Towards Selective HLA Mismatching in Clinical Transplantation

Frans H. J. Claas

In this issue, Kosmoliaptsis et al. (*1*) describe a new algorithm to determine the immunogenicity of a mismatched human leukocyte antigen (HLA) alloantigen with respect to the humoral immune response. Both in organ and hematopoietic stem-cell transplantation, the best transplant results are obtained with fully HLA-matched donor recipient combinations. However, because of the enormous polymorphism of the HLA system, only a minority of the patients can be actually transplanted with such a donor and as a consequence most patients will be transplanted with an HLA-mismatched donor. Epidemiological studies have shown that not every HLA mismatch will have the same negative impact on graft function and survival (*2*). This differential immunogenicity of HLA mismatches is not an intrinsic property of the HLA mismatch but seems to be dependent on both the mismatched HLA antigen and the HLA phenotype of the recipient. This was the conclusion of epidemiological studies showing a poor survival in one group of the donors-recipient combinations and an excellent survival in another group with a similar number of mismatches. The challenge, however, is to predict the immunogenicity of a particular HLA mismatch for an individual patient. HLAMatchmaker, a computer algorithm developed by René Duquesnoy, has been the first important tool developed for this purpose. Based on the knowledge of the exact amino sequence of the HLA alleles, each HLA antigen is defined as a string of polymorphic sites, originally consisting of three amino acids (triplets) but in later versions of the program as a more complex structure (eplets) (*3*, *4*). The principle of the algorithm is that in a patient antibodies will not form against polymorphism sites, which are present on the self-HLA antigens. By comparing the string of polymorphisms present on the mismatched HLA antigen with those of the patient's own HLA antigens, one can indeed predict the immunogenicity of a foreign HLA antigen with respect to the humoral immune response. An almost linear relationship between the number of foreign polymorphic sites on a mismatched HLA antigen and the incidence and strength of HLA antibody formation was observed in several studies (*5*, *6*). In this issue of *Transplantation*, Kosmoliaptsis et al. (*1*) go one step further and demonstrate that the immunogenicity of a HLA mismatch depends not only on the number of foreign amino acids but also on the difference in physiochemical disparity, both with regard to hydrophobicity and electrostatic charge, of the polymorphic amino acid involved. Further refinement of these types of analyses will enable a more accurate prediction of donor HLA mismatches, which will have a low immunogenicity for the recipient and will probably lead to a better graft survival and a lower sensitization grade of the recipient in case of graft rejection.

So far, these types of predictions have been restricted to the humoral alloimmune response, which plays a pivotal role in hyperacute, acute, and chronic allograft rejection.

It is a challenge to develop similar predictive models for the cellular alloimmune response. Although current immunosuppressive drugs seem to be adequate for the treatment of cell-mediated rejection of organ transplants, cytotoxic T cells still play an important role in the development of graft-versus-host disease after hematopoietic stem-cell transplantation. Here, the strategy to predict immunogenicity should probably be different as preliminary data show that for a cytotoxic T-cell response, foreign HLA antigens with only a few amino acid differences are more immunogenic than those with many amino acid differences (*7*). The differential immunogenicity of a particular HLA mismatch for the humoral versus the cellular alloimmune response is a complicating factor if one would like to select the optimal HLA-mismatched donor for a patient. Which algorithm should one apply? Considering the impact of the humoral immune response especially on chronic graft rejection, it is worthwhile to start to validate strategies as described by Kosmoliaptsis et al. (*1*) in a larger patient cohort.

Department of Immunohaematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands.
Address correspondence to: F.H.J. Claas, Ph.D., Department of Immunohaematology and Blood Transfusion, Leiden University Medical Center, Albinusdreef 2, Building 1, L1-106, Portocabins, P.O. Box 9600, 2300 RC, Leiden, The Netherlands.
E-mail: fhjclaas@lumc.nl
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