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Molecular Mechanisms for Contribution of MHC Molecules to Autoimmune Diseases

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Abstract

It will soon be 50 years since the first MHC associations with human disease were described. These seminal studies opened a flourishing area of research, yet much remains to be discovered. Genome-wide association studies of autoimmune diseases have demonstrated that the MHC region has effect sizes that supersede those for any non-MHC locus for most diseases. Thus, an understanding of how particular MHC alleles confer susceptibility will be essential for a comprehensive understanding of autoimmune disease pathogenesis. Here we review recent exciting findings in this important field.

Part I: Genetics

Associations with MHC class I, class II or both

A striking feature is that autoimmune diseases with characteristic autoantibodies are typically associated with MHC class II alleles, whereas seronegative diseases most often are associated with MHC class I alleles. Still many diseases demonstrate multiple MHC associations, in part due to the high degree of linkage disequilibrium in the MHC locus. For instance, diseases like celiac disease, type 1 diabetes and autoimmune thyroid diseases are associated with the HLA-DR3-DQ2 haplotype yet also have associations to the class I alleles encoding HLA-B8 and HLA-A1 which are part of an extended, conserved haplotype. This has given rise to the notion of primary and secondary disease associations, with interest focused on the primary associations. However, by studying large cohorts of patients and ethnically matched controls and carefully controlling for linkage disequilibria, it has become clear that there are often multiple independent associations with alleles of different HLA loci. This has been demonstrated for type 1 diabetes where, in addition to the established

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association with the MHC class II genes, independent contributions were mapped to the MHC class I genes *HLA-B* and *HLA-A*, in particular *HLA-B*39[1]*. In multiple sclerosis it was shown that variation in the *HLA-A*, gene is esponsible for an independent protective effect [2]. This protective effect was mapped to *HLA-A**02:01, and evidence for an independent signal in a region that does not contain any MHC class I or II genes points to involvement of non-HLA risk allele(s) within the MHC *[3]. Analysis of SLE similarly showed that the best model for SLE association includes both classical loci *HLA-DRB1**03:01, *HLA-DRB1**08:01, and *HLA-DQA1**01:02, as well as two SNPs, one of which is located in the class III region [4]. Notably, it common that alleles conferring susceptibility and protection are both detected, illustrating the complex role of MHC genes in human diseases.

Epistatic interaction of MHC with aminopeptidease genes in class I associated diseases

For several MHC class I associated diseases a new avenue of research has been opened involving aminopeptidases. Genome wide association studies have revealed association between polymorphisms in the aminopeptidase gene *ERAP1* and ankylosing spondylitis which is restricted to HLA-B27–positive disease [5]. Recent analysis using the so-called Immunochip further revealed association of ankylosing spondylitis with three additional aminopeptidase genes (*LNPEP* and *ERAP2* located in the same region as *ERPA1* as well *NPEPPS* which is located on another chromosome) [6]. Analysis of the impact of non-synonymous substitutions in has revealed clear effects on enzyme activity for generation of ligands that can bind HLA-B27, although the effects appear to be complex and depend on many factors including the sequence of the peptide substrates (reviewed in [7,8]). Notwithstanding, it seems reasonable that genetic variation in these aminopeptidases impact susceptibility to ankylosing spondylitis by affecting the peptide ligands of HLA-B27 either quantitatively or qualitatively, thereby impacting antigen presentation to CD8 T cells. It could also affect folding and stability of HLA-B27 which is ligand dependent. Impaired folding/stability could eventually lead to increased production of IL-23 and IL-17 by endoplasmic stress responses [9] or recognition of HLA-B27 heavy chain homodimers on the cell surface by KIR receptors [10].

The *ERAP1* gene is also associated with susceptibility to psoriasis and Behçet's disease, and in both diseases there is evidence for similar epistatic interactions between *MHC* and *ERAP1* as observed in ankylosing spondylitis. In psoriasis, the epistatic interaction is with HLA-C (particularly *HLA-C***06:02)[11]and in Behçet's disease with *HLA-B**51 *[12]. In psoriasis Immunochip analysis revealed that *ERAP1* and *ERAP2* polymorphisms give independent signals of association [13]. Importantly, the epistatic interaction between *ERAP1* and *MHC* suggests that these genes act along the same pathogenic pathway underscoring that generation of peptide ligands for binding to MHC class I proteins is a key step in the pathogenesis of these diseases.

HLA dependent autoantibodies

Several studies have highlighted the importance of HLA class II polymorphisms with emergence of autoantibodies. This is well known in celiac disease where antibody formation to the autoantigen transglutaminase 2 is strictly dependent on the subject being positive for

HLA-DQ2 or HLA-DQ8 [14]. Studies of HLA association in seropositive and seronegative rheumatoid arthritis patients have demonstrated that anti-citrullinated protein antibody (ACPA) positive and negative rheumatoid arthritis are genetically distinct [15]. Similarly, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis seems to consist of two genetically distinct subsets as myeloperoxidase-specific ANCAs are primarily associated with HLA-DQ polymorphisms whereas proteinase 3-specific ANCAs are primarily associated with HLA-DP polymorphisms [16]. In SLE the association of *HLA-DRB1** 03:01 with anti-Ro and anti-La antibody-positive SLE is much stronger than in SLE without these autoantibodies [17]. Analyzing for association of islet autoantibodies in type 1 diabetes with HLA polymorphisms, it was found that particular antibody specificities are associated with different HLA genes [18]. Specifically, development of antibodies to GAD65 is primarily associated with *HLA-DQB1*, while antibodies to IA-2A are most strongly associated with *HLA-DRB1*. These data suggest that distinct T cell specificities account for association of different HLA alleles with particular autoantibodies. Also, there is disease heterogeneity with qualitative different immune responses contributing to the pathogenesis.

Part II: Effect of key polymorphisms on MHC structure and peptide specificity

In many autoimmune diseases, susceptibility is associated with particular HLA allele(s), but not closely related alleles that differ only at a few positions in the peptide binding groove. Such comparisons among disease-associated and non-associated alleles have enabled definition of key structural features, with a classical example being the involvement of a non-aspartic acid at HLA-DQ β57 in type 1 diabetes [19]. More recently, massive SNP typing has allowed analysis of associations with disease not only by allele, but also by comparing individual amino acids at each position of a classical MHC molecule.

In 1987, Gregersen and Winchester proposed the ‘shared epitope’ hypothesis for HLA-DR alleles associated with susceptibility to rheumatoid arthritis, which highlighted the importance of residues on the DRβ chain helix, including DRβ 71-74 [20]. A recent study examined genome-wide SNP data on large patient populations to identify key polymorphic MHC residues in this disease *[21]. Three amino acid positions in DRβ1 (11, 71 and 74) as well as singleamino acid polymorphisms in HLA-B (pos. 9) and HLA-DPβ1 (pos. 9) were concluded to almost completely explain the MHC association. Interestingly, the most significant association was observed for DRB1 codon 11, for which aliphatic residues (Val and Leu) are associated with risk to rheumatoid arthritis, while a polar residue (Ser) is highly protective. Position 11 is in tight linkage disequilibrium with position 13, but conditioning on position 11 eliminated with effect of position 13 (but not vice versa). Significant associations were also observed for position 71 (Lys, Arg increase, Glu reduces risk), as well as position 74 (only Ala increases risk). DRβ 71 and 74 shape the P4 pocket of the groove, while DRβ 11 and 13 are located in the neighboring P6 pocket (**Figure 1a-c**). The polymorphisms in the P4 pocket are relevant for the binding of citrullinated peptides, as described below. The functional role of polymorphisms in the P6 pocket remains to be determined.

A similar approach was used to identify key polymorphic HLA-DR residues for multiple sclerosis [3]. The most significant variant in the MHC was the *HLA-DRB1** 15:01 allele, consistent with many prior studies [22,23]. Statistically independent effects for five other *HLA-DRB1* alleles (*03:01, *13:03, *04:04, *04:01, *14:01) were also identified. Interestingly, the most significant amino acid position in DRβ1 chain mapped to position 71, and there was a smaller signal contributed by polymorphisms at positions 74, 57 and 86 (which explained most but not all of the *HLA-DRB1* effect). These results are interesting from a structural perspective because both DRβ 71 and 74 are located in the P4 pocket of the groove (**Figure 2d-f**). The *HLA-DRB1** 15:01 allele that is most strongly associated with multiple sclerosis has a small side chain (Ala) at DRβ 71 while the majority of alleles have a charged amino acid at this position (Lys, Arg, Glu). The P4 pocket of DRB1*15:01 protein is therefore larger and more hydrophobic, and a crystal structure demonstrated occupancy of this pocket by an aromatic peptide residue [24] (**Figure 2f**). These results will be valuable for defining key peptide ligands in this disease.

It is important to keep in mind that a given amino acid may not have the same affect across allotypes due to different neighboring polymorphic amino acids. This is illustrated by the effect of a non-aspartic acid residue at position 57 of HLA-DQβ, which is the case for both HLA-DQ8 and HLA-DQ2. The P9 pocket of HLA-DQ8 has a strong preference for binding of negatively charged anchors, yet this is not the case for HLA-DQ2 [25].

Part III: Mechanisms for induction of autoimmunity to self-peptide/MHC complexes

Once of the most interesting – and challenging – questions is how autoimmunity is induced. Significant progress has been made in delineating several important molecular mechanisms.

Post-translational modification of peptides

There are several examples how post-translational modifications can be involved in the pathogenesis of autoimmune disease by interplaying with predisposing HLA molecules. The importance of this mechanism was first delineated in celiac disease where deamidation of glutamine to glutamic acid by transglutaminase 2 (gain of negative charge) creates gluten-derived peptides that bind with substantially higher affinity and with slower off-rate to disease-associated HLA-DQ2 and HLA-DQ8 molecules [26]. Another important example is RA where modification of arginine to citrulline (loss of positive charge) plays a role in disease pathogenesis [27,28]. Autoantibodies specific for citrulline can be detected years before clinical symptoms of RA, but only in subjects with RA-associated HLA-DR risk alleles (such as *HLA-DEB1**04:01 and *04:04) [29,30]. Smoking is an important environmental risk factor that increases protein citrullination in the lung, providing an intriguing example for how an environmental risk factor is related to MHC-associated disease susceptibility at a molecular level [31,32].

Crystal structures demonstrated how citrullinated peptides are bound by RA-predisposing DRB1*04:01 and *04:04 proteins, as well as the RA non-associated DRB1*04:02 protein **[33](**Figure 2**). The citrulline side chain forms a hydrogen bond with a key residue of the

'shared epitope', DRβ 71 Lys (DRB1*04:01) or Arg (DRB1*04:04)(Figure 2a). Interestingly, a citrulline side chain is also accommodated in the P4 pocket of the non-associated *DRB1**04:02 molecule where it forms salt bridges with DRβ 71 Glu and DRβ 70 Asp (Figure 2c). Peptide elution studies demonstrated that DRB1*04:02 binds peptides with unmodified arginine at P4, while the disease-associated DRB1*04:01 and *04:04 proteins do not bind such peptides. These data indicate that the absence of presentation of an unmodified peptide is a critical feature, suggesting differential negative selection of T cells in the thymus by the different DR4 allotypes.

The most straightforward mechanism for post-translational modification to explain MHC association with disease is by creation of neoepitopes which only bind to the susceptibility alleles and to which T cell have not been negative selected against in the thymus. The two examples mentioned above, celiac disease and rheumatoid arthritis, do not fit this simple concept. In the case of celiac disease the modified antigen is foreign whereas in the case of rheumatoid arthritis the post-translationally modified peptides bind both to the susceptibility and resistant HLA alleles. This simple concept should however not be ruled out as for most autoimmune diseases the true autoantigens have not yet been defined. Interestingly, in type 1 diabetes improved binding of several candidate epitopes to HLA-DQ susceptibility allotypes was observed after deamidation by transglutaminase 2 [34]. Yet more complex mechanisms may apply, like in rheumatoid arthritis, where differential thymic selection of T cells by unmodified peptides seems to be involved. Further, post-translational modification can be implicated in the pathogenesis of autoimmune diseases by affecting uptake of antigen into antigen presenting cells. This might be the mechanism underlying improved antigenicity of a chromagranin A epitope relevant to type 1 diabetes after transglutaminase 2 treatment [35]. Antibodies to post-translationally modified residues, like in celiac disease (anti-deamidated gluten antibodies) and rheumatoid arthritis (anti-ACPA), should in particular promote antigen uptake and presentation via involvement of Fc-receptors. Other mechanisms include interference with antigenic processing as shown for citrullination of a vimentin peptide and cathepsin L digestion **[33] and improved T cell recognition of antigen. Two recent reviews discuss in depth how post-translational modification of antigens can be implicated in autoimmune diseases [36,37].

Small-molecule based modification of peptide presentation to T cells

Recent work has provided compelling examples for modification of peptide presentation by small molecules in important clinical settings, including adverse drug reactions and chronic beryllium disease. The best-studied example of adverse drug reactions involves abacavir, a reverse transcriptase inhibitor used for treatment of HIV infection. This drug reaction occurs exclusively in individuals carrying *HLA-B** 57:01 (relative risk of >1,000) [38]. In such individuals abacavir induces a strong CD8 T cell response [39]. Crystal structures showed that abacavir binds non-covalently to B*57:01 across the bottom of the peptide binding groove where it alters the selectivity of the F-pocket that accommodates the C-terminal peptide side chain **[40,41] (**Figure 3**). Abacavir thus induces drastic changes in the peptide repertoire, exposing normally tolerant T cells to previously unseen neo-self epitopes that induce abacavirdependent T cell responses **[40,41]. Substantial changes in the peptide

repertoire were also seen for a second drug, carbamazepine, that can cause severe bullous skin disease in subjects with the *HLA-B** 15:02 allele **[40].

Chronic beryllium disease is a granulomatous lung disorder which develops in some individuals after exposure to beryllium (Be). The disease has an association with DPβ 69 Glu expressing DP alleles, of which *DPB1**02:01 is the most prevalent [42]. The patients have Bespecific CD4 T cells in the lungs [43] which are restricted by disease-associated MHC molecules [44,45]. The crystal structure of a Be^{2+} specific T cell receptor (TCR) bound to a complex of HLA-DP2, self-peptide and Be^{2+} was recently solved **[46]. Surprisingly, the TCR does not contact the Be^{2+} cation which is buried in a highly acidic pocket of DP2 created by negatively charged DP2 and peptide residues. The Be^{2+} cation alters the local conformation of the DP2 – self-peptide complex and thereby induces T cell responses to DP2 bound self-peptides. Thus, there are important conceptual similarities to abacavir and carbamazepine hypersensitivity where MHC-peptide complexes are altered by small molecule ligands. It is also possible that Be^{2+} modifies the repertoire of DP2-bound peptide (as observed for abacavir), but this question remains to be addressed. In chronic beryllium disease a restricted, public TCR repertoire of Be^{2+} specific T cells has been characterized [47], similar to a public TCR repertoire of gluten-reactive T cells in celiac disease [48,49]. Gluten-reactive public TCRs which are specific for deamidated gluten peptides do not contact the Glu anchor residue of the gluten epitopes in the P4 or P6 pockets *[50]. Thus, a common theme emerges: small molecule ligands (metal cations, drugs) or post-translational modifications (citrullination, deamidation) important in human disease frequently do not interact with the TCR. Rather, the T cell response is caused by changes in the peptide repertoire and/or the conformation of selfpeptide – MHC complexes. The previously sharply defined distinction between autoimmunity and allergy is also becoming blurred. An exciting unanswered question is whether *cellular metabolites*, in particular those preferentially synthesized in particular tissues, can modify selfpeptide presentation and cause autoimmune disease.

Outlook

Major progress has thus been made in defining critical molecular events through which MHC proteins confer susceptibility to human autoimmune diseases. In the future, it will be important to use our growing understanding of the molecular mechanisms of MHC-linked disease susceptibility to develop innovative strategies that benefit patients with autoimmune diseases.

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Highlights

- The MHC is the most important genetic risk factor in common autoimmune diseases
- For one disease there can be independent contributions by several distinct MHC loci
- Presentation of peptide ligands by MHC can be modified by small molecules
- T cells recognize post-translationally modified peptides and peptides with modified presentation

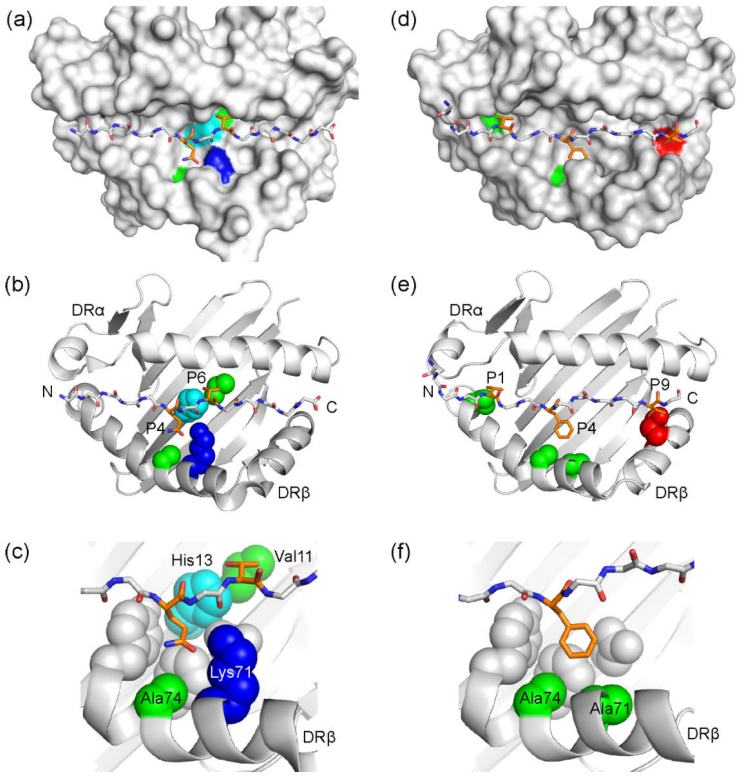

Figure 1. HLA-DR polymorphisms associated with the pathogenesis of RA and MS

(a-c) Key polymorphic DRβ chain residues associated with RA localize to two neighboring pockets, P4 (DRβ Lys71 and Ala74) and P6 (DRβ Val11 and His13) (PDB ID 1J8H). The P4 peptide side chain forms a salt bridge with DRβ Arg71 (**c**). (**d-f**) Key polymorphisms of the MS-associated HLA-DRB1*15:01 molecule are located to the P4 pocket of the peptide binding groove, DRβ Ala71 and Ala74 (PDB ID 1BX2). Smaller contributions are made by polymorphic residues in the P1 and P9 pocket. Comparison of RA and MS-associated HLA-DR proteins highlights the important contribution of DRβ 71 to the shape and charge of the P4 pocket: In the MSassociated DRB1*15:01 molecule, the P4 is large and hydrophobic (DRβ Ala71), while this pocket is smaller and positively charged in the RA-associated DRB1*04:01 protein (DRβ Lys71). DR molecules are shown as surfaces (**a, d**) or ribbon diagrams (**b, c, e, f**).

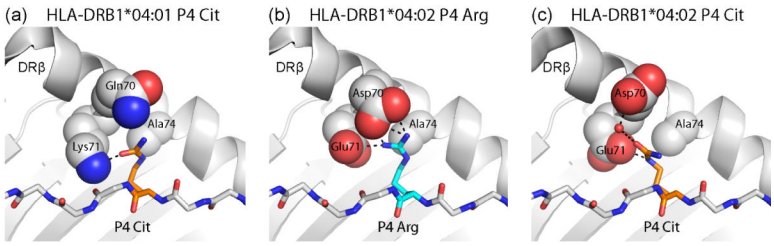

Figure 2. Binding of citrulline versus arginine peptide side chains in the P4 pocket of HLA-DR proteins

Arginine can be modified enzymatically to citrulline, resulting in loss of its positive charge. (**a**) The P4 pocket of the RA-associated DRB1*04:01 molecule can accommodate citrulline, which forms a hydrogen bond to DRβ Lys71. In contrast, arginine cannot be accommodated, due to the positive charge of DRβ Lys71 (PDB ID 4MCY). (**b, c**) The DRB1*04:02 protein is not associated with susceptibility to RA and differs at positions 70 and 71 from RA-associated HLA-DR molecules (PDB ID 4MDJ and 4MDI). Both arginine (**b**) and citrulline (**c**) can be accommodated in the P4 pocket. Arginine forms salt bridges with DRβ Glu71 and Asp70 (**b**), and citrulline forms hydrogen bonds with these two DR residues (**c**).

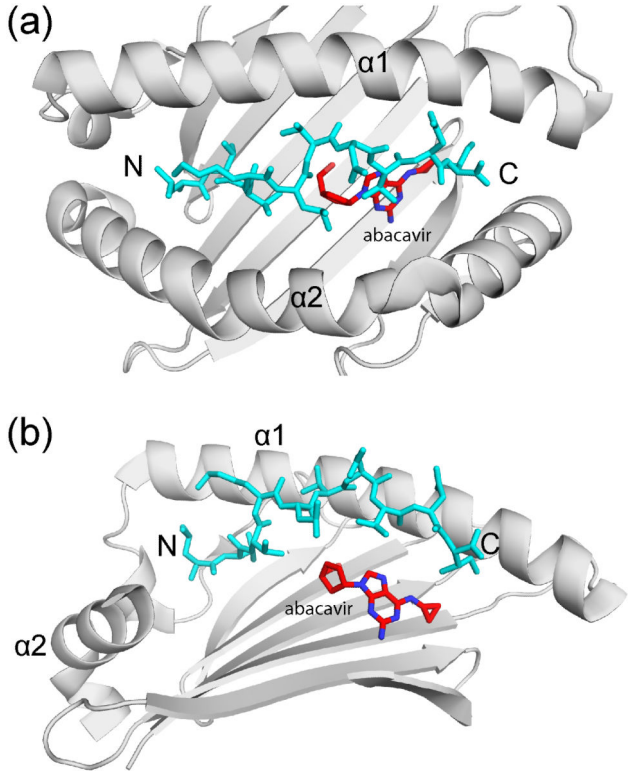

Figure 3. Induction of T cell mediated immunopathology by binding of a small molecule drug in the MHC class I groove

Crystal structure of a HLA-B57:01 – peptide complex with bound abacavir, an anti-retroviral drug (PDB ID 3VRJ). Top view (**a**) and side view (**b**) of the peptide binding groove, showing how abacavir (red) is bound underneath the peptide (blue). In the side view, the HLA-B α2 helix has been removed to aid visualization of abacavir. The α1 and α2 helices of the HLA-B heavy chain are indicated as well as the N and C terminus of the bound peptide (N and C, respectively).