EDITORIAL

CURRENT OPINION

Epitope based human leukocyte antigen matching for transplantation

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Human leukocyte antigen (HLA) antibodies represent important risk factors for transplant rejection and failure. They are now being recognized as specific for epitopes which can be defined structurally with amino acid differences between HLA alleles. Donor-recipient compatibility should, therefore, be assessed at the epitope rather than the antigen level. HLAMatchmaker is a computer algorithm that considers each HLA antigen as a series of small configurations of polymorphic residues referred to as eplets as essential components of HLA epitopes. Previous Current Opinion articles describe the HLAMatchmaker algorithm and its usefulness in HLA epitope matching and antibody testing for organ transplantation [1,2]. There is now a website-based International Registry of Antibody-Defined HLA Epitopes (http://www.epregistry.com.br) [3]. Its goal is to develop a repertoire of HLA epitopes that have been verified by specific antibodies.

HLA epitopes can be defined structurally by molecular modeling and amino acid sequence differences between antibody-reactive and nonreactive alleles. Each HLA antigen is viewed as a collection of epitopes that can be determined according to general concepts how antibodies bind with protein epitopes. Antibodies have three heavy-chain and three light-chain Complementarity Determining Region loops that bind to a protein epitope. So-called structural epitopes may have up to 25 contact residues, each one has a centrally located 'functional' epitope consisting of a few residues and which plays a dominant role in the specificity of binding with antibody. HLAMatchmaker considers eplets equivalent to functional epitopes and eplets represent key elements of HLA epitopes that elicit specific antibodies. Eplets are annotated by position numbers in the amino acid sequence and standard single-letter polymorphic residues within a radius of about 3 Ångstroms. The general dimension of a structural epitope is 700–900 square Ångstrom dimensions, and one can calculate that other antibody-contacting residues on the HLA molecular surface are within a radius of about 15 Ångstroms of an eplet.

HLA epitopes have two distinct characteristics namely antigenicity, that is, their reactivity with antibody, and immunogenicity, that is, their ability of inducing an antibody response. This histocompatibility issue of *Current Opinion in Organ Transplantation* has three articles on basic concepts about HLA class I epitopes and one article addressing the clinical importance of class II matching at the epitope level.

Mallon, Bradley, Taylor and Kosmoliaptsis conclude from their structural modeling studies of HLA molecules that the physiochemical properties of polymorphic amino acids can predict HLA epitope immunogenicity and antigenicity. Electrostatic forces are particularly important determinants of the specificity and the affinity of antibody binding. The polymorphic residues of HLA epitopes form distinct electrostatic motifs, whereas other parts of HLA molecules have conserved electrostatic motifs although they may have differences at the amino acid sequence level. This article compares the topographic pattern of electrostatic potential of the Bw4 and Bw6 HLA epitopes. Substitutions of critical amino acids leading to abrogation of antibody-binding induce dramatic changes of the electrostatic patterns. Surface electrostatic properties of Bw4 epitopes may be linked to technique-dependent differences in reactivity with specific antibody.

The article by Duquesnoy gives illustrations how single-antigen bead assays have shown that HLA antibodies recognize epitopes that are equivalent to eplets or are represented by eplets paired with other residue configurations. Residue differences within eplet-defined structural epitopes may also explain technique-dependent variations in

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antibody reactivity determined in Ig-binding, C1q binding and lymphocytotoxicity assays. These findings can be explained with the concept that antigen–antibody complex formation leads to the release of free energy to stabilize binding and to induce conformational changes in the antibody molecule to expose the C1q binding site and subsequent activation of the complement cascade. This article addresses two general perspectives of HLA epitope immunogenicity: HLA antibody responses correlate with the numbers of eplets on mismatched HLA antigens and the recently proposed nonself-self paradigm of epitope immunogenicity may help explain the production of epitope-specific antibodies.

The article by Lutz addresses the structural aspects of HLA Bw4 and Bw6 epitopes recognized by antibodies and natural killer cells. Molecular modeling, X-ray crystallography and site-directed mutagenesis studies have refined our understanding of these epitopes, which are defined by residues in the 77–83 amino acid sequence. Moreover, residues in other locations as well as HLA-bound peptides may lead to heterogeneity of Bw4 epitopes recognized by antibodies and KIR3DL1 allotypes. Thus, Bw4 and Bw6 should be considered families of structurally related epitopes.

As reported elsewhere, HLA matching at the epitope level is relevant in clinical transplantation [1,2]. More than 10 years ago, Eurotransplant applied HLAMatchmaker to their acceptable mismatch program for highly sensitized patients [4]. This class I epitope-based strategy is highly effective: 60% of these patients are transplanted within 2 years and long-term survivals of transplants are similar to those of nonsensitized patients. Eurostam, a large collaborative study coordinated by Frans Claas at Leiden University Medical Center, is currently underway to explore the implementation of a Europe-wide acceptable mismatch program.

Wiebe and Nickerson describe their experience with acceptable mismatching at the class II epitope level. The development of donor-specific HLA antibodies represents a significant risk of graft failure in low-risk renal transplant patients. Although such antibodies react with both class I and class II HLA

mismatches, it has been noted that most class II-reactive antibodies appear late posttransplant and that patients respond poorly to therapy. Epitope loads of class II mismatches are much better predictors of donor-specific antibody development than the numbers of mismatched antigens or alleles. Highly immunogenic HLA-DR and HLA-DQ epitopes can be identified and could potentially be avoided at the time of organ allocation.

In summary, these reports offer a better understanding of HLA epitopes. They provide further support of the usefulness of HLA matching at the epitope level, including the serum analysis of HLA antibodies and the identification of acceptable mismatches for sensitized patients. An important question is how to prevent or reduce HLA sensitization of nonsensitized transplant patients. There are new opportunities because we can now determine epitope loads of mismatched antigens and we have begun to recognize the highly immunogenic epitopes. Epitope loads permit risk assessments for antibody-mediated rejection and in the current clinical setting this information will be useful in the monitoring and management of patients who have received a transplant. Eventually, a new epitope-based permissible mismatch strategy might be applied to identify suitable donors with minimal risks for allosensitization, thereby improving transplant outcomes.
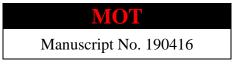
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Conflicts of interest

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