The HLA Complex in Biology & Medicine: A Resource Book

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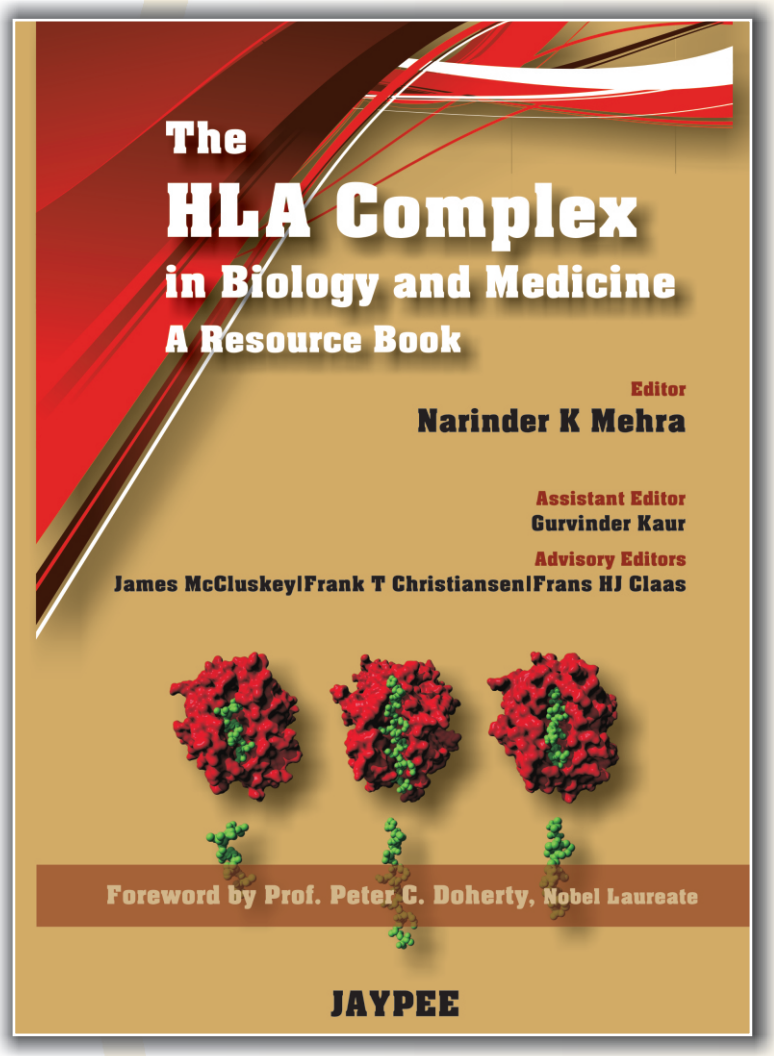

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A comprehensive guide to the HLA system for basic scientists, immunologists, physicians and surgeons carrying up-to-date information on MHC and its role in immune response, HLA and disease associations, biological significance, history, role of HLA system in organ and hematopoietic stem cell transplantation

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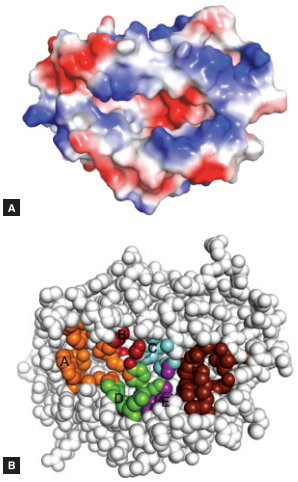
Contents



Figs 6.2A and B: The antigen binding cleft of class I molecules contains 6 major pockets (A-F) that determine the specificity of peptide binding. (A) The cleft of a mouse class I molecule with the peptide removed revealing the shape and charge of the empty specificity pockets. Electronegative, red; electropositive, blue. Adapted with permission from ref 176. (B) Space filling model of a human class I molecule depicting the antigen-binding cleft, with those residues occupying the major specificity pockets coloured A, orange; B, red; C, cyan; D, green; E, purple; F, brown

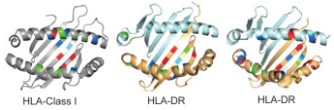
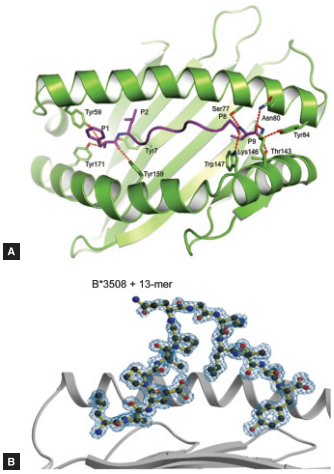
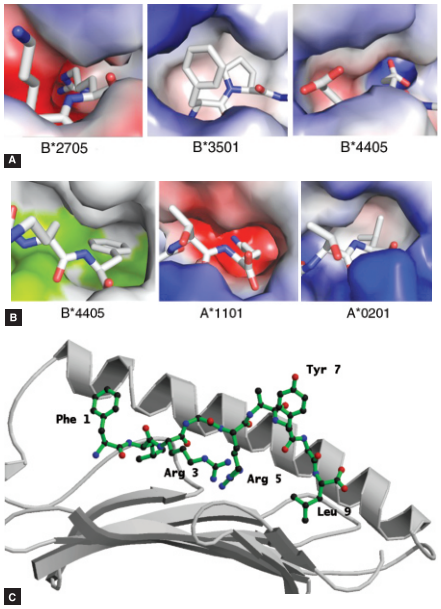


Fig. 6.3: Location of polymorphisms in the antigen-binding cleft of HLA molecules. The residues that are most polymorphic are coloured such that red>blue>green. Note the α-chain of DR is essentially monomorphic so the polymorphism in DR is centred in one half of the cleft. Adapted with permission from ref.176

between the dominant anchor sites, minor anchor sites and the h-bonding network at the peptide termini. Nonetheless, peptides longer than 8-10 amino acids can occasionally bind class I molecules (estimated to be approximately 5% of class I epitopes) and these are not accommodated in the current algorithm-based methods for predicting T-cell determinants as discussed below and tabulated in Table 6.2 (Burrows et al, 2006). Hence these longer ligands are not as easily predicted. The termini of longer peptides (>10 residues) generally remain tucked into the cleft such that the central part of the peptide bulges upwards from the Antigen-binding cleft to accommodate the extra residues (Archbold et al, 2009; Bell et al, 2009; Green et al, 2004; Robbins et al, 1995; Speir et al, 2001; Tynan et al, 2005a; Tynan et al, 2007), Figures 6.4B and C. HLA class I-peptide complexes are sometimes abbreviated as pMHC-I or pHLA-I.

The relatively conserved structure of the membrane-proximal α3 domain of the class I molecule interacts with CD8 co-receptor molecules on T-cells via a flexible loop of the α3 domain (residues 223-229) that is clamped





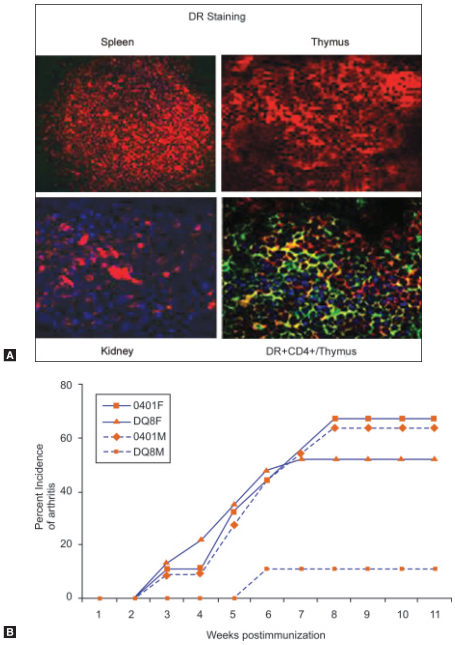
Figs 6.5A to C: The differing architecture of the B and F pockets governing selection of dominant anchor residues. (A) The electronegative B pocket of HLA-B*2705 contrasts with the occluded B pocket of HLA-B*3501, and the electropositive B pocket of HLA-B*4405. (B) The hydrophobic F pocket of HLA-B* 4405 selects different side chains to the electronegative F pocket of HLA-A*1101 and neutral F pocket of HLA-A*0201. Electronegative, red; electropositive, blue; neutral, white; green, aromatic. (C) the nonamer peptide FLRGRAYGL bound to HLA-B*0801 showing the three anchor residues P3Arg, P5Arg and P9 Leu. The peptide is shown as a ball and stick in green. HLA-B*0801 alpha-1 helix and cleft floor in grey. The alpha-2 helix has been removed to show the peptide. Fig. 6.5C is adapted with permission from reference 145

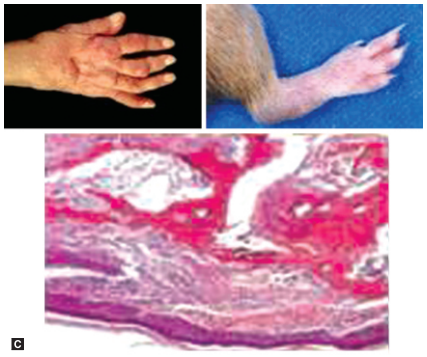
comprising a high proportion of all newly translated products in living cells (Princiotta et al, 2003; Schubert et al, 2000; Yewdell et al, 1999; Yewdell et al, 2001). Many of these polypeptides are ubiquitinated and thus marked out for degradation by the proteasome (Hershko and Ciechanover, 1998; Pamer and Cresswell, 1998). Since these peptides are largely derived from molecules synthesized within the cell, the peptide loading of HLA class I molecules on most cell types requires infection of host cells or gene transcription leading to cytoplasmic translation of proteins for presentation to the immune system.

The peptides presented by class I molecules are recognized by antigen specific T-cells of the CD8

Role of Shared Epitope in Arthritis

While, HLA-DRB1*0401 renders a person susceptible to develop arthritis, DRB1*0402 which differs by 3 amino acids in the 'P4 pocket' of the antigen binding groove is associated with resistance. To determine the mechanism by which *0402 gene provides protection against arthritis, our group generated transgenic mice lacking endogenous class II molecules but expressing DRB1*0402 gene, *0402.AEo mice. These mice do not develop CIA.[83] We decided to determine if a difference in antigen presentation was the reason for susceptibility/protection provided by the two subtypes of DR4. For the purpose, presentation of DR4-restricted CII-derived immunodominant peptide by *0401 and *0402 mice was investigated. While both molecules were found to bind the peptide, *0402 mice showed a very low response as compared to their *0401 counterparts. Further, *in vivo* and *in vitro* studies in *0402.AEo mice showed that the protection from arthritis in *0402 mice could be due to i) negative selection of autoreactive cells in thymus, ii)





Figs 17.4A to C: (A) Expression of DR4 in various organs. Spleen, thymus, and kidney of DRB1*0401.AEo mice were studied by immunostaining with PE-conjugated anti-DR antibody and with DAPI. Thymus was also stained for CD4-PE and DR-FITC. Overlap of CD4 and DR staining showed some CD4+ cells positive for DR. (B) Incidence and onset of arthritis in male and female DRB1*0401.AEo mice show increased susceptibility and earlier onset in female DR4.AEo mice compared to males. DQ8.AEo mice do not show any sex-bias in CIA. (C) The phenotype and histopathology of arthritis in human and mouse show similarities. Right panel shows an arthritic paw. Hematoxylin and eosin staining of the section of paw of an arthritic DR4.AEo mouse shows infiltration of cells in the synovium and erosive arthritis in the digital joint. Left panel shows an arthritic hand

positive selection of T regulatory cells in thymus, iii) generation of higher numbers of regulatory cells in the periphery that can suppress antigen-specific proliferation and lead to the production of anti-inflammatory cytokines like TGFβ and IL-10 and iv) increased activation induced cell death. Indeed all of these factors together could be important for resistance to disease development.

The data with the DR transgenic mice demonstrating that genetic polymorphism of DR molecules modulates CIA, are similar to the studies conducted in the mouse CIA model. Based on these findings, a new hypothesis was proposed, suggesting that the 'shared epitope' shaped the T cell repertoire by serving as a self peptide for DQ molecules.[29] Thus high affinity DR-derived peptides binding to DQ molecules would negatively select an autoreactive T cell, while a low affinity DR-derived peptide would positively select the T cell. This hypothesis was tested *in vitro* by T cell proliferation to peptide 65-79 derived from RA-associated molecules, *0401 and *0404 and RA resistant *0402 molecule in the DQ8 mice. Observations from these studies suggested that HV3 peptides comprising of aa 65-79 derived from the non RA associated DRB1 molecules are highly immunogenic, while those derived from the RA associated DRB1 alleles fail to induce a DQ8 restricted T cell response (84). Intersetingly, *0401/DQ8 mice generated milder response to HVR3 peptide of *0401and a higher response to *0402 peptide. On the other hand, *0402/DQ8 mice did not generate an appreciate response to any peptide suggesting a possible deletion of self-reactive cells in the thymus (Fig. 17.5). This data suggested that presentation of self-derived peptide by the DQ molecule in thymus may delete self-reactive T cells in individuals with RA resistant haplotypes while RA susceptible haplotypes may select autoreactive cells due to low binding affinity. From these studies one can extrapolate that DRB1 polymorphism can modulate HLA-DQ mediated disease. Indirect support for this hypothesis comes from binding studies which show that DQ molecules bind multiple CII peptides compared to DR molecules.[31]

Salient Features

- A multi-authored book with contributions from a group of leading and well-established investigators to cover a wide range of topics in biology and medicine.
- This resource book contains four major sections dealing with: (i) Immune System in General including the Cytokine Cascade, (ii) General Features of the Human MHC, including Population Database and Non-classical HLA Molecules, (iii) MHC and Disease Associations and, (iv) A Major Section dealing with the Transplantation Issues.
- Special chapters deal with the History of HLA and its latest nomenclature as well as the biological significance of minor histocompatibility antigens. It carries a detailed description of the killer immunoglobulin-like receptors (KIRs) in health, disease and transplantation. Special emphasis has been given to the section on HLA and disease associations covering particularly the autoimmune, mycobacterial and rheumatological diseases.
- Separate chapters deal with host determinants in HIV-1 infection and involvement of HLA in drug sensitivity. The section on transplantation deals not only with HLA matching strategies for long-term graft survival, but more importantly for antibody analysis, cross matching and post-transplant antibody monitoring.
- The book has been designed to introduce the young doctors and researchers to comprehend the role of HLA in hematopoietic stem cell transplantation and the importance of unrelated donor marrow registries.
- This volume is invaluable for introducing graduate students to the full spectrum of HLA-related knowledge while serving also as a conceptual and technical source book for both those focused on or other aspect of HLA-related research and clinical/surgical practice. In addition, it will be a primary point of contact for individuals working in other areas who suddenly find that their research is drawing them into the complexities of HLA genetics.
- The focus is essentially on the immunological role of HLA and how that relates to infectious disease resistance, autoimmunity, graft and organ transplantation.
- This book thus serves those who need to understand how the HLA system impacts on medicine while at the same time providing accounts of practical issues relevant to tissue typing, transplant immunology and clinical immunogenetics.

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