Molecular mimicry and immune-mediated diseases

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ABSTRACT Molecular mimicry has been proposed as a pathogenetic mechanism for autoimmune disease, as well as a probe useful in uncovering its etiologic agents. The hypothesis is based in part on the abundant epidemiological, clinical, and experimental evidence of an association of infectious agents with autoimmune disease and observed cross-reactivity of immune reagents with host 'self' antigens and microbial determinants. For our purpose, molecular mimicry is defined as similar structures shared by molecules from dissimilar genes or by their protein products. Either the molecules' linear amino acid sequences or their conformational fits may be shared, even though their origins are as separate as, for example, a virus and a normal host–self determinant. An immune response against the determinant shared by the host and virus can evoke a tissue-specific immune response that is presumably capable of eliciting cell and tissue destruction. The probable mechanism is generation of cytotoxic cross-reactive effector lymphocytes or antibodies that recognize specific determinants on target cells. The induction of cross-reactivity does not require a replicating agent, and immune-mediated injury can occur after the immunogen has been removed—a hit-and-run event. Hence, the viral or microbial infection that initiates the autoimmune phenomenon may not be present by the time overt disease develops. By a complementary mechanism, the microbe can induce cellular injury and release self antigens, which generate immune responses that cross-react with additional but genetically distinct self antigens. In both scenarios, analysis of the T cells or antibodies specifically engaged in the autoimmune response and disease provides a fingerprint for uncovering the initiating infectious agent.—Oldstone, M. B. A. Molecular mimicry and immune-mediated diseases. *FASEB J.* **12**, 1255–1265 (1998)

Key Words: autoimmune disease · microbial agent · insulin-independent diabetes mellitus · sequence sharing

AUTOIMMUNE DISEASES are multifactorial. In addition to a genetic link and, in several instances, a major histocompatibility complex (MHC)[2] disease association (1–3), other factors (including environmental ones) must be involved. For example, there is strong clinical/epidemiological evidence that monozygotic twins show a striking discordance for several autoimmune diseases like insulin-dependent diabetes, multiple sclerosis, and HLA-B27-associated ankylosing spondylitis (4–6). In addition, when the antibody or T cell receptor associated with disease has been available for structural analysis, primarily somatic mutations, suggesting an antigen-driven process rather than germline mutations, have been found (7, 8). Other evidence comes from observations that human viral infections are often associated with autoimmune responses (reviewed in ref 9). Hence, newly formed autoimmune responses or those already present are enhanced after infection by a wide variety of human DNA and RNA viruses. In addition, experimental acute and persistent infections with either DNA or RNA viruses have induced, accelerated, or enhanced autoimmune responses and caused autoimmune disease. Perhaps the best-known instance occurs during evaluation of the New Zealand mouse model (10). In this system of genetically defined mice that spontaneously develop autoimmune disease, persistent infection with a DNA virus like polyoma or an RNA virus like lymphocytic choriomeningitis virus speeds up the time when antibodies to DNA, red blood cells, and other autoantigens appear. Thus, the kinetics and severity of the resulting autoimmune disease are dramatically accelerated. More germane is the NZW mouse, which normally does not develop autoimmune response or disease but contains the necessary gene(s) to develop the anti-DNA and other autoimmune responses and disease and does so after viral infection. Others have reported epidemiologic and serologic correlations between viral infections and autoimmune diseases like multiple sclerosis (MS) (11, 12), insulin-dependent diabetes mellitus (IDDM) (13, 14), bacterial infections, and ankylosing spondylitis (AS) (15). 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 (14, 16). Inoculation of the isolated virus into mice produced diabetes, thereby fulfilling Koch's postulates (16). Several viruses have been associated with MS (17–20), and there is abundant epidemiologic evidence of a close association of viral infection with exacerbations of this demyelinating disease (11, 12, 20). Robust epidemiologic evidence correlates the occurrence of certain bacterial infections such as *Klebsiella pneumoniae, Shigella flexneri, Salmonella,* and *Yersinia* with the initial onset of acute Reiter's syndrome, followed by AS in HLA B27⁺ individuals (15, 21). Last, there are transgenic models in which mice expressing an autoimmune gene and/or its T cell recognition (TCR)/antibodies required to develop autoimmune disease do not do so unless there is an environmental switch, i.e., movement from a pathogen-free animal facility to a standard vivarium (22, 23).

Microbial agents or viruses can induce autoimmune responses and diseases by a variety of mechanisms, several of which may occur during an infection. For example, proteins of certain infectious agents have a proliferative effect on unique lymphocyte subsets and hence act as polyclonal activators. Viruses can preferentially infect/destroy a particular T cell subset, leading to an imbalance in the immune response. In other instances, infectious agents can up-regulate Th.1 cytokines, thereby increasing selected expression of molecules such as MHC glycoproteins, as well as activation and costimulatory molecules such as B7.1/CD28. Several microbial agents have been found to encode superantigens that can selectively activate subset(s) of T cells (24–26). In other cases, viruses may break self tolerance by de novo release of self epitopes presumably by direct injury caused by the virus or secondarily by the virus-specific T cells generated. Either way, damage can occur by a procedure called epitope spreading (27, 28). Microbes can also direct the release of cytokines and chemokines, important regulators of immune responses. These molecules can act as growth, differentiation, or chemotactic factors for different Th populations and regulate expression of MHC class I and class II molecules. Thus, an infectious agent could release a cytokine-like interferon that induces the expression of MHC determinants. In addition, microbes—especially viruses—can infect and selectively replicate in unique lymphocyte subsets and, by their presence, activation, or replication, cause immunosuppression or immunoenhancement. Last, microbes can contain chemical structures that mimic normal host 'self' proteins, an event termed molecular mimicry (**Fig. 1**). Several possibilities are listed in **Table 1**. Of these, molecular mimicry is the focus of this review. Whereas there is heightened suspicion that infectious agents and molecular mimicry play a role in several autoimmune diseases, direct evidence has been hard to come by. There are a number of reasons for this discrepancy: for instance, the organism initiating the autoimmune process may be cleared by the host immune response, thus removing our ability to isolate it. However, the initiated immune response would continue the process against cross-reactive 'self' determinant, a 'hit-and-run' scenario.

DEVELOPMENT OF MOLECULAR MIMICRY CONCEPT

The initial clues that molecular mimicry might play a role in autoimmune diseases were found in the early 1980s associated with the development and use of monoclonal antibody technology. It was first noted while generating monoclonal antibodies that the phosphoprotein of measles virus and a protein of herpes simplex virus type 1 cross-reacted with an intermediate filament protein of human cells (29; **Fig. 2**). The intermediate filament protein was identified as vimentin, and the monoclonal antibody against measles virus phosphoprotein was shown to react with an
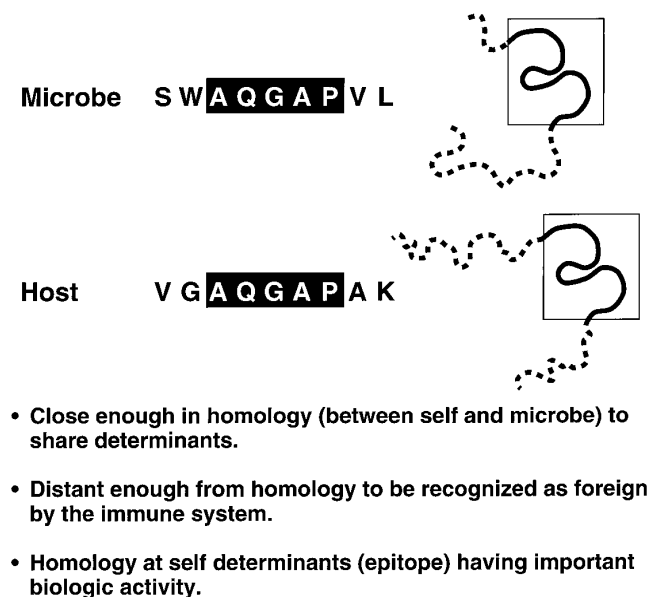

Microbe S W **A Q G A P** V L

Host V G **A Q G A P** A K

- **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.**

Figure 1. Illustration of the molecular mimicry concept along with associated guidelines. The sharing of a linear amino acid sequence or a conformation fit between a microbe and a host 'self' determinant is the initial stage of molecular mimicry. Autoimmunity may occur if the host immune response against the microbe cross-reacts with the host's 'self' sequence and if the host sequence comprises a biologically important domain, i.e., the encephalitogenic site of a myelin protein incriminated in CNS or demyelinating disease, the component of the acetylcholine receptor important for synapse formation, or the hypervariable region of MHC molecule (HLA B27) associated with disease.

TABLE 1. *Infectious agents can trigger autoimmune disease by activation of autoreactive T cells via:*

1. Up-regulation of Th-1 cytokines and/or other selected molecules: MHC, B7.1/CD28
2. Preferential infection/destruction of CD4 T cell subset
3. Virus-encoded super antigens
4. De novo by self epitopes released secondary to virus-specific, T cell-mediated damage: epitope spreading
5. Cross-reactive with a viral epitope(s): molecular mimicry

antigenic determinant on the intermediate filament molecule different from the reaction caused by antibody to herpes simplex virus protein. A number of similar cross-reactivities between viral proteins and host 'self' determinants were subsequently recorded. The observations were firmly established as a result of a collaborative study with the laboratories of Abner Notkins, Hilary Koprowski, and our own that documented roughly 5% of monoclonal antibodies made against 15 different kinds of viruses cross-reacted with 'host–self determinants' when over 800 independent monoclonal antibodies were studied (30, 31; **Fig. 3**). In these experiments, monoclonal antibodies made against representative DNA and RNA viruses such as herpes simplex, cytomegalo, Epstein-Barr, vaccinia virus, myxoviruses, paramyxoviruses, arenaviruses, flaviviruses, orthoviruses, rhabdoviruses, coronaviruses, and human retroviruses were studied. On the basis of needing five to six amino acids to induce a monoclonal antibody response, the probability of 20 amino acids occurring in six identical residues between two proteins is 20^6 or 1 in 128,000,000. Others showed

MOLECULAR MIMICRY DETECTION

Figure 2. Left panel reproduces data that first suggested the molecular mimicry concept. Monoclonal antibody to measles virus P protein (MV-P) was found to react with cytokeratin (cytoK; see ref 29 for details). The right panel shows that a monoclonal antibody to measles virus nucleoprotein also reacts with molecule(s) on the surface of T lymphocytes (see ref 31 for details).

Molecular Mimicry: Viruses-Host Antigens

Monoclonal Antibodies

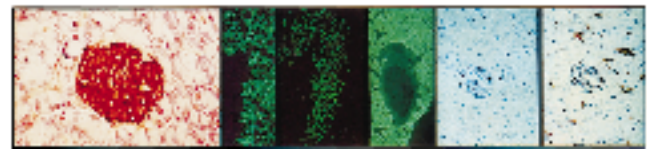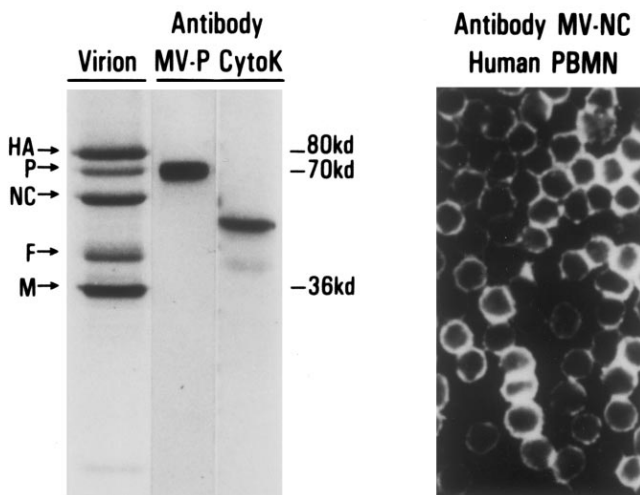| Reactive with Virus	No. Tested	Reactive with Uninfected Tissues
Coxsackie B	68	3
Japanese Encephalitis	34	6
Lymphocytic Choriomeningitis	174	3
Theiler's Virus	54	9
Measles	89	5
Rabies	80	2
Vesicular Stomatitis	37	2
Herpes Simplex (I)	20	1
Vaccinia	16	1
Dengue	134	2
Cytomegalovirus		
Human	25	2
Mouse	14	0
Human Immunodeficiency Virus	110	9
Total	815	45

Figure 3. Update on combined data from studies of molecular mimicry of the reactivity of monoclonal antiviral antibodies with normal mouse tissue (see refs 30, 31). Lower panels document reactivity of several antiviral monoclonal antibodies that react with host tissues or cells. Left panel: antibody to herpes simplex virus 1 GP reacts with β cells of the islets of Langerhans or their product. Center panel shows monoclonal antibodies to measles virus, Japanese encephalitis virus, and coxsackie B4, which react with growth hormone cells of the anterior lobe of the pituitary, hippocampal neurons, and myocardium (ventricle only and not smooth muscle around the vessel). Right panel displays a monoclonal antibody to HIV GP41 that reacts with astrocytes and the specificity control where addition of HIV GP41 peptide to the monoclonal antibody blocks staining (see Yamada et al., ref 33).

that T lymphocytes obtained from the spinal fluids of patients with viral infections or with MS cross-reacted with a specific viral determinant as well as a specific host myelin protein.

Biologic evidence was obtained over the next few years in several animal models indicating that molecular mimicry was more than an epiphenomenon (reviewed in ref 9). An early observation used myelin basic protein and allergic encephalomyelitis. The myelin basic protein sequences that cause allergic encephalitis are known and the encephalitogenic site of 8–10 amino acids has been mapped for several different animal species. With the use of computer-assisted analysis (32), several viral proteins were uncovered that showed significant homology with the encephalitogenic site of myelin basic protein, including fits between the myelin basic protein and nucleoprotein of the hemagglutinin of influenza virus, core protein of adenovirus, EC-LF2 protein of Epstein-

Barr virus, and hepatitis B virus polymerase as well as others. However, the best fit occurred between the myelin basic protein encephalitogenic site in the rabbit and hepatitis B virus polymerase (HBVP). It was then shown that inoculation of HBVP peptide peripherally into rabbits caused perivascular infiltration localized to the central nervous system, reminiscent of disease induced by inoculation of whole myelin basic protein or the peptide component of the encephalitogenic site of myelin basic protein (34; **Fig. 4**). Further, a specific immune response to both cellular and humoral to myelin basic protein occurred. Thereafter, several other animal models were developed showing cross-reactivity between a microbe and self antigen leading to disease. For example, coxsackie B3 virus shared sequence homology with heart myosin or other myocardial proteins (i.e., GAP junction), and experimental manipulations in experimental animals led to myocardial necrosis and myocarditis (35–37). Another early example of sequence homologies, immune cross-reactivity, and disease in animals was autoimmune uveitis with cross-reactivity between S-antigen and viral peptides (38).

CORRELATION OF MOLECULAR MIMICRY WITH HUMAN DISEASE

The next step, and the most difficult to definitively prove, was showing the relevance of molecular mimicry to naturally occurring human disease. Various correlations ranging from reasonably convincing to less so have been published. **Table 2** lists a number of such correlations. Several examples are selected here for a more detailed discussion.

The large majority of patients with the autoimmune disease myasthenia gravis (MG) have antibodies against the acetylcholine receptor (AChR). Purification of antibodies from MG patients using the human AChR α-subunit amino acids 157 to 170 provided IgG antibodies that bound to native AChR and inhibited the binding of α-bungarotoxin to the receptor (39). The human AChR α-subunit amino acids 160–167 showed specific immunologic cross-reactivity with a shared homologous domain on herpes simplex virus glycoprotein D, residues 286–293, by both specific binding and inhibition assays. Antibodies to the human AChR α-subunit bound to herpes simplex virus-infected cells. The data of immunologic cross-reactivity of the AChR 'self epitope' with herpes simplex virus and the presence of cross-reactive antibodies in the sera of MG patients suggest that this virus may be associated with the initiation of some cases of myasthenia (39).

IDDM results from autoimmune destruction of insulin-making beta cells in the islets of Langerhans believed to be caused by autoreactive T lymphocytes. Clinical studies have shown a high correlation with immune response to glutamate decarboxylase (GAD) and patients progressing to or having IDDM. Epidemiologic evidence has correlated IDDM with several viral infections, including coxsackie B virus, which has been shown, albeit rarely, by Koch's postulates to be associated with cases of acute IDDM (13, 14, 16). A component of GAD amino acids 247–279 was shown to be recognized by patients with increased risk of IDDM and to share sequence similarity with the P2-C protein of coxsackie B virus. Evaluation of patients with IDDM, of high risk to develop IDDM, or healthy controls showed that peripheral blood mononuclear cells from 4 of 16 newly diagnosed IDDM patients (25%) or 7 of 15 patients (47%) with high risk of developing IDDM (having islet cell au-
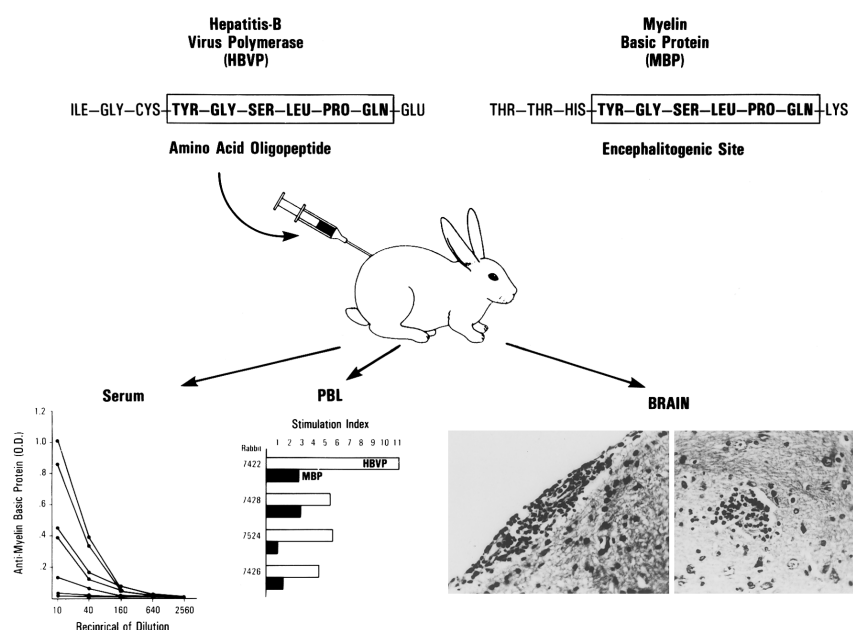

Figure 4. Experimental demonstration that molecular mimicry could cause disease. New Zealand rabbits inoculated with 10 amino acid peptide from hepatitis B virus polymerase generated specific T (proliferation) and B (antibody) lymphocyte responses to myelin basic proteins. Rabbits developed histopathologic evidence of lesion of allergic encephalomyelitis (see ref 34 for details).

TABLE 2. *Compilation of several diseases reported to be possibly associated with mechanism of molecular mimicry*

Disease	Cross-reactive immune responses	References
Primary biliary cirrhosis	Pyruvate dehydrogenase complex Anti-mitochondrial response HLA DRα Microorganisms: *E. coli, S. cerevisial*	63–66
Rasmussen's encephalitis	Antiglutamate receptor (GLUR3) response Microorganisms	66, 67
Multiple sclerosis	Myelin proteins Viruses: corona, measles, mumps, EBV, herpes, etc.	18, 19, 47, 68–71
Myasthenia gravis	Acetylcholine receptor Neurofilaments Herpes	39, 72, 73
Guillain-Barré	Peripheral nerve Gangliosides *Campylobacter jejuni*	74–76
Insulin-dependent diabetes	Islet antigens (GAD 65, proinsulin carboxypeptidase H) Coxsackie B Rotaviruses Hepatitis C, herpes, rhino-, hanta-, and faviviruses Retroviral	40, 77–80
Myocardial (heart)	ADP/ATP carrier protein Cardiac myosin Myocardial cell surface protein Coxsackie B3, streptococci	35–37, 81, 82
Celiac	Gliadin Enterocyte surface molecules Adenoviruses Enteric microbes	83, 84
Graft vs. host transplantation	Aminopeptidase N HLA molecule Cytomegalovirus	85, 86
Pemphigus	Desmosomes VH-CDR3	87
Herpes stomal keratitis	Herpes simplex Corneal antigen(s)	88
Autoimmune uveitis	S-antigen IRBP Viruses	38, 89
Peptic ulcer/gastric CA	*H. pylori* Self antigens on gastric mucosa	90
Pathogenesis in:		
HIV		91–94
Lyme disease		95
Streptococcal		82, 96
Syphilis		97
Prion protein disease		98
Trypanosoma		99–102

toantibodies with IDDM) proliferated to both GAD and coxsackie B viral peptides; however, none of the 13 healthy controls did (40, 41), suggesting a possible association for a virus like coxsackie B with IDDM.

Recently, Honeyman et al. (41) reported that a dominant peptide (aa 805 to 820) from IA-2 islet protein, which is a molecular target of pancreatic islet autoimmunity in type 1 diabetes in humans, had 56%
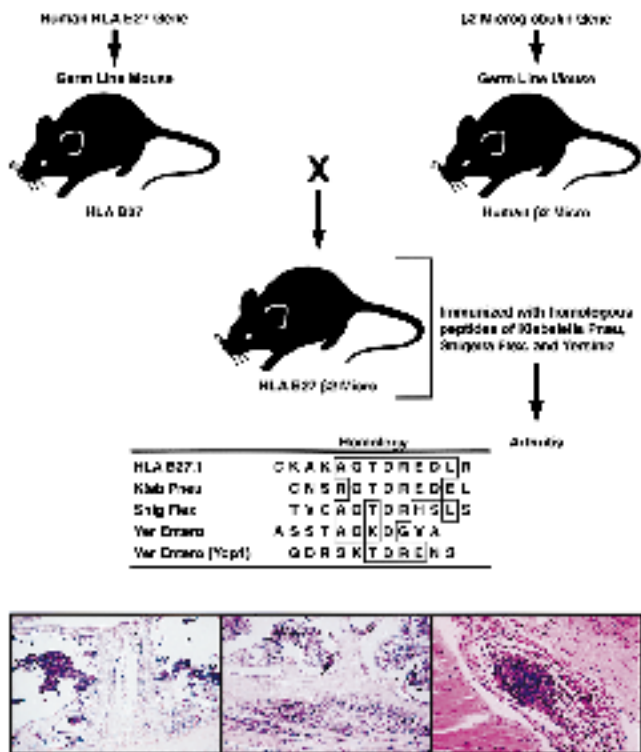
Autoantibodies to HLA B27 in Sera of Patients with Ankylosing Spondylitis

Patient Group Studied	no. pts.	Antibodies in the sera to:	
		CKAKAQTDREDLR (HLA B27.1 aa67-79)	CNSRQTDREDELI (K. pneu. nit. aa184-196)
HLA B27+ with AS	59	15 (25%)	19 (32%)
B27	24	7 (29%)	11
B27.1	27	7 (26%)	8
B27.2	5	0	1
B27.3	1	0	0
B27.4	0	0	0
B27.3,4	1	1	0
B27.1,2	1	0	0
HLA B27+ no AS	31	0 (0%)	
B27	22	0	0
B27.1	7	0	0
B27.2	1	0	0
B27 J	1	0	0
HLA B27nil with AS	5	0 (0%)	0
Non HLA typed	104	1 (0.9%)	1 (0.9%)

Sequences for HLA B27 subtypes are:

HLA B27.1 aa 69-78	AKAQTDREDL	
HLA B27.2 aa 69-78	AKAQTDRENL	
HLA B27.3 aa 69-78	AKAQTDRESL	

Figure 5. *A*) 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 $\beta2$ microglobulin and human CD8 leads to inflammatory response in joints and the vertebral column. Antibodies to HLA B27 are also found in these mice, but not in other mice given non-cross-reactive peptides. The control mice also fail to demonstrate inflammatory lesions (left panel). *B, C*) Correlation of antibodies to HLA B27 and *K. pneumoniae* nitrogenase peptide in patients with Reiter's disease (*B*) or ankylosing spondylitis (*C*) (for details, see refs 43, 44).

identity and 100% similarity for 9 aa with a sequence in VP7, a major immunogenic protein of human rotavirus. The contiguous sequence of VP7, had 75% identity and 92% similarity over 12 aa with a known T cell epitope in GAD. Further, the IA-2 immunodominant peptide showed significant identity with hepatitis C virus and hemophilus influenza. Three other distinct IA-2 peptides shown 71 to 100% similarity over 7 to 12 aa to herpes, rhino-, hanta-, and flaviviruses.

One of the interesting and still controversial findings for an association of microbes with disease by the mechanism of molecular mimicry occurs with AS and bacterial infections (42–46). Epidemiologi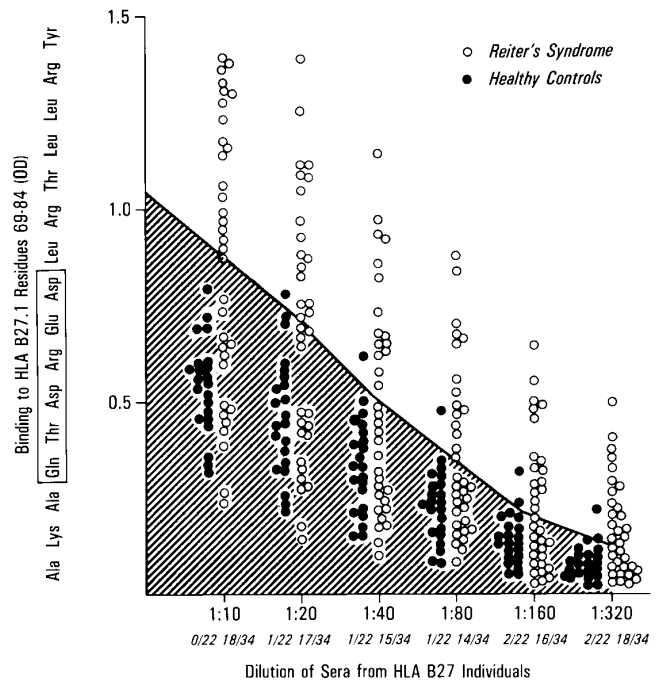c, bacteriologic, and immunologic evidence is firm for a correlation between AS, the hypervariable region of HLA B27, and several bacterial infections including those of *S. flexneri, Yersinia entercolytica*, and *K. pneumoniae*. Over 90% of individuals developing AS have the HLA B27 haplotype. In a *S. flexneri* epidemic of about 150,000 cases in Finland in the 1940s, 344 infected individuals developed Reiter's syndrome; of these, 82 went on to develop AS. Amino acid sequence homology between enteric bacteria associated with Reiter's syndrome and thus AS with the hypervariable region of HLA B27 was observed (**Fig. 5**). When transgenic mice were created to express human HLA B27 and challenged with cross-reactive peptides derived from proteins of such bacteria, immune responses occurred with inflammatory cells lo-

calized to joints and vertebral columns in approximately 40% of inoculated mice (M. B. A. Oldstone, S. Shyp, P. Peterson, and D. LaFace, unpublished observations; Fig. 5). Patients with AS showed antibodies in their circulation that cross-reacted with both the hypervariable region of HLA-B27 as well as a closely homologous sequence from *K. pneumoniae* nitrogenase (43, 44). Subsequently, a transgenic rat model was developed in which expression of HLA-B27 was associated with a clinical and histopathologic picture reminiscent of AS (45). AS-like disease occurred in rats in a normal vivarium and did not occur in rats housed in germ-free conditions (23). When germ-free rats were colonized with bacteria, they developed arthritis (46). Besides molecular mimicry, other investigators (23, 46) raised the possibility that HLA B27 may be associated with delayed or disordered clearance of the associated bacterial pathogens.

To apply a greater degree of specificity and a more stringent approach to the study of molecular mimicry and potential associated diseases (32), Wucherpfennig and Strominger (47) as well as Hammer et al. (48) imposed a structural requirement for molecular mimicry searches. Wucherpfennig and Strominger used the known structure for MHC class II disease-associated molecules with peptide binding and TCR for a known immunodominant myelin basic protein peptide. By database search, a panel of 129 peptides from microbes were obtained that matched the molecular mimicry motif, and these were tested on several T cell clones obtained from the cerebral spinal fluid of multiple sclerosis patients (47). Eight peptides (seven of viral and one of bacterial origin) were found to efficiently activate three of these clones, whereas 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 TCR than previously appreciated, an observation supported by other recent reports (49–51). Hammer et al. (48) analyzed the possible peptide motifs that bound to HLA-DR β chain associated with autoimmune disease. The influence of single key residues was tested by using site-directed mutations. A selection of peptides binding to rheumatoid arthritis-linked DR allotypes was shown to be critical for position aa 71 of DR β and 57 of DQ β (48). Extension of these findings to IDDM (47, 48) suggested that IDDM 'autoimmune' peptide would bear a negative charge at P9 in order to bind preferentially to diabetes-associated DQ allele. In toto, these findings should assist in identification of potential peptides (self? viral? microbe?) associated with the pathogenesis of autoimmune disease. One variation on this theme to help explain MHC linkage with autoimmune disease and infectious agents is that MHC-derived self peptides prominent in selecting the T cell repertoire may be mutated and/or share immunologic cross-reactive epitopes with microbial antigens. Others (51) have shown that a six amino acid peptide can sensitize myelin basic protein-specific T cells to cause EAE and have used this information to identify viral and bacterial proteins (peptides) that share similar amino acids. Of interest will be experiments using such viral or microbial agents to initiate/potentiate or perhaps block the autoimmune EAE disease.

USING MOLECULAR MIMICRY MODELS TO DISSECT THE PARAMETERS REQUIRED FOR THE ACTIVATION AND ASSOCIATION OF VIRUS-INDUCED AUTOIMMUNE DISEASE

To dissect the pathogenetic mechanisms by which viral infection can break tolerance or unresponsiveness to self and the sequential events involved in the autoreactive cascade that leads to autoimmune disease, we and others have designed and exploited transgenic mouse models. An illustration of a model we developed for analysis of virus-induced IDDM is shown in **Fig. 6**, with the model described in refs 52 and 53. The cardinal observations uncovered through the analysis of this model are as follows. *1)* Lymphocytes in the periphery are ignorant or unresponsive to the 'self' protein, but can be activated in the absence of viral infection by coexpressing cytokines like interferon-γ or activation molecules such as B7.1 in the target (β cells) area. *2)* Infection by the same virus from which the 'self' protein was used as a transgene or a closely related virus that both cross-reacts and induces sufficient effector cytotoxic T lymphocytes (CTLs) also causes the autoimmune disease. *3)* If the transgene is expressed only in the target tissue, the autoimmune disease occurs rapidly, with kinetics of disease occurring by 10–4 days. Such positively selected high affinity effector T cells kill beta cells in the islets of Langerhans. The effector cell is a CD8 CTL and killing is dependent on perforin and interferon-γ. However, if the transgene is also expressed in the thymus, then the kinetics for initiation of disease after viral infection is prolonged. *4)* Depending on the MHC haplotype, disease takes between 1 and 7 months to occur. *5)* Whereas the rapid-onset autoimmune disease uses high affinity effector CTL, in contrast to the slow-onset autoimmune disease, the majority of high affinity T cells have been selected out in the thymus (negative selection) and only low affinity cells are available in the periphery to participate in causing the autoimmune disease. *6)* For low affinity CD8$^+$ T cells to produce disease, they require help from CD4, but such help is not necessary for the rapid-onset disease. *7)* Expression of Th.2 cytokine such as interleukin 4 (IL-4) retards the auto-
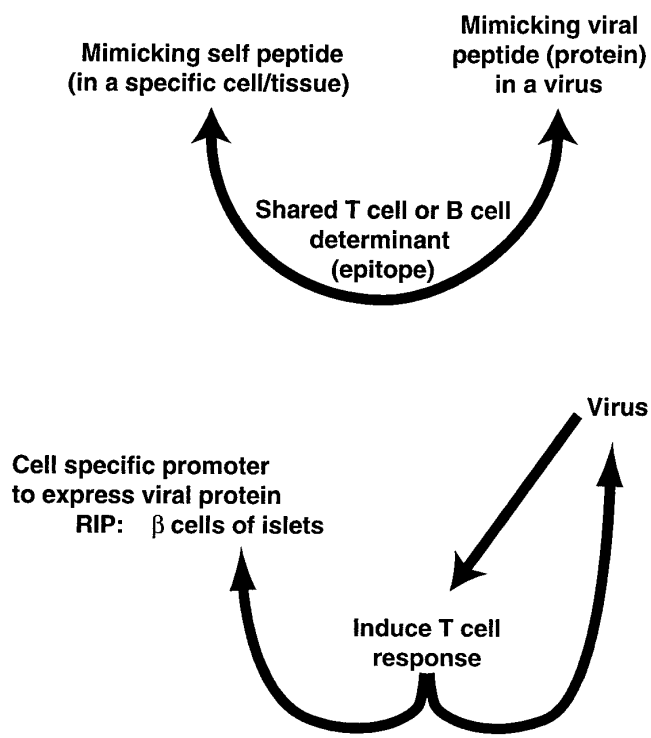
Figure 6. Molecular mimicry transgenic model designed to study insulin-dependent diabetes mellitus (IDDM). The viral gene product is placed in the β cells of the islets of Langerhans using the rat insulin promoter and transgenic technology. In a second scenario, the transgene is inserted and expressed in the thymus as well as the β cells of the islets. Because the transgene (viral gene) is inserted in the germline of the host and passed to subsequent progeny, it is in essence a host 'self' gene. Using both models allows the study of the mechanisms and kinetics by which immunologic tolerance is broken, peripheral low affinity (transgene expressed in the thymus) or high affinity (transgene not expressed in the thymus) effector T cells are activated, home to the islets, and cause autoimmune disease. These models allow the design of therapeutic approaches to prevent or reverse the disease process at different steps along the way.

immune diabetes. **Table 3** tabulates these findings (details can be found in refs 52–60; M. G. von Herrath, B. Coon, H. Mazarguil, J. E. Gairin, and M. B. A. Oldstone, unpublished results).

These observations allow the design of therapeutic approaches to halt the virus-induced IDDM. When the cytokine profile in the islets of Langerhans milieu was changed from a Th.1 to a Th.2 phenotype (γ-interferon to IL-4, TGF-β), IDDM was blocked even though this therapy had no demonstrable effect on precursor frequency of the effector CD8+ CTL (58; R. Mueller-Hoenger, M. G. von Herrath, X. Zhang, G. Patstone, T. Krahl, B. Coon, M. B. A. Oldstone, and N. Sarvetnick, unpublished results). A second successful therapeutic approach was to design a peptide that could bind at high affinity to the MHC allele involved in the IDDM (59; M. G. von Herrath, B. Coon, H. Mazarguil, J. E. Gairin, and M. B. A. Oldstone, unpublished results). IDDM did not occur by

this means; CD4+ and CD8+ T cells did not accumulate in the islets, but were found around them (peri-islitis). Further, the precursor frequency of the effector CD8+ T cells was diminished by several-fold, below a level required to cause IDDM. Another successful approach was to abort the expression of MHC class I molecule by coexpressing the E3 transcriptional complex of adenovirus in β cells of the islets of Langerhans (60). The focal reduction of MHC class I expression in the islets was associated with a normal precursor frequency of CD8+ CTLs in the spleen and blood. However, effector T cells did not localize in the islets, destruction of islets did not occur, and IDDM did not develop.

In addition to uncovering the pathogenetic mechanisms and providing therapeutic design to control the autoimmune disease, the transgenic model also proved efficacious for analysis of 'self' determinants that may be associated with or potentiate the autoimmune disease. In the transgenic model used (Fig. 6), since the specific amino acids required to bind to the MHC allele associated with the IDDM, as well as their binding motif, are known and fit within the MHC groove and residue recognition by TCR (59, 61, 62), a database search not dissimilar from the approach used by Wucherpfennig and Strominger (47) was undertaken. Twenty-one host self peptides were uncovered, synthesized, and studied for their direct binding to the D^b MHC allele. Those showing high

TABLE 3. *Lessons for virus-induced IDDM learned from the molecular mimicry transgenic model*

1. Lymphocytes in periphery are ignorant (tolerant) to the transgene (viral protein)
    i. Activated by cytokines or activation molecules
       IFN-γ
       B7.1
   ii. Activated by virus (specific or cross-reactive to the transgene) infection
2. IDDM can be rapid (<21 days) or slow (30 to 120 days) in onset
    i. Rapid onset
       • transgene in target cell (tissue) only
       • CD8+ T cell dependent
       • high affinity CTL
   ii. Slow onset
       • transgene in target cell and thymus
       • CD8+ T and CD4+ T cell dependent
       • low affinity CTL
       • association of thymic expression and MHC haplotype for time to develop IDDM
            4 to 5 log difference in affinity H-2^d vs. H-2^b
3. IDDM caused by CD8+ antiviral (self) CTL
    • dependent on perforin
4. IDDM dependent on specific cytokine profile in the islets
    • dependent on interferon-γ
    • associated with Th1 helper cytokine profile
    • prevented by IL-4
5. IDDM requires at least one virus (antiself) CD8+ specific T cell per 1500 total CD8+ T cells; 1/6000 or less does not cause diabetes

affinity binding (by competition assay, <100 nM) were then selected. As the effector CD8 T cell (anti-viral) (anti-'self') was known, the ability of the peptide to stimulate the auto(viral) T cell and cause it to proliferate, release cytokines, or lyse a 'self' peptide-coated target was determined and the ability of such activated T cells to transfer disease was monitored (M. B. A. Oldstone, J. E. Gairin, and M. G. von Herrath, unpublished results). Thus, there is the opportunity to obtain autoreactive T cells to 'self' antigen and use this information to uncover the infectious agent that initiated (was associated with) the autoimmune process.

In summary, 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 uncover the initiating infectious agent as well as recognizing the 'self' determinant, understanding the pathogenetic mechanism(s) involved, and designing strategies for treatment and prevention of autoimmune disorders. The availability of computer databanks, structural information on specific MHC alleles, MHC mapping to particular autoimmune diseases, and the ability to identify the anchoring and flanking sequences of a peptide that binds to that MHC allele or bind to the TCR provide the opportunity to critically evaluate and identify microbial causes of autoimmune diseases. The application and use of transgenic models designed to evaluate molecular mimicry offer the opportunity to understand the sequence of events leading to the pathology and design of specific and unique therapies in order to reverse or prevent the autoimmune process and disease. **FJ**

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