DOI: 10.1111/petr.12774

EDITORIAL

WILEY

The eplet load concept in clinical transplantation

Donor-specific HLA antibodies frequently cause allograft rejection and transplant failure; such antibodies recognize epitopes. Each HLA antigen can be viewed as a collection of epitopes that can be defined structurally by so-called eplets representing small configurations of polymorphic amino acid residues.[1] Matching at the epitope level can be performed by comparing the eplet 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 eplets. The so-called eplet load of a donor HLA antigen mismatch depends on the recipient's HLA type with its own repertoire of self-eplets to which no antibodies can be made.

Several research groups have demonstrated that HLA antibody responses in transplant recipients and pregnant women correlate well with eplet loads of mismatched antigens. This means that eplet matching outperforms the traditional HLA antigen-based matching and offers new opportunities to minimize the risk of de novo HLA donor-specific antibodies and enhance transplant success.

This issue of Pediatric Transplantation has two reports about implementing a new epitope-based allocation strategy to identify donors for kidney transplant patients.

Bryan, Chadha, and Warady with the Midwest Transplant Network (Kansas, USA) describe a new histocompatibility paradigm for pediatric kidney transplantation whereby donors are selected on the basis of DR and DQ eplet mismatching.[2] This paradigm emerged from recent data by Wiebe et al., who reported less class II HLA antibody development and longer graft survival of kidney transplants from donors with lower DRB and DQ eplet loads.[3] Furthermore, DR and DQ eplet mismatching is associated with antibody-mediated rejection and transplant glomerulopathy.[4]

Although class II HLA matching has traditionally been based solely on serologically defined DR antigens and more recently molecular DRB1 types, it should be noted that each DRB1 haplotype has alleles controlled by other class II loci and all of them can induce antibodies associated with transplant rejection. More than 35 years ago, matching for HLA-DQ (then called MB) was shown to benefit kidney transplant survival[5] and numerous reports demonstrate significant effects of HLA-DQ antibodies on transplant outcome. Many transplant programs have added the polymorphisms of DQB and DQA in determining donor–recipient compatibility. DRB matching should also include the alleles of the DRB3/4/5 loci because they can elicit antibody responses; often enough such antibodies react with epitopes shared with DRB1 alleles.

Donor–recipient eplet-based matching requires HLA typing information at the high-resolution (four-digit) allele level. All HLA antigens have multiple corresponding alleles with differences in their eplet repertoires; some alleles are mismatched for a given eplet whereas others are matched. Bryan et al. are now collecting transplant outcome data to determine optimal eplet load thresholds for class II mismatch permissibility. Such information may lead to new strategies of identifying suitable donors for transplant recipients.

Kausman, Walker, Cantwell, Quinlan, Sypek, and Ierino at the Royal Children's Hospital in Melbourne, Australia, began to apply an epitope-based allocation system in pediatric transplantation in early 2014.[6] Depending on the HLA type of the recipient, mismatched HLA alleles have different numbers of non-self-eplets and after establishing threshold values, these investigators excluded potential donors with high epitope loads. The impact of such exclusions on donor availability can be quantitated as a percentage determined in a similar way as the calculated PRA for sensitized patients. One can expect that lower threshold values for epitope loads will decrease HLA antibody responses and enhance transplant success, but they will also diminish access to the donor pool. From a practical viewpoint, the selection of a threshold value should consider a balance between the feasibility and the success of a transplant.

Kausman et al. present also preliminary post-transplant follow-up data in comparisons with controls that included a historical group transplanted at the same institution by traditional matching criteria. Although the HLA antigen mismatches were similar for these groups, the eight patients transplanted according to the new strategy had a much lower incidence of donor-specific antibodies and all of them had functioning grafts after 1 year.

Both reports address the importance of DR, DQ, and DP. Depending on the recipient's phenotype, many DR antigen mismatches have low DR and DQ eplet loads and they could be considered permissible mismatches especially if the DP eplet load is low.

As HLA class I-reactive antibodies are associated with graft rejection and transplant failure, an epitope-based determination of mismatch permissibility should also include eplet loads of HLA-A, HLA-B, and HLA-C mismatches. Depending on the HLA type of the recipient, such loads can vary from very low and even zero to very high. Kausman et al. used a threshold of 10 class I eplets for each antigen, but surprisingly, they found no differences in the class I eplet loads between the study and control groups.[6] However, the clinical relevance of class I eplet loads cannot be ruled out but deserves further investigation.

HLAMatchmaker has two types of programs. The antibody analysis program uses an eplet repertoire designed for an optimization of epitope specificity determinations; many eplets have residue similarities in overlapping sequence positions. The eplet matching

programs use smaller repertoires of eplets selected on the basis that a given mismatched residue in an antibody-accessible molecular position can be used just once. This avoids redundancies in the eplet loads.

The current eplet matching programs have two limitations. First, they make no distinctions between eplets that have experimentally been verified as epitopes with informative antibodies and eplets that are still theoretical considerations. The International Registry of HLA epitopes (www.Epregistry.com.br) has eplet lists for each locus together with antibody-verified eplets. For the latter, the repertoires must be considered incomplete and more studies with informative antibodies are needed.

Second, the matching does not consider the relative immunogenicity of antibody-verified eplets, that is, how often there is specific antibody response. Some preliminary studies have shown high frequencies of specific antibodies against certain eplets but not against others. Such empirical studies may provide some information about eplet immunogenicity, but a better approach would be to understand the immunological principles of the antibody response to a HLA mismatch.[7]

Altogether, mismatch permissibility criteria could be based on eplet loads in combination with information about the immunogenicity of antibody-verified eplets. Even without an eplet-based donor selection strategy, a determination of a donor's eplet load allows a risk assessment for post-transplant HLA antibodies and this will be helpful in the clinical management of the transplant recipient.

CONFLICT OF INTEREST

The author has no conflict of interests to disclose as described by Pediatric Transplantation.

Rene J. Duquesnoy, PhD
Department of Pathology, *University of Pittsburgh Medical Center, Pittsburgh, PA, USA*

REFERENCES

1. Duquesnoy RJ, Marrari M. HLAMatchmaker-based definition of structural human leukocyte antigen epitopes detected by alloantibodies. *Curr Opin Organ Transplant*. 2009;14:403–409.
2. Bryan C, Chadha V, Warady B. Donor selection in pediatric kidney transplantation using DR and DQ eplet mismatching: a new histocompatibility paradigm. *Pediatr Transplant*. 2016;20:926–930.
3. Wiebe C, Pochinco D, Blydt-Hansen TD, et al. Class II HLA epitope matching-A strategy to minimize de novo donor-specific antibody development and improve outcomes. *Am J Transplant*. 2013;13:3114–3122.
4. Sapir-Pichhadze R, Tinckam K, Quach K, et al. HLADR and -DQ eplet mismatches and transplant glomerulopathy: a nested case-control study. *Am J Transplant*. 2015;15:137.
5. Duquesnoy RJ, Annen K, Marrari M, Kauffman Jr HM. Association of MB compatibility with successful intrafamilial kidney transplantation. *N Engl J Med*. 1980;302:821–825.
6. Kausman JY, Walker AM, Cantwell LS, Quinlan C, Sypek MP, Ierino FL. Application of an epitope-based allocation system in paediatric kidney transplantation. *Pediatr Transplant*. 2016;20:931–938.
7. Duquesnoy RJ. The antibody response to a HLA mismatch: putting together the pieces of a puzzle. *Am J Transplant*. 2015;15:3019–3020.