HLA compatibility in organ transplantation

C. Stavropoulos-Giokas

Department of Immunology and National Tissue Typing Center, General Hospital ‘Georgios Gennimatas’, Athens, Greece

Introduction

The ultimate goal of transplant biologists is the induction of clinical tolerance (antigen-specific unresponsiveness), allowing the long-term survival of human allografts without the need of HLA compatibility, without continuous recipient immunosuppression, and without the concomitant risks of infection, malignancy, and/or specific drug side-effects. Several approaches to solve this problem have proved successful in animal models and are being tested in humans.

Opelz and Terasaki, and their collaborators, first reported improved clinical outcome in transplant patients who received blood transfusions [1]. This seminal observation gave rise to a series of experimental protocols using blood, and/or blood products, for the induction of tolerance in animal models and in clinical practice [2]. Wood has recently reviewed the use of tolerance inducing doses of class I MHC-antigens in various forms for the induction of specific unresponsiveness to alloantigens [3]. Recent studies confirm that pre-treatment with soluble, or membrane-bound, donor class I MHC-antigens is capable of inducing immune unresponsiveness to a subsequent organ transplant, although Poutsiel-Noble et al. question whether class II MHC-antigen alone can induce specific unresponsiveness in vivo [4]. In parallel to these ‘whole molecule’ strategies of tolerance induction, the use of synthetic peptides, corresponding to class II HLA sequences, may be used for the in vitro definition of the immunogenic epitopes of the HLA antigens [5].

The epitope map of these HLA antigens will be useful in the future for induction of T cell energy and/or tolerance, overcoming probably the multiple problems from the HLA incompatibility.

HLA matching in transplantation: present of history?

The role of tissue matching as a criterion for organ allocation is still a subject of debate, as other factors are also important determinants of graft outcome, such as the cause of the donor’s death, ischaemic damage of the allograft and diabetes mellitus in the recipient.

Most multicentre analyses of HLA matching showed a steady fall in graft survival as the number of HLA-A, -B and -DR mismatches increases from 0 to 6 [6]. Attitudes toward HLA matching for kidney-donor allocation differ within Europe and North America and between the two continents. For example, in the UK, in those countries covered by Eurotransplant, and in the USA, but not in Canada, donor kidneys that have no known HLA-A, -B or -DR mismatches are shared nationally. After this practice was introduced, the number of kidney transplants being well matched for HLA doubled in the UK and increased 7-fold in the USA.

Sharing kidneys nationally when there is one or more HLA mismatches is much more controversial. This policy is favoured in certain parts of Europe where the population is genetically homogeneous and where distances between regions that share kidneys are short. In these areas most transplants have only one or two A, B, DR mismatches [7]. In the USA this practice has been resisted mainly for two reasons: (i) the long cold ischaemia times, when kidneys have to be shipped over long distances and (ii) the possibility that the cross-match turns out to be positive.

Concerning the HLA matching for other organs, the potential benefits of HLA matching on cardiac transplant survival have generally been obscured by the short cardiac cold ischaemia time, donor–recipient cardiac size constraints, absence of a long-term life support alternative to transplantation, and the severe prognosis of refractory cardiac failure [8]. In contrast to the data obtained in kidney and heart transplantation, liver transplants do not show an effect of HLA matching.

Correspondence and offprint requests to: Cathrine Stavropoulos-Giokas, Department of Immunology and National Tissue Typing Center, General Hospital ‘Georgios Gennimatas’, 154 Mesogion Ave, 11527, Athens, Greece.

© 2001 European Renal Association–European Dialysis and Transplant Association
In the future, histocompatibility will probably be definable in operational terms based on the relative immunogenicity of functional epitopes on HLA molecules. A review of studies that cited the percentage of patients with HLA specific antibody after transplantation showed that de novo development of antibody correlated with rejection or graft loss [9]. As most of the HLA specific antibodies are directed to antigens that share specific serological reaction patterns (cross-reactive group epitope clusters, CREGs), this relation between development of antibody and rejection or graft loss may account for the benefits of CREG matching [10,11].

Matching and cross-reactive epitope groups (CREGs)

Allocation on the basis of HLA is clearly a disadvantage for minority groups, who have different HLA antigen frequencies than the donor pool. When transplanted, non-Caucasian recipients tend to receive a higher number of mismatches, resulting in a poor graft survival and an increased level of sensitization after graft failure [12].

Two approaches have been described to enhance transplantation and increase graft survival in case of HLA mismatches. One includes the definition of specific HLA mismatches leading to either reduced or improved graft survival, i.e. taboo vs permissible mismatches. The second approach, mainly advocated in the US, is the introduction of matching for CREGs, which would significantly increase the chance of a recipient to receive a ‘well-matched’ kidney. All HLA antigens are classified in 10 groups based on the reactivity and specificity of HLA specific antibodies. Furthermore, unlike the distribution of HLA antigens, the distribution of CREGs is similar across ethnic groups, so CREG matching may result in a more equitable racial distribution of organs. Thus, for non-Caucasian recipients, implementation of CREG matching could lead to an increase in the number of ‘6-antigen matched’ transplants from 4 up to 30%, and 10% better graft survival at 5 years. However, in contrast to this approach, other data suggest improvement of graft survival by matching on the level of HLA split antigens rather than the broad HLA antigens. Recently, the use of CREGs was also shown to be very helpful in the determination of acceptable mismatches for highly sensitized patients [10].

It appears that the knowledge of the immunogenic HLA epitopes will be very helpful in the future to reduce the need for the HLA compatibility in the way that it is known nowadays. Consequently, CREG matching potentially might result in improved graft survival for Caucasians and African-Americans, decreased chance on positive cross-matches, reduced number of rejection episodes, and reduced number of broadly sensitized patients after a failed transplant, as the number of antibody inducing HLA epitopes is limited by this matching procedure [13].

‘Epitope(s) compatibility against HLA incompatibility’: future or dream?

Studies demonstrate that the current practice of class I HLA antigen matching in organ transplantation tells us little about the true degree of antigenic compatibility between a potential recipient and his donor. The one exception is in the rare situation of a perfect match for all private epitopes, for compatibility of these determinants dictate, by definition, compatibility for the public epitopes as well. For example, a donor who is HLA-A28, -B17 would be high compatible with a recipient who is HLA-A2, -A9, even though based on traditional concepts, this pair would be classified as fully HLA disparate. Moreover, in clinical transplantation, it appears that not all the patients have the innate capacity to respond to a vascularized allograft, even in a situation of complete HLA incompatibility. For example, patients who reject an HLA incompatible renal transplant rarely produce HLA specific antibodies against all incompatibilities. Moreover, in 1988 Welsh et al. reported the successful transplantation of kidneys bearing previously mismatched HLA-A and -B locus antigens [14]. In these patients, satisfactory graft survival rates were achieved provided the patient had not produced antibody to the mismatched antigen or to a cross-reactive group. The obvious question is whether the immunogenicity of mismatched donor HLA antigens is affected by the recipient’s HLA type. Such an influence would mean that the same donor mismatches would have different effects in recipients with different HLA types.

The above evidence strongly support the fact that there is a genetic basis for control of allograft responses. Furthermore, from the elegant study of Fuller et al. it seems that the humoral response to a specific foreign class I HLA allopeptide (Bw4) could be possibly predicted according to the recipient’s class II HLA phenotype [15]. Finally, the ultimate goal would be an accurate ability to predict peptide binding to MHC-molecules, in order to develop the tools to perform a rational identification of immunogenic epitopes. This would eventually require that other specific mechanisms involved in antigen processing and presentation (e.g. proteasomes, the transporter associated with antigen presentation, TAP, etc.) should be considered in addition to the specificity of the MHC complex.

Conclusion

In conclusion, it would in the future be possible that HLA matching will probably be definable in operational terms, based on the relative immunogenicity of functional epitopes on HLA molecules. Moreover,
based on the experience gained from CREG matching and the acceptable mismatches, the obvious question is whether the production of synthetic peptide analogues will be able to block the recognition of the dominant HLA determinant. If this is true, the use of synthetic peptides, corresponding to HLA sequences, will represent a new type of immunosuppressive agent for use in transplantation and new strategies for the induction of organ allocation would be applied.

References

15. Fuller TC, Fuller A. The humoral immune response against an HLA class I allodeterminant correlates HLA-DR phenotype of the responder. Transplantation 1999; 68: 173–182