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Letter to the Editor

HLA Epitopes and Tolerance Induction Protocols

To the Editor:

R. A. Montgomery addresses in a recent editorial ''One Kidney for Life'' the concept that transplantation tolerance is now feasible at least in some cases (1). This would benefit recipients by sparing them the toxicities of chronic immunosuppression and by potentially eliminating the need for retransplantation. He points out that young and highly sensitized patients although posing significant ethical and biological barriers to tolerance protocols, might be expected to benefit disproportionately.

A significant barrier to current tolerance protocols is posed by donor-specific antibodies. One can expect that minimizing such humoral immune responses will enhance the success of tolerance protocols.

Donor-specific antibodies are produced against HLA mismatches. It is now recognized that HLA antibodies recognize epitopes rather than antigens. Each HLA antigen can be viewed as a collection of epitopes with polymorphic amino acid descriptions that reflect general concepts how antibodies interact with protein epitopes (2). Matching at the epitope level can be done by comparing the epitope repertoires of donor and recipient. HLAMatchmaker is a computer algorithm on the www.HLAMatchmaker.net website that can be used as a quantitative tool to determine the degree of a mismatch, that is the number of mismatched epitopes. The so-called epitope load of a donor HLA antigen mismatch depends on the recipient's HLA type which represents a repertoire of self-epitopes to which no antibodies can be made. A given HLA antigen may have a low epitope load and is structurally compatible for one group of recipients but can have a high epitope load for other another group of recipients.

As summarized in a recent review (3) there is ample documentation that donor-specific anti-class I antibody responses (seven publications) and anti-class II HLA antibody responses (two publications) in transplant recipients and pregnant women correlate well with epitope loads of mismatched antigens. HLA-epitope matching outperforms traditional antigen-based matching and has the potential to minimize the risk of *de novo* HLA donor-specific antibody development.

The design of a clinical tolerance protocol should include information about epitope loads of mismatched donor HLA antigens. The successful induction of tolerance might be more readily achieved for donor mismatches with low epitope loads because the immunological barrier would be less. An analysis of the mismatched epitope repertoire of the transplant donor may also permit a determination which epitopes have induced specific tolerance and which epitopes have induced specific antibodies. Such information might identify highly immunogenic epitopes that adversely affect the success of a tolerance protocol. Epitope-based matching could eventually lead to new strategies for HLA mismatch permissibility to reduce alloimmunization and increase transplant survival.

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Disclosure

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