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\textsubscript{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 DR\alpha and the polymorphic DR\beta 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 DR\alpha chain; however, the size of this pocket is controlled by the Val/Gly dimorphism at position 86 of the DR\beta chain (15, 18). When glycine is present at DR\beta86, aliphatic or aromatic residues can anchor the peptide; with valine at DR\beta86, 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 \beta chain (positions \beta71 and \beta57) control the charge permitted at peptide position P4 (\beta71) and P9 (\beta57) (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 \beta 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 DRβ67-71 cluster (L--QK) (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 filaggrin) 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 polymorphic DPβ67-71 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 |
|---|---|---|
| **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) |
| Charge at DRβ71 | Negative (E) | L, Q, R, G (0401) |
| Charge at peptide position 4 | Positive (K or R) | Positive (R) |
| 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 DRB67-71 cluster, from the DR4 subtype associated with RA. The PV-associated molecule has a negative charge (Glu) at the critical position (DRB71); the neighboring position (DRB70) is also negatively charged. The DR4 subtype associated with PV is the only one that carries a negative charge at DRB71, a positive charge (Arg) is found at DRB71 in the RA-associated DR4 molecules. DRB67 (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 DRB71 could therefore account for susceptibility to two different autoimmune syndromes associated with structurally similar DR4 subtypes (Table 1). DR4 alleles associated with RA have a positive charge at DRB71 (Arg), while the DR4 allele associated with PV has a negative charge at DRB71 (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 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^{2+}-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

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 | F | F | F |

PVA.1 (res. 78-93)  ATQKI TYRISVGVD
PVA.2 (res. 97-111) FG1FVVDKNTGDI
PVA.3 (res. 190-204) LNSKIAF KIQS0QEA
PVA.4 (res. 206-220) TPMFLLSRNTGEVRT
PVA.5 (res. 251-265) CECNIKV KDVNDNF
PVA.6 (res. 512-526) SARTLN RYTGPYT
PVA.7 (res. 762-786) QSGT MRTRHSTGGTN

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.

**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 DRB71 controls the charge found at peptide position P4 (relative to the first MHC anchor, residue P1). For DQ-associated autoimmune diseases, the charge at DQB57 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 autogressive T cells.
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 P4 and P6, the motif of P7 and P9 were used; for P4 only positively charged residues (Lys, Arg) were considered. Only seven peptides from this selection of peptides were positively charged at P4, conformed to the motif, and had a negative charge at P9, which is characteristic for the disease-associated molecule that carries a negative charge at P9. In contrast, only three peptides were positive at P4 and P9, which is characteristic for the disease-associated molecule that carries a negative charge at P9. In the case of DR4-linked autoimmunity, the charge at peptide positions 4 and 9 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 and 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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