearance of these bacterial pathogens.

Several other informative animal models were developed to show cross-reactivity between a microbe and self-antigen leading to autoimmune disease (reviewed in Cunningham and Fujinami 2000, Oldstone 1989, 1998). One interesting example is presented in publications from the laboratories of Harvey Cantor and Priscilla Schaffer (Zhao et al. 1997) for herpes simplex virus with corneal antigens. Others are reviewed in this volume. Steve Miller and his associates describe a Theiler's virus-induced molecular mimicry model of multiple sclerosis, whereas Larry Steinman and colleagues report on molecular mimicry and peptide protection of EAE. The last chapter in the series on animal models of infection is from my laboratory and focuses on the principles of how molecular mimicry works and the quantitation of cross-reactive antigen-specific T cells required for disease in a transgenic model of type I diabetes.

## 5

### **Equating Human Autoimmune Disease with Molecular Mimicry**

The most difficult step in the process described here is to definitively prove the relevance of molecular mimicry to human autoimmune disease. Various correlations ranging from those that are reasonably convincing to those that are less so have been published (reviewed in Oldstone 1998). Two examples are selected for brief mention. The first is the autoimmune disease myasthenia gravis. The majority of these patients have antibodies against the acetylcholine receptor (AChR). Purification of antibodies from patients with myasthenia gravis using the human AChR  $\alpha$ -subunit from amino acids 157 to 170 as a probe uncovered, as expected, immunoglobulin G antibodies that bound to native AChR and inhibited the binding of  $\alpha$ -bungarotoxin to its receptor. In addition, the human AChR  $\alpha$ -subunit from amino acids 160 to 167 showed specific immunologic cross-reactivity with a shared homologous domain on herpes simplex virus glycoprotein D, residues 286 to 293, by both specific binding and inhibition assays. Antibodies, including monoclonals,

to the human AChR  $\alpha$ -subunit bound to herpes simplex virus-infected cells (Schwimmbeck et al. 1989). The data on the immunologic cross-reactivity of the AChR “self-epitope” with herpes simplex virus and the presence of cross-reactive antibodies in the sera of patients with myasthenia gravis suggest the possibility that this virus may be associated with some cases of myasthenia gravis.

In another study, Wucherpfennig and Strominger (1995) imposed a structural requirement for molecular mimicry searches. These investigators used the known structures for MHC class II disease-associated molecules that bind to specific peptides and the T cell receptor for a known immunodominant myelin basic protein peptide. A database search produced a panel of 129 peptides from microbes that matched the molecular mimicry motif, and these were tested with several T cell clones obtained from the cerebrospinal fluid of patients with multiple sclerosis. Eight peptides (seven of viral origin and one of bacterial origin) were found to efficiently activate three of these clones. In contrast, only one of the eight peptides would have been identified as an appropriate molecular mimic by sequence alignment. These observations indicated that a single T cell receptor could recognize several distinct but structurally related peptides from multiple pathogens, suggesting more permissivity for the T cell receptor than has been previously appreciated (also see Mason 1998). This issue is further explored in this volume by K.W. Wucherpfennig.

In this volume, for additional studies of human disease, K. Bachmaier and J. Penninger review their body of work associating chlamydia-induced molecular mimicry and other microbial infections with immune responses to cardiac antigens and resultant heart disease; and John Stuart discusses HTLV-1-induced molecular mimicry and tropical sprue myelopathy. Betty Diamond presents recent provocative findings of molecular mimicry between anti-DNA antibodies and the NR2 glutamate receptor in systemic lupus erythematosus.

## 6

### **Overview of Autoimmune Responses and Infections**

The autoimmune response is often a pathway of immunity that attacks one's own tissues and causes disease. Most autoimmune diseases are organ (tissue) specific, and they develop when lymphocytes or their products (cytokines, antibodies, perforin, etc.) react with a limited number of antigens in that tissue. The molecular mechanisms leading to autoreactive immune responses resemble those generated against foreign antigens such as bacteria, parasites, or viruses. However, in autoimmune disease either incomplete clonal deletion

or formation of clonal anergy of T cells establishes a population of cells that is potentially intolerant but under special circumstances able to react with the host's antigens. Autoimmune disorders are, then, characterized by the breaking of immunologic tolerance or of unresponsiveness to self-antigens. What is the evidence suggesting that some infectious agents, primarily viruses, can similarly break immunologic tolerance and are thus implicated in autoimmune diseases?

The evidence suggesting the involvement of viruses or other infectious agents in human autoimmune diseases came initially from studies of identical twins that clearly implicated environmental factors as a cause, because genetic factors alone could not be responsible. Genetic studies in such autoimmune diseases as multiple sclerosis, diabetes, AS, etc., were complemented by epidemiological evidence incriminating local events (geography) or multiple infections with these diseases (Eastmond and Woodrow 1977; Ebers et al. 1987; Gamble 1980; Green 1990; Jury et al. 1996; Kurtzke 1993; Merriman and Todd 1995; Panitch 1994; Theofilopoulos 1995). Indeed, it is well known that newly forming autoimmune responses or those previously present are enhanced after infection by numerous human DNA and RNA viruses (reviewed in Oldstone 1998). In fact, after infection, patients can mount immune responses to nucleic acids, cytoskeletal proteins, myosin, and lymphocytes, etc., as shown over 45 years ago by the great Swedish immunologist Asterid Fagraeus. Additionally, experimental acute and persistent infections with a DNA or RNA virus have induced, accelerated, or enhanced autoimmune responses and caused autoimmune disease. The New Zealand mouse family is a genetically defined group in which certain strains spontaneously develop autoimmune disease. For example, among their several typical autoimmune responses, NZB mice develop antibodies to DNA and red blood cells, whereas NZB×NZW (F1) mice develop antibodies to DNA and other nuclear antigens, closely resembling the picture of humans with systemic lupus erythematosus. When NZB or (NZB×W) F1 mice are persistently infected with either a DNA (polyoma) or an RNA (lymphocytic choriomeningitis virus, LCMV) virus, their autoimmune responses occur earlier, reach higher titers, and lead to disease sooner than in their uninfected counterparts (Tonietti et al. 1970). More interestingly, NZW mice compared to NZB and (NZB×W) F1 mice normally have no or only moderate autoimmune responses. However, NZW mice contain the necessary gene(s) for autoimmune disease and develop markedly accelerated autoimmune responses and acquire a lupus-like disease after infection by polyoma virus or LCMV. Other viruses, including retroviruses, cause a similar phenomenon. In human autoimmune diseases like multiple sclerosis, insulin-dependent diabetes mellitus (IDDM), or AS, the incidence of disease varies in monozygotic twins, again indicating that

other factors, in addition to genetics and most likely environmental, play a role (Green 1990; Jury et al. 1996; Merriman and Todd 1995; Oldstone 1998; Theofilopoulos 1995). Some have observed that infectious agents or cytokines released in the presence and/or absence of preexisting infections can break tolerance in potentially autoreactive CD4<sup>+</sup> T or CD8<sup>+</sup> T cells. Others have reported epidemiological and serological correlations between certain viruses and autoimmune diseases like multiple sclerosis (Ebers et al. 1987; Kurtzke 1993; Panitch 1994) and IDDM (Gamble 1980; Honeyman et al. 1998; Notkins and Yoon 1984). For example, Coxsackie B virus and rubella virus have been linked with IDDM. In a few instances, Coxsackie B virus has been directly isolated from pancreatic tissues of individuals with acute IDDM. Inoculation of this virus into mice then produced IDDM, fulfilling Koch's postulates (Yoon et al. 1989), although this occurrence is rare.

## 7

### Summary

In conclusion, molecular mimicry is but one mechanism by which autoimmune diseases can occur in association with infectious agents. The concept of molecular mimicry remains a viable hypothesis for framing questions and approaches to uncovering the initiating infectious agent as well as recognizing the "self"-determinant, understanding the pathogenic mechanism(s) involved, and designing strategies for the treatment and prevention of autoimmune disorders. The *Oxford Dictionary* defines hypothesis as "a supposition or conjecture put forward to account for certain facts and used as a basis for further investigation by which it may be proved or disproved." In many instances, hard data derived in experimental systems clearly indicate molecular mimicry as a mechanism for disease causation. For others, especially human disorders, the evidence can be strongly suggestive, but additional information is required before molecular mimicry can be accepted or rejected as biological reality. The availability of computer data banks, structural information on specific MHC alleles, and MHC maps for particular autoimmune diseases is crucial for answering such questions. Further, the ability to identify anchoring and flanking sequences of a peptide that binds to the MHC allele or T cell receptor in question provides the opportunity to better identify the microbial causes of autoimmune diseases. The application and use of transgenic models designed to evaluate molecular mimicry enable us to understand the sequence of events that leads to the related pathological effects as well as to design specific and unique therapies that can reverse or prevent the autoimmune destructive process.

**Acknowledgements** This is Publication Number 16970-NP from the Departments of Neuropharmacology and Infectology, The Scripps Research Institute, La Jolla, CA. This work was supported in the past and currently in part by USPHS Grants DK-058541, AI-009484, AI-045927, and AI-036222.

## References

- Atkinson MA, Bowman MA, Campbell L, Darrow BL, Kaufman DL, MacLaren NK (1994) Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. *J Clin Invest* 94:2125–2129
- Bachmaier K, Neu N, de la Maza LM, Pal S, Hessel A, Penninger JM (1999) Chlamydia infections and heart disease linked through antigenic mimicry. *Science* 283:1335–1339
- Brewerton D, Caffrey M, Hart F, James D, Nichols A, Sturrock R (1973) Ankylosing spondylitis and HLA B27. *Lancet* i:904–907
- Cunningham MW (2004) T cell mimicry in inflammatory heart disease. *Mol Immunol* 40:1121–1127
- Cunningham MW, Fujinami RS (eds) (2000) *Molecular mimicry*. ASM Press, Washington DC
- Dales S, Fujinami RS, Oldstone MBA (1983a) Serologic relatedness between Thy1.2 and actin revealed by monoclonal antibody. *J Immunol* 131:1332–1338
- Dales S, Fujinami RS, Oldstone MBA (1983b) Infection with vaccinia favors the selection of hybridomas synthesizing auto-antibodies against intermediate filaments, among them one cross-reacting with the virus hemagglutinin. *J Immunol* 131:1546–1553
- Dell A, Antone SM, Gauntt CJ, Crossley CA, Clark WA, Cunningham MW (1991) Autoimmune determinants of rheumatic carditis: localization of epitopes in human cardiac myosin. *Eur Heart J* 12:158–162
- Dixon FJ (1963) The role of antigen antibody complexes in disease. *Harvey Lecture* 58:21–52
- Dyrberg T, Oldstone MBA (1986) Peptides as probes to study molecular mimicry and virus-induced autoimmunity. *Curr Topics Microbiol Immunol* 130:25–37
- Dyrberg T, Petersen JS, Oldstone MBA (1990) Immunological cross-reactivity between mimicking epitopes on a virus protein and a human autoantigen depends on a single amino acid residue. *Clin Immunol Immunopathol* 54:290–297
- Eastmond CJ, Woodrow JC (1977) Discordance for ankylosing spondylitis in monozygotic twins. *Ann Rheum Dis* 36:360
- Ebers G, Bulman D, Sadovnik A, Paty DW, Warren S, Hader W, Murray TJ, Seland TP, Duquette P, Grey T et al. (1987) A population-based study of multiple sclerosis in twins. *N Engl J Med* 315:1638–1642
- Froude J, Gibofsky A, Buskirk DR, Khana A, Zabriskie JB (1989) Reactivity between streptococcus and human tissue. *Curr Topics Microbiol Immunol* 145:5–26
- 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

- Fujinami RS, Oldstone MBA, Wroblewska Z, Frankel ME, Koprowski H (1983) Molecular mimicry in virus infection: cross-reaction of measles phosphoprotein or of herpes simplex virus protein with human intermediate filaments. *Proc Natl Acad Sci USA* 80:2346–2350
- Gamble DR (1980) The epidemiology of insulin-dependent diabetes with particular reference to the relationship of virus infection to its etiology. *Epidemiol Rev* 2:49–70
- Gilliland B, Mannik M (1986) Ankylosing spondylitis and Reiter's syndrome (pp 1986–1988) and rheumatoid arthritis (pp 1977–1986). In: Harrison TR (ed) *Harrison's Principles of Internal Medicine*, 10th Edition. McGraw Hill, New York
- Green A (1990) The role of genetic factors in development of IDDM. *Curr Topics Microbiol Immunol* 164:3–17
- Hafer-Macko C, Hsieh ST, Li CY, Ho TW, Sheikh K, Cornblath DR, McKhann GM, Asbury AK, Griffin JW (1996) Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. *Ann Neurol* 40:635–644
- Hammer RE, Maika SD, Richardson JA, Tang JP, Taurog JD (1990) Spontaneous inflammatory disease in transgenic mice expressing HLA-B27 and human  $\beta 2m$ : an animal model of HLA-B27-associated human disorders. *Cell* 63:1099–1112
- Honeyman MC, Stone NL, Harrison LC (1998) T-cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. *Mol Med* 4:231–239
- Hudrisier D, Riond J, Burlet-Schiltz O, von Herrath MB, Lewicki H, Monsarrat B, Oldstone MBA, Gairin JE (2001) Structural and functional identification of major histocompatibility complex class I-restricted self-peptides as naturally occurring molecular mimics of viral antigens. *J Biol Chem* 276:19396–19403
- Jury KM, Loeffler D, Eiermann TH, Ziegler B, Boehm BO, Richter W (1996) Evidence for somatic mutation and affinity maturation of diabetes associated human autoantibodies to glutamate decarboxylase. *J Autoimmun* 9:371–377
- Kaplan MH (1963) Immunologic reactivity of streptococcal and tissue antigens. *J Immunol* 90:595–606
- Khare SD, Luthra HS, David CS (1996) Role of HLA-B27 in spondyloarthropathies. *Curr Topics Microbiol Immunol* 206:85–97
- Kurtzke JF (1993) Epidemiologic evidence for multiple sclerosis as an infection. *Clin Microbiol Rev* 6:382–427
- LaFace DM, Vestberg M, Yang Y, Srivastava R, DiSanto J, Flomenberg N, Brown S, Sherman LA, Peterson PA (1995) Human CD8 transgene regulation of HLA recognition by murine T cells. *J Exp Med* 182:1315–1325
- Lane DP, Hoeffler WK (1980) SV40 large T shares an antigenic determinant with a cellular protein of molecular weight 68,000. *Nature* 288:167–170
- Mason D (1998) A very high level of crossreactivity is an essential feature of the T-cell receptor. *Immunol Today* 19:395–404
- Merriman TR, Todd JA (1995) Genetics of autoimmune disease. *Curr Opin Immunol* 7:786–792
- Notkins AL, Yoon JW (1984) Virus-induced diabetes mellitus. In: Notkins AL, Oldstone MBA (eds) *Concepts in Viral Pathogenesis*. Springer-Verlag, New York, pp 241–247
- Oldstone MBA (1987) Molecular mimicry and autoimmune disease. *Cell* 50:819–820

- Oldstone MBA (ed) (1989) Molecular mimicry. *Curr Topics Microbiol Immunol*, Vol. 145
- Oldstone MBA (1998) Molecular mimicry and immune-mediated diseases. *FASEB J* 12:1255–1265
- Oldstone MBA, von Herrath M, Lewicki H, Hudrisier D, Whitton JL, Gairin JE (1999) Use of a high-affinity peptide that aborts MHC-restricted cytotoxic T lymphocyte activity against multiple viruses in vitro and virus-induced immunopathologic disease in vivo. *Virology* 256:246–257
- Panitch HS (1994) Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* 36:S25
- Rath HC, Herfarth HH, Ikeda JS, Grenther WB, Hamm TE Jr, Balish E, Taurog JD, Hammer RE, Wilson KH, Sartor RB (1996) Normal luminal bacteria, especially *Bacteroides* species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rates. *J Clin Invest* 98:945–953
- Schwimbeck P, Oldstone MBA (1989) *Klebsiella pneumoniae* and HLA B27 associated diseases of Reiter's syndrome and ankylosing spondylitis. *Curr Topics Microbiol Immunol* 145:45–67
- Schwimbeck PL, Dyrberg T, Drachman D, Oldstone MBA (1989) Molecular mimicry and myasthenia gravis: An autoantigenic site of the acetylcholine receptor  $\alpha$ -subunit that has biologic activity and reacts immunochemically with herpes simplex virus. *J Clin Invest* 84:1174–1180
- Schwimbeck PL, Yu DTY, Oldstone MBA (1987) Autoantibodies 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 auto-immune disease. *J Exp Med* 166:173–181
- Shrinivasappa J, Saegusa J, Prabhakar B, Gentry M, Buchmeier M, Wiktor T, Koprowski H, Oldstone M, Notkins A (1986) Molecular mimicry: frequency of reactivity of monoclonal antiviral antibodies with normal tissues. *J Virol* 57:397–401
- Taurog JD, Richardson JA, Croft JT, Simmons WA, Zhou M, Fernandez-Sueiro JL, Balish E, Hammer RE (1994) The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic mice. *J Exp Med* 180:2359–2364
- Theofilopoulos A (1995) The basis of autoimmunity. II. Genetic predisposition. *Immunol Today* 16:150–159
- Tishon A, LaFace DM, Lewicki H, van Binnendijk RS, Osterhaus A, Oldstone MBA (2000) Transgenic mice expressing human HLA and CD8 molecules generate HLA-restricted measles virus cytotoxic T lymphocytes of the same specificity as humans with natural measles virus infection. *Virology* 275:286–293
- Toniatti G, Oldstone MBA, Dixon FJ (1970) The effect of induced chronic viral infections on the immunologic diseases of New Zealand mice. *J Exp Med* 132:89–109
- 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
- Yoon JW, Austin M, Onodera T, Notkins AL (1989) Virus-induced diabetes mellitus: isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *N Engl J Med* 300:1173–1179



- Yuki N, Susuki K, Koga M, Nishimoto Y, Odaka M, Hirata K, Taguchi K, Miyatake T, Furukawa K, Kobata T, Yamada M (2004) Carbohydrate mimicry between human ganglioside GM1 and *Campylobacter jejuni* lipooligosaccharide causes Guillain-Barre syndrome. Proc Natl Acad Sci USA 101:11404–11409
- Zhao ZS, Granucci F, Yeh L, Schaffer P, Cantor H (1997) Molecular mimicry by herpes simplex virus type 1: autoimmune disease after viral infection. Science 275:1344–1347