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Editorial

The Antibody Response to HLA Mismatch: Putting Together the Pieces of a Puzzle

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The antibody response to an HLA mismatch remains a major obstacle for successful transplantation because it frequently leads to transplant failure. It is now well recognized that HLA antibodies recognize epitopes that can be structurally defined. This concept is clinically relevant in the management of sensitized candidates considered for acceptable mismatches and for nonsensitized patients who ought to be transplanted with no or few epitope mismatches (1). The identification of permissible mismatches that minimize HLA antibody responses represents a challenging new approach that requires the application of new scientific concepts. This issue of the *American Journal of Transplantation* includes an article titled ''Predicted Indirectly Recognizable HLA Epitopes Presented by HLA-DRB1 Are Related to HLA Antibody Formation During Pregnancy,'' by Spierings' group at the University Medical Center in Utrecht, The Netherlands (2). This work represents an extension of a previous publication on transplant cases (3).

These investigators address the concept that helper T cells respond specifically to mismatched epitopes presented by DRB1 molecules expressed on B cells committed to HLA antibody responses. This so-called indirect allorecognition leads to T cell activation and the release of various cytokines that promote further B cell differentiation, including affinity maturation, immunoglobulin class switching and the appearance of plasma cells. In this pregnancy model of the HLA antibody response, an artificial neural network–based computer algorithm was used to predict which mismatched class I peptides derived from the child may bind to the binding groove of maternal DRB1 molecules. The demonstration that class I antibody responses correlate with predicted indirectly recognizable HLA epitopes presented by HLA class II (PIRCHE-II) numbers supports the validity of this algorithm. The limitation of the current predictor algorithm is the absence of other class II molecules such as DRB3, DRB4, DRB5, DQ, and even DP, which can also be expected to present class I peptides to T cell receptors.

PIRCHE-II represents a piece of the puzzle of the HLA antibody response. Other considerations must address the question of how HLA epitopes activate B cells to become antibody producers. During B cell development, rearrangements of VH and VL immunoglobulin genes lead to the expression of a repertoire of B cell receptors that can recognize epitopes on autologous proteins including self HLA molecules. These receptors have three heavy chain and three light chain complementarity-determining regions (CDRs) that can make contact with so-called structural epitopes involving multiple residues distributed over a surface area of 700–900 square Angstroms. The third CDR of the heavy chain (CDR-H3) has the most variability in sequence length and amino acid composition and plays a primary role in the specific recognition of the so-called functional epitope or hot spot within the structural epitope. These B cell receptors have very low avidity with self epitopes; however, through reorientation of CDR-H3, they can potentially bind well to nonself epitopes, and such interactions will activate the B cell as the first step toward antibody production.

The nonself–self paradigm of HLA epitope immunogenicity is based on the hypothesis that HLA antibodies originate from B cells with low-avidity receptors for epitopes on their own HLA molecules (4). Their interactions with self HLA epitopes will not induce B cell activation, but exposure to HLA mismatches with nonself functional epitopes, referred to as *eplets*, may lead to alloantibody production. Accordingly, an antibody-defined HLA epitope on the immunizing allele must consist of a nonself eplet surrounded primarily by self residues of the corresponding structural epitope of an allele of the antibody producer. Several studies have shown that antibody-verified epitopes are defined by eplets together with self residues (1,5).

We must raise the question of how the interaction of a mismatched eplet with the B cell receptor provides the triggering signal for B cell activation. That receptor has been programmed to see a self eplet, although with minimal avidity; however, with greater avidity, it can recognize a nonself eplet in the same sequence location. Kosmoliaptsis and colleagues proposed that the relative immunogenicity of HLA mismatches can be predicted from physiochemical properties of

amino acids constituting epitopes (6). Electrostatic differences between self and nonself eplets in the same molecular surface location may provide additional understanding of the immunogenicity of an HLA mismatch. On interactions with B cell receptors, such differences may lead to the release of free energy as a trigger for B cell activation.

The nonself–self paradigm, the electrostatic potential model and PIRCHE-II represent complementary theories directed toward understanding HLA mismatch immunogenicity. At present, these concepts are difficult to validate with direct experimental methods that analyze the early phases of the B cell response. Moreover, these theories have their limitations. The nonself–self paradigm cannot predict the repertoire of B cell receptors for self HLA epitopes, and the electrostatic potential of an eplet can be studied only in relation to its B cell receptor. PIRCHE-II does not consider which peptides emerge after proteolytic processing of internalized receptor-bound HLA molecules and which ones are in the grooves recognized by T cells.

At this time, we can use only indirect approaches such as antibody specificity analysis, molecular assessments of histocompatibility and structural analysis of HLA–antigen–antibody complexes to study the immunogenicity of HLA epitopes, and it is important to know the repertoire of antibody-verified epitopes. Such investigations could lead to better understanding of HLA epitope immunogenicity and how this can be applied to permissible mismatch strategies.

Disclosure

The author of this manuscript has no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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