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Review

Immunogenetics and immunology of transplantation in Leiden

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ABSTRACT

The historical observation of Jon van Rood that pregnancy can lead to the induction of HLA antibodies (1) was the start of a long history of research on immunogenetics and immunology of transplantation in Leiden. Some of the current research topics are presented in this mini-review. These include amongst others the differential immunogenicity of HLA mismatches in clinical transplantation, a special strategy to transplant highly sensitized patients, new tools to monitor donor specific memory B cells, new parameters for risk assessment in transplant recipients and the importance of the innate immune response in transplantation.

Contents

1. Introduction

Ever since the historical observation by Jon van Rood et al. in 1958 [1] that pregnancy can lead to the induction of HLA antibodies, research in Leiden has been focused on the immunogenetics and immunology of transplantation. Major contributions in the past concerned the unraveling of the complex genetics of the HLA system [2,3] and the role of histocompatibility testing in transplantation [4]. Actually, on the basis of these studies the international organ exchange organization "Eurotransplant" and the Dutch hematopoietic stem cell registry "Europdonor" have been founded by van Rood as head of the Department of Immunohematology and Blood Transfusion at the Leiden University Medical Center. At the moment this laboratory is serving not only as the HLA laboratory for the transplant centers in Leiden and Rotterdam, but also as the National Reference laboratory for histocompatibility testing and the Eurotransplant Reference laboratory.

Next to clinical responsibilities, transplantation related research is performed in close collaboration with the Department of Nephrology. Some highlights of the current projects are described in this short review.

2. Differential immunogenicity of HLA mismatches in clinical transplantation

The best transplant results are obtained when donor and recipient are fully HLA matched, but due to the enormous complexity of the HLA system with its different loci and the more than 10,000 different alleles, such a donor is not available for every patient.

We have to accept that the majority of renal patients will be transplanted with a mismatched donor. However, not every HLA

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mismatch has the same impact on graft survival. Some HLA mismatches are associated with an excellent graft survival, while others do elicit a detrimental immune response [5]. The immunogenicity of an HLA mismatch is not an intrinsic property of that HLA antigen, but depends on the structure of that particular HLA molecule in comparison with the structure of the HLA molecules of the patient. In collaboration with Rene Duquesnoy in Pittsburgh, who developed the so called HLAMatchmaker algorithm [6], we were able to show that the number of polymorphisms (i.e. triplets, eplets or epitopes) present on the mismatched HLA antigen and absent on the patient's own HLA antigens plays a determinative factor whether a patient will form antibodies after an HLA mismatched renal transplantation [7]. The large collection of human monoclonal antibodies directed against the different HLA class I antigens developed by Arend Mulder [8,9] has been instrumental for the identification of the relevant antibody epitopes.

We have tried to develop a similar Matchmaker algorithm to predict T cell alloreactivity, which is the dominant allo-immune response after hematopoietic stem cell transplantation. The current algorithm can indeed predict T cell alloreactivity in vitro [10] but is not capable of predicting survival after allogeneic stem cell transplantation.

It is clear from these and other studies that future matching strategies in organ transplantation should be based on epitope matching rather than antigen matching [11].

It remains to be established whether a similar approach is also feasible in hematopoietic stem cell transplantation.

3. Impact of external factors on the allo-immune response

The strength of an allo-immune response is not only dependent on structural aspects of the mismatched HLA antigens. Several studies by our group have shown that the non-inherited maternal HLA antigens are less immunogenic than other HLA mismatches [12–14]. Confrontation with maternal cells or maternal HLA antigens during pregnancy probably leads to the development of regulatory T cells affecting the allo-immune response later in life, as reflected by a lower incidence of allo-antibodies [12] and a better outcome of kidney- [13,15] and hematopoietic stem cell transplants [14,16].

The other side of the coin is the fact that viral infection will lead to the development of memory T cells, which cross-react with foreign HLA molecules leading to a more aggressive allo-immune response. Recent studies from our group have shown that this so called heterologous immunity occurs very often but is only predictable in a small number of cases [17,18].

4. Transplantation of highly sensitized patients

The presence of donor specific HLA antibodies leading to a positive complement-dependent cytotoxicity cross match is considered a contra-indication for transplantation [19]. The introduction of more sensitive solid phase assays for the detection of HLA antibodies has been very useful for the determination of the specificity of the antibodies causing a positive cross match but has also led to a lot of confusion on the clinical relevance of donor specific antibodies not reactive in complement-dependent cytotoxicity [20]. A consensus meeting on the technical aspects and clinical relevance of these solid phase assays has resulted in some guidelines [21], but this discussion will certainly continue the coming years. Clinical decision-making and risk assessment before transplantation are preferentially based on the combination of cell based and solid phase assays. Like most centers, the laboratory in Leiden is using such an approach for the definition of acceptable and non-acceptable mismatches [22]. A proper antibody screening also enables the identification of non-sensitized patients for whom a prospective cross match can be omitted safely [23] as was also shown by our national policy in The Netherlands.

A completely different group of patients are those, who have formed antibodies against many different HLA antigens, the so-called highly sensitized patients. Highly sensitized patients tend to accumulate on the waiting lists of the different transplantation programs due to the fact that the serological cross matches with the majority of the donors will be positive. Our group has been instrumental in the development of the acceptable mismatch program, which is used within Eurotransplant to enhance transplantation of highly sensitized patients [24]. The basis of the program is the identification of those HLA mismatches towards which the patients have never formed antibodies. All donors, who have an HLA type comprising only antigens matching the patient's own HLA type and one or more acceptable mismatches, are expected to give a negative cross match with the sera of this patient. When such a donor becomes available in one of the countries participating within Eurotransplant (i.e. Austria, Belgium, Croatia, Germany, Hungary, Luxemburg, Slovenia and The Netherlands), the kidney is mandatorily shipped to the recipient center, solely on the basis on a negative virtual cross match. The cross match is then performed in the recipient center. Introduction of this program has increased the transplantation rate of these highly sensitized patients with excellent results [25].

However, not all patients can be transplanted by this approach. Especially patients with rare HLA phenotypes compared to the donor population remain on the waiting list. For these patients, a FP7 project of the EU called “Eurostam” has been initiated in order to make an inventory on the basis of simulation studies. These studies will reveal whether extension of the donor pool with European populations with a different HLA composition compared to the Eurotransplant donor population will be beneficial for their chance to be transplanted. The first results of these simulations show that this approach will certainly be useful for a number of these difficult to transplant patients.

5. New tools to monitor donor-specific B cell reactivity

In case a candidate for a renal transplant has been sensitized, either due to pregnancy, blood transfusion, or a previous transplant, pre-existing donor-reactive antibodies may exist. The presence of these antibodies usually is a contra-indication for transplantation. Alternatively, there also are situations in which patients have been previously immunized, but no serum HLA antibodies are detectable at time of transplantation [26]. In these patients, donor-reactive memory B cells may be present that can rapidly respond upon re-challenge with allo-antigens present on the transplanted organ. Similarly, after desensitization strategies for those patients having high HLA antibody levels, there may be memory B cells present despite the reduction of HLA antibody titers [27,28]. We have previously shown that drugs included in standard immunosuppressive protocols are not all directly targeting B cells [29,30]. Therefore, the clinical consequences of these pre-existing donor-reactive memory B cells upon transplantation are yet to be fully elucidated.

We have recently developed an HLA class I-specific memory B cell ELISPOT assay that allows for determining the level of donor-reactive memory B cells prior to transplantation [31]. This assay is based on polyclonal activation of peripheral blood B cells [32], followed by the detection of HLA class I-specific B cells by monomeric HLA molecules in ELISPOT format. We have shown that we can detect HLA class I-specific memory B cells in pregnancy-immunized females, as well as in HLA-immunized patients on the transplant waiting list [31]. By determining the burden of donor-reactive memory B cells prior to transplantation, the established pre-transplant immunological risk profile based on HLA antibodies [33] can be extended towards the memory compartment.

The HLA class I-specific memory B cell ELISPOT assay can potentially also be used to monitor the humoral allo-immune response after transplantation. The problem with monitoring post-transplant HLA-specific