Commentary

Selective Binding of Self Peptides to Disease-associated Major Histocompatibility Complex (MHC) Molecules: A Mechanism for MHC-linked Susceptibility to Human Autoimmune Diseases

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Human autoimmune diseases have a striking genetic association with particular alleles of major histocompatibility complex (MHC) class I or II genes. The field was established by the seminal discovery of HLA-B27-linked susceptibility to ankylosing spondylitis, a chronic inflammatory joint disease (1, 2). MHC-associated susceptibility has now been documented for a variety of human autoimmune diseases, including insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis (RA), pemphigus vulgaris (PV), multiple sclerosis, and myasthenia gravis, just to name a few (3–8). A genome-wide search for diabetes susceptibility genes using microsatellite markers has demonstrated that several genes contribute to the disease process, but that the MHC is the most important susceptibility locus (9). Despite this remarkable progress, several critical questions remain to be answered to establish a causal relationship between the genetics and the immunopathogenesis: (a) Is the role of MHC molecules in autoimmunity based on the presentation of (self) peptides? (b) What is the biochemical nature of these peptides? (c) Are these peptides specific for a particular disease associated MHC molecule and the target organ of the immune attack? (d) What mechanisms induce an autoaggressive T cell response to these self determinants?

Recent developments in the field, particularly the structural characterization of MHC–peptide complexes and the identification of allele-specific peptide–binding motifs, have transformed the field (10–13). Based on this knowledge, the structural basis for MHC-linked susceptibility to autoimmune diseases can be reassessed at a level of detail sufficient for solving longstanding questions in the field. Motifs for peptide binding to MHC class I and II molecules were defined by sequence analysis of naturally processed peptides and by mutational analysis of known epitopes. MHC class I–bound peptides were found to be short (generally 8–10 amino acids long) and to possess two dominant MHC anchor residues; MHC class II–bound peptides were found to be longer and more heterogeneous in size (10–17). The size heterogeneity has made it more difficult to define MHC class II–binding motifs based on sequence alignments; the crystal structure of HLA-DR1 has, however, clearly demonstrated that there is a dominant hydrophobic anchor residue close to the NH_2 terminus of the peptide, and that secondary anchor residues are found at several other peptide positions (13, 15, 18).

The peptide-binding site of human HLA-DR molecules is generated by the first domains of the conserved DRα and the polymorphic DRβ chain. A prominent hydrophobic pocket that is highly conserved between human DR molecules accommodates the primary anchor residue. Most residues that shape this pocket are from the DRα chain; however, the size of this pocket is controlled by the Val/Gly dimorphism at position 86 of the DRβ chain (15, 18). When glycine is present at DRβ86, aliphatic or aromatic residues can anchor the peptide; with valine at DRβ86, the pocket is smaller so that tyrosine and tryptophan cannot be accommodated (13, 19). In the HLA-DR1 structure, shallower pockets accommodate other peptide side chains, particularly side chains of P4, P6, P7, and P9 (relative to the first anchor P1). Peptide residues at these positions appear to contribute to the specificity of peptide binding to different DR molecules (13).

The fact that both the primary pocket and the hydrogen bonding network along the peptide main chain are highly conserved among different DR molecules accounts for the fact that a number of high affinity peptides bind to a number of different DR molecules ("promiscuous" binding) (13, 17, 20). How can this observation be reconciled with the hypothesis that the association of different class II alleles is based on selective peptide binding to the disease-associated molecules? The answer to this question, which is the focus of this review, relates to the following facts: (a) Selective and nonselective peptides have been identified (17, 20). (b) Charged residues at two key positions in the class II β chain (positions β71 and β57) control the charge permitted at peptide position P4 (β71) and P9 (β57) (for positioning of P4 and P9 in HLA-DR pockets see reference 13). (c) Nonselective peptides do not carry a charge at these positions (P4 or P9). (d) Peptides with charged residues at P4 and/or P9 can only bind if an opposing charge (or no charge) is present at the respective position in the MHC class II β chain (21).

A large body of epidemiological work has documented the association of RA with the following DR alleles: DR4 (DRB1*0401, DRB1*0404) and DR1 (DRB1*0101), with the DR4 alleles conferring a higher risk than DR1 (22). The risk is dramatically increased when the subject is homozygous or heterozygous for DRB1*0401 and/or DRB1*0404. The importance of DR4 in the development of arthritis is also underscored by the following observations: The vast

majority of patients (93%) with a particularly severe form of arthritis (Felty's syndrome), which is associated with splenomegaly and high titers of rheumatoid factor, carry the DRB1*0401 allele (23). DR4 is also associated with chronic arthritis in patients with Lyme disease since the presence of DR4 significantly prolongs the clinical duration of arthritis after infection with *Borrelia burgdorferi* (24). The observation that arthritis is associated with three DR alleles that are structurally similar led to the development of the "shared epitope" hypothesis since DRB1*0401, 0404 and 0101 share critical polymorphic residues in the DR β67-71 cluster (L--QR) (Table 1) (22). These residues (particularly DRβ71) appear to be critical in defining the selectivity of peptide binding to the disease-associated molecules.

The paper by Hammer et al. in this issue (21) compares the requirements for selective binding to these DR4 subtypes, particularly between DRB1*0404 (RA associated) and DRB1*0402 (not RA associated), which differ only in the DRβ67-71 region. Using the random peptide library in bacteriophage that they had previously developed, both molecules were found to have identical requirements at the primary anchor residue P1 (aliphatic amino acids or phenylalanine, corresponding to DRβ86 Val) and at P6 (preference for Ser, Thr, Asn, or Val) (25). However, requirements for peptide binding were dramatically different for peptide position 4.

Peptides with a negative charge at P4 bound to DRB1*0404 (RA associated), but not to DRB1*0402; the reverse was true for peptides with a positive charge at P4. Site-directed mutagenesis demonstrated that DRβ71 was responsible for this effect: peptides with a negative charge at P4 were selective for DRB1*0404, which has a positive charge at DRβ71 (Arg), while peptides with a positive charge at P4 were selective for DRB1*0402, which has a negative charge at DRβ71 (Glu). The authors used these criteria to search among candidate antigens for RA (link protein, collagen, heat shock protein 65, and fillagrin) for peptides that may have selective binding for the RA-associated DR4 subtype, and they identified 14 peptides from these candidate antigens (25).

Based on these observations and on the extensive work carried out to define MHC class II peptide-binding motifs, we would like to propose a model to explain the linkage of human autoimmune diseases to particular MHC class II genes. The model is based on the fact that two different autoimmune diseases, RA and PV, are linked to DR4 subtypes that differ only in the DRβ67-71 cluster (4, 5, 26). PV is an autoimmune disease of the skin in which high titer autoantibody production to an epidermal cell adhesion molecule (desmoglein 3) results in a loss of keratinocyte adhesion (acantholysis) and subsequent severe blister formation (27). In different ethnic groups, the disease is associated either with

Table 1. *Selectivity of Peptide Binding to DR4 Antigens Associated with Different Autoimmune Diseases: Structural Criteria for Candidate Peptides in PV and RA*

	PV	RA
Disease-associated DR4 molecule	DRB1*0402	DRB1*0401, DRB1*0404
Polymorphic DRβ chain residues at DRβ 67, 70, 71, 86	I, D, E, V	L, Q, R, V (0404)
		L, Q, R, G (0401)
Charge at DRβ71	Negative (E)	Positive (R)
Charge at peptide position 4	Positive (K or R)	Negative (D or E)
Criteria for selective peptides	P1: V, L, I, M, F	P1: V, L, I, M, F
	P4: K, R	P4: D, E
	P6: S, T, N, V	P6: S, T, N, V
Autoantigen	Epidermal adhesion molecule (Desmoglein 3)	Unknown
T cell response	TH2	TH1
Pathogenetic mechanism	Autoantibodies	T cell mediated
Clinical manifestations	Loss of epidermal cell adhesion, severe blister formation	Joint inflammation

Immunological and clinical characteristics of DR4-associated autoimmune diseases, PV, and RA. In pemphigus, autoantibody formation to an epidermal adhesion molecule results in blister formation; in rheumatoid arthritis, T cells are thought to induce a chronic inflammatory reaction of the joint synovia that results in cartilage destruction. Pemphigus and RA are associated with DR4 subtypes that differ only in the polymorphic DRβ 67-71 cluster on the DRβ chain helix. Of these residues, DRβ 71 is critical in defining which peptides will bind selectively to either the pemphigus- or the RA-associated DR4 molecule. In the pemphigus-associated DRB1*0402 molecule, DRβ71 is negatively charged; in the arthritis associated DRB1*0401 and 0404 molecules, it is positively charged. The reverse charge is found at peptide position P4: peptides selective for the pemphigus DRB1*0402 molecule have a positive charge at P4, while a negative charge is found at P4 for peptides selective for the RA-associated DR4 molecules. Based on these data motifs for selective binding of peptides to either PV- or RA-associated DR4 molecules can be defined.

a DR4 allele (DRB1*0402) or with a rare DQ1 allele (DQB1*05032); only a small fraction of PV patients have neither susceptibility gene (4, 5, 28, 29). The DR4 subtype associated with pemphigus differs only at three positions, all in the DRβ67-71 cluster, from the DR4 subtype associated with RA. The PV-associated molecule has a negative charge (Glu) at the critical position (DRβ71); the neighboring position (DRβ70) is also negatively charged. The DR4 subtype associated with PV is the only one that carries a negative charge at DRβ71, a positive charge (Arg) is found at DRβ71 in the RA-associated DR4 molecules. DRβ67 (Leu, Ile) does not appear to be involved in peptide binding and probably acts as a TCR contact residue (13, 30).

The charge of a polymorphic residue at DRβ71 could therefore account for susceptibility to two different autoimmune syndromes associated with structurally similar DR4 subtypes (Table 1). DR4 alleles associated with susceptibility to RA have a positive charge at DRβ71 (Arg), while the DR4 allele associated with PV has a negative charge at DRβ71 (Glu). Peptides selective for either DR4 molecule may therefore differ significantly in their charge at P4: Peptides with a negative charge at P4 would be expected to bind to the RA-associated molecules, but not the pemphigus-associated DR4 molecule; in contrast, a positive charge would be expected for the pemphigus peptide(s) at position 4 (Table 1). Because of the conserved nature of these molecules, other peptide anchor residues (P1 and P6) would not be expected to be different for these DR4 subtypes.
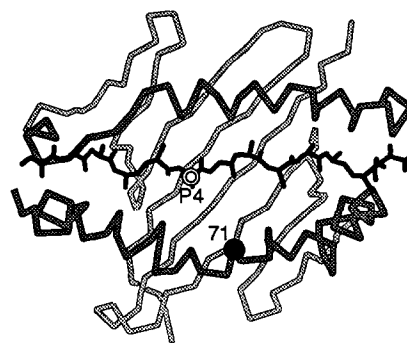
This model now allows the prediction of T cell epitopes of a known autoantigen that are selectively presented by the disease-associated MHC molecule (Table 2). The existence of self peptides that are indeed selectively presented by the disease-associated molecule and are the target of autoreactive

DR4-associated Autoimmune Diseases

	DRβ 71	P4
Rheumatoid Arthritis	Arg	Asp, Glu
Pemphigus	Glu	Lys, Arg

DQ-associated Autoimmune Diseases
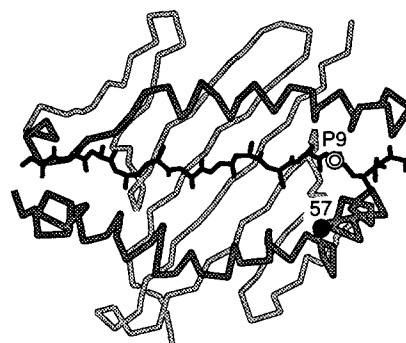
	DQβ 57	P9
Diabetes	Val	Asp, Glu
Pemphigus	Asp	Lys, Arg

Figure 1. Polymorphic MHC class II residues critical for peptide binding are associated with different human autoimmune diseases. An α carbon diagram of the peptide-binding cleft of an HLA-DR molecule (13, 15) is shown with a peptide in the site. Among the DR4 associated diseases, the charge at position DRβ71 controls the charge found at peptide position P4 (relative to the first MHC anchor, residue P1). For DQ-associated autoimmune diseases, the charge at DQβ57 is important. The fact that residues critical for selective peptide binding are associated with susceptibility to autoimmune diseases indicates that MHC-linked susceptibility is almost certainly caused by the presentation of (self) peptides that activate autoaggressive T cells.

Table 2. *Candidate Peptides for PV: Desmoglein 3 Peptides That Match the DRB1*0402 Binding Motif*

| Motif	1	4	6
	V	K	S
	L	R	T
	I		N
	M		V
	F		
PV A.1 (res. 78–93)	ATQKITYRISGVGID		
PV A.2 (res. 97–111)	FGIFVVDKNTGDINI		
PV A.3 (res. 190–204)	LNSKIAFKIVSQEPA		
PV A.4 (res. 206–220)	TPMFLLSRNTGEVRT		
PV A.5 (res. 251–265)	CECNIKVKDVNDNFP		
PV A.6 (res. 512–526)	SARTLNNRYTGPYTF		
PV A.7 (res. 762–786)	QSGTMRTRHSTGGTN		

The DRB1*0402 motif was used to define peptides of the autoantigen desmoglein 3 that may bind selectively to the disease-associated DRB1*0402 molecule. Seven peptides from this large protein (999 amino acids) were found to match the motif. T cell recognition of one (or several) of these peptides may initiate the autoimmune process in pemphigus. res, residues.

T cells would explain the genetic association of the disease with the MHC. The target antigen of pemphigus vulgaris is an epithelial adhesion molecule of the cadherin family (desmoglein 3) (27). Desmoglein 3 mediates Ca⁺⁺-dependent adhesion between keratinocytes; the autoantibodies interfere with cell adhesion with resulting blister formation (31). The autoantibodies are thought to be pathogenic since a transient

blistering disease is also seen in newborns of affected mothers, a condition caused by the transfer of maternal immunoglobulin to the fetus. Transfer of serum- or desmoglein 3–specific antibodies to mice also results in acantholysis (32).

The criteria for selective DRB1*0402-binding were therefore used to localize candidate T cell epitopes of desmoglein 3 (Table 2). For P1 and P6, the by now well-defined anchor residues (P1: Val, Leu, Ile, Met, and Phe; P6: Ser, Thr, Asn, or Val) were used; for P4 only positively charged residues (Lys, Arg) were considered. Only seven peptides from this large protein (130 kD, 999 amino acids) matched the motif. Selective presentation of one or several of these peptides by the PV-associated DRB1*0402 molecule to T cells may be critical for initiating autoimmunity in PV.

The model that charge–charge interactions between polymorphic MHC class II molecules and peptides are critical in selective peptide binding and therefore in autoimmunity can be taken one step further (Fig. 1). In a different ethnic group, PV is associated with a rare DQ1 subtype (DQB1*05032) that differs from the common DQ1 subtype only at position 57 of the DQβ chain (29). In the PV-associated molecule, DQβ57 is negatively charged (Asp); in the common DQ1 subtype, it is not. The same position on the DQβ chain has also been implicated in susceptibility to diabetes. In diabetes, however, the reverse is true: DQ2 and DQ8 molecules associated with susceptibility to diabetes do not have a negative charge at DQβ57 (3).

Based on these observations, it becomes clear that two polymorphic positions in the MHC class II β chain (position 71 of DRβ and position 57 of DQβ) are critical for selective peptide binding and the development of autoimmunity. Based on the criteria described above, a diabetes-linked peptide would be expected to have a negative charge at P9 since such a peptide would only bind to DQ molecules that do not have the same charge at DQβ57. In contrast, for the DQ1-associated cases of pemphigus, a peptide with a positive charge at P9 may be selective for the disease-associated molecule that carries a negative charge at DQβ57. In the case of DR4-linked autoimmunity, the charge at peptide position 4 confers selectivity to the disease-associated DR4 molecule: RA peptides have a negative charge at P4, PV peptides a positive charge at P4. Motifs for selective peptide binding may therefore prove to be tremendously useful in the identification of key epitopes that initiate human autoimmune diseases. This approach may not only be useful for identifying peptides in PV, RA, or diabetes, but also for other autoimmune diseases where residues critical in peptide binding have been linked to disease susceptibility.

The observation that single amino acid substitutions in the peptide-binding site of MHC class II molecules appear to be responsible for MHC-linked susceptibility to autoimmunity poses an interesting question: why are the resulting autoimmune syndromes so different in terms of their tissue localization and the immunological effector mechanisms? In pemphigus, autoantibodies induce a blistering disease of the skin; in RA, T cells mediate a chronic inflammatory process that results in cartilage destruction. The immunological attack may be primarily dictated by resident antigen presenting cells in the target organ: skin keratinocytes or Langerhans cells may primarily induce a TH2-mediated T cell response with resulting autoantibody production, while APC in the synovia may trigger a TH1-like T cell response and a chronic inflammatory state. Selection of tissue-specific self-peptides by disease-associated MHC molecules may therefore decide between these different fates.

Peptide motifs for MHC class II binding and T cell receptor for antigen recognition are also crucial for the identification of viral and bacterial peptides that mimic critical structural features of immunodominant self peptides and activate autoaggressive T cells. This approach was successfully used to identify viral and bacterial mimicry peptides of an immunodominant myelin basic protein peptide (residues 85–99). These mimicry peptides were derived from common human pathogens, such as influenza type A virus, human papillomavirus, Epstein-Barr virus, and herpes simplex type 1 virus, and they efficiently activated MBP-specific T cell clones from multiple sclerosis patients (33).

The elegant work by Hammer and co-workers, as well as that by many other laboratories in defining the structural basis of MHC class II–restricted peptide presentation, allows us to probe some of the fundamental questions in autoimmunity. With respect to questions addressed in the opening remarks, the following working hypotheses can be formulated: (a) The association of particular MHC alleles with autoimmune syndromes is almost certainly caused by the presentation of peptides as polymorphic residues critical in peptide binding are associated with susceptibility. (b) Peptides selective for the disease-associated molecules can be identified using structural motifs that consider the charge–charge interactions at critical MHC–peptide interaction points (21). (c) Structural motifs for MHC binding and for T cell receptor recognition of important T cell epitopes can be used to identify viral and bacterial mimicry peptides that have sufficient structural similarity with immunodominant self peptides to initiate the activation and clonal expansion of autoaggressive T lymphocytes (33).

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References

1. Brewerton, D.A., F.D. Hart, M. Caffrey, A. Nicholls, D.C.O. James, and R.D. Sturrock. 1973. Ankylosing spondylitis and HL-A 27. *Lancet.* i:904–907.

2. Schlosstein, L., P.I. Terasaki, R. Bluestone, and C.M. Pearson. 1973. High association of an HL-A antigen, W27, with ankylosing spondylitis. *N. Engl. J. Med.* 288:704–706.

3. Todd, J.A., J.I. Bell, and H.O. McDevitt. 1987. HLA-D gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. *Nature (Lond.).* 329:599–604.

4. Ahmed, A.R., E.J. Yunis, K. Khatri, R. Wagner, G. Notani, Z. Awdeh, and C.A. Alper. 1990. Major histocompatibility complex haplotype studies in Ashkenazi Jewish patients with pemphigus vulgaris. *Proc. Natl. Acad. Sci. USA.* 87:7658–7662.

5. Ahmed, A.R., R. Wagner, K. Khatri, G. Notani, Z. Awdeh, C.A. Alper, and E.J. Yunis. 1991. Major histocompatibility complex haplotypes and class II genes in non-Jewish patients with pemphigus vulgaris. *Proc. Natl. Acad. Sci. USA.* 88:5056–5060.

6. Lanchbury, J.S., and G.S. Panayi. 1991. Genetics of RA: the HLA shared epitope hypothesis and its implications. *Br. J. Rheumatol.* 30(Suppl. 2):6–9.

7. Spielman, R.S., and N. Nathenson. 1982. The genetics of susceptibility to multiple sclerosis. *Epidemol. Rev.* 4:45–65.

8. Protti, M.P., A.A. Manfredi, R.M. Horton, M. Bellone, and B.M. Conti-Tronconi. 1993. Myasthenia gravis: recognition of a human autoantigen at the molecular level. *Immunol. Today.* 14:363–368.

9. Davies J.L., Y. Kawaguchi, S.T. Bennett, J.B. Copeman, H.J. Cordell, L.E. Pritchard, P.W. Reed, S.C.L. Gough, S.C. Jenkins, S.M. Palmer, et al. 1994. A genome-wide search for human type I diabetes susceptibility genes. *Nature (Lond.).* 371:130–136.

10. Madden, D.R., J.C. Gorga, J.L. Strominger, and D.C. Wiley. 1991. The structure of HLA-B27 reveals nonamer self-peptides bound in an extended conformation. *Nature (Lond.).* 353:321–325.

11. Rötschke, O., and K. Falk. 1991. Naturally-occurring peptide antigens derived from the MHC class-I-restricted processing pathway. *Immunol. Today.* 12:447–455.

12. Rötschke, O., and K. Falk. 1994. Origin, structure and motifs of naturally processed MHC class II ligands. *Curr. Opin. Immunol.* 6:45–51.

13. Stern, L.J., J.H. Brown, T.S. Jardetzky, R. Urban, J.L. Strominger, and D.C. Wiley. 1994. Crystal structure of the human class II MHC protein HLA DR1 complexed with an influenza virus peptide. *Nature (Lond.).* 368:215–223.

14. Jardetzky, T.S., W.S. Lane, R.A. Robinson, D.R. Madden, and D.C. Wiley. 1991. Identification of self peptides bound to purified HLA-B27. *Nature (Lond.).* 353:326–329.

15. Brown, J.H., T.S. Jardetzky, J.C. Gorga, L.J. Stern, R.G. Urban, J.L. Strominger, and D.C. Wiley. 1993. Three-dimensional structure of the human class II histocompatibility antigen HLA-DR1. *Nature (Lond.).* 364:33–39.

16. Chicz, R.M., R.G. Urban, W.S. Lane, J.C. Gorga, L.J. Stern, D.A.A. Vignali, and J.L. Strominger. 1992. Predominant naturally processed peptides bound to HLA-DR1 are derived from MHC-related molecules and are heterogeneous in size. *Nature (Lond.).* 358:764–768.

17. Chicz, R.M., R.G. Urban, J.C. Gorga, D.A.A. Vignali, W.S. Lane, and J.L. Strominger. 1993. Specificity and promiscuity among naturally processed peptides bound to HLA-DR alleles. *J. Exp. Med.* 178:27–47.

18. Jardetzky, T.S., J.C. Gorga, R. Busch, J. Rothbard, J.L. Strominger, and D.C. Wiley. 1990. Peptide binding to HLA-DR1: a peptide with most residues substituted to alanine retains MHC binding. *EMBO (Eur. Mol. Biol. Organ.) J.* 9:1797–1803.

19. Busch, R., C.M. Hill, J.D. Hayball, J.R. Lamb, and J.B. Rothbard. 1991. Effect of a natural polymorphism at residue 86 of the HLA-DR β chain on peptide binding. *J. Immunol.* 147:1292–1298.

20. O'Sullivan, D., T. Arrhenius, J. Sidney, M.-F. Del Guercio, M. Albertson, M. Wall, C. Oseroff, S. Southwood, S.M. Colon, F.C.A. Gaeta, and A. Sette. 1991. On the interaction of promiscuous antigenic peptides with different DR alleles: identification of common structural motifs. *J. Immunol.* 147:2663–2669.

21. Hammer, J., F. Gallazzi, E. Bono, R.W. Karr, J. Guenot, P. Valsasnini, Z.A. Nagy, and F. Sinigaglia. 1995. Peptide binding to HLA-DR4 molecules: correlation with rheumatoid arthritis association. *J. Exp. Med.* 181:1847–1855.

22. Gregerson, P.K., J. Silver, and R.J. Winchester. 1987. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum.* 30:1205–1213.

23. Lanchbury, J.S., E.E. Jaeger, D.M. Sansom, M.A. Hall, P. Wordsworth, J. Stedeford, J.I. Bell, and G.S. Panayi. 1991. Strong primary selection for the Dw4 subtype of DR4 accounts for the HLA-DQw7 association with Felty's syndrome. *Hum. Immunol.* 32:56–64.

24. Steere, A.C., E. Dwyer, and R. Winchester. 1990. Association of chronic Lyme arthritis with HLA-DR4 and HLA-DR2 alleles. *N. Engl. J. Med.* 323:219.

25. Hammer, J., P. Valsasni, K. Tolba, D. Bolin, J. Higelin, B. Takacs, and F. Sinigaglia. 1993. Promiscuous and allele-specific anchors in HLA-DR binding peptides. *Cell.* 74:197–203.

26. Scharf, S.J., A. Friedmann, C. Brautbar, F. Szafer, L. Steinman, G. Horn, U. Gyllensten, and H.A. Erlich. 1988. HLA class II allelic variation and susceptibility to pemphigus vulgaris. *Proc. Natl. Acad. Sci. USA.* 85:3504.

27. Amagai, M., V. Klaus-Kovtun, and J.R. Stanley. 1991. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. *Cell.* 67:869–877.

28. Scharf, S.J., C.M. Long, and H.A. Erlich. 1988. Sequence analysis of the HLA-DR β and DQ loci from three pemphigus vulgaris patients. *Hum. Immunol.* 22:61–69.

29. Sinha, A.A., C. Brautbar, F. Szafer, A. Friedmann, E. Tzfoni, J.A. Todd, L. Steinman, and H.O. McDevitt. 1988. A newly characterized HLA-DQ β allele associated with pemphigus vulgaris. *Science (Wash. DC).* 239:1026–1029.

30. Wucherpfennig, K.W., D.A. Hafler, and J.L. Strominger. 1995. Structure of human T cell receptors specific for an immunodominant myelin basic protein peptide: positioning of T cell receptors on HLA-DR2/peptide complexes. *Proc. Natl. Acad. Sci. USA.* In press.

31. Takeichi, M. 1990. Cadherins: a molecular family important in selective cell-cell adhesion. *Annu. Rev. Biochem.* 59:237–252.

32. Amagai, M., S. Karpati, R. Prussick, V. Klaus-Kovtun, and J.R. Stanley. 1992. Autoantibodies against the amino-terminal cadherin-like binding domain of pemphigus vulgaris antigen are pathogenic. *J. Clin. Invest.* 90:919–926.

33. Wucherpfennig, K.W., and J.L. Strominger. 1995. Molecular mimicry in T cell mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell.* 80:695–705.