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Opinion

The Holy Grail to Clinical Transplant Tolerance Is Paved with HLA Epitopes

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The long-term success of solid organ transplantation is hindered by the barrier of donor-recipient incompatibility activating cellular and humoral immune responses that lead to rejection and irreversible allograft dysfunction. A variety of transplantation antigens are responsible for allograft rejection including HLA molecules, non-HLA antigens and ABO blood group antigens. They can elicit immune responses involving different types of T-cells including effector CD4 lymphocytes, cytotoxic CD8 lymphocytes, helper T-cells and regulatory T-cells. A diverse repertoire of B-cells participates in the humoral component of the immune response including memory B-cells, antibody-secreting B-cells (plasmablasts), regulatory B-cells and cytokine producing effector B-cells. During the immune response, T-cells and B-cells interact with each other and with other types of cells including dendritic cells, macrophages and monocytes. The considerable complexity of the immune response to an allograft manifests itself with multiple cell-mediated and antibody-

mediated mechanisms of transplant rejection. There might also be a lack of immune damage to the graft despite the presence of donor-specific antibodies and lymphocytes.

Another aspect of the immune response to an allograft is the development of immunological tolerance which prevents rejection and leads to long-term function of organ transplants without the need of immunosuppressive drugs. Specific tolerance can be demonstrated by a lack of antibody formation and/or a non-responsiveness at the cellular level upon re-exposure of the same antigen as used to induce tolerance. Various mechanisms include T-cell and B-cell anergy, depletion of lymphocytes and the activation of suppressor cells that downregulate specific immune responses.

The transplant community considers the induction of immunological tolerance of an allograft as a Holy Grail. Many methods have been tried, rather often unsuccessfully, to induce clinical transplant tolerance including different drug protocols and administration of monoclonal antibodies to costimulatory molecules such as CD80/CD86 and CD40/CD154. Desensitization of highly sensitized transplant patients represents a related topic.

A special issue of Human Immunology published in May 2018 has eighteen reports devoted to the induction of renal transplant tolerance with the transfer of donor bone marrow cells to achieve chimerism [1]. Tolerant recipients have increased levels of autologous circulating regulatory T-cells and there are also correlations with some biological markers. These protocols work best for HLA-matched transplants which are generally known to have the best long-term survival rates. Tolerance induction with hematopoietic cell infusions appear less successful for one HLA-haplotype mismatched transplants from living donors and for HLA mismatches from deceased donors this approach has remained a considerable challenge.

A principal role of B-cells is the production of antibodies that are deleterious to a transplant and successful tolerance induction must prevent the development of such antibodies. This can be accomplished through the activation of regulatory T-cells, but B-cells can also display regulatory functions important in transplant tolerance. Transcriptional B-cell gene signatures and B-cell phenotypic analyses have yielded limited clinically useful information.

This paper is part of a special issue on “Multiple Aspects of Transplant Tolerance”. It is not intended as a review but rather, it presents a personal viewpoint about antibody responses to HLA mismatches and how this information can be applied in achieving transplant tolerance. In the clinical setting, HLA mismatches are determined at the antigen or allele level and so-called donor-specific antibodies (DSA) offer estimates of humoral immune responses. Such assessments are however, incomplete because antibodies react specifically with epitopes on HLA molecules.

Structural modelling and amino acid sequence comparisons can define epitopes on class I HLA-ABC and class II HLA-DR, DQ, DP alleles [2, 3]. So-called eplets defined by residues within a 3 Angstrom radius of a polymorphic amino acid are considered functional components of HLA epitopes. Each HLA allele consists of a string of eplets and the International Registry of HLA Epitopes (www.Epregistry.com.br) shows which eplets have been verified experimentally with specific antibodies. Matching at the epitope level is done by aligning the eplet strings of each donor HLA allele with recipient alleles. Depending on recipient’s HLA type, a given donor allele will have different numbers of mismatched eplets; this is called the eplet load and can be determined with HLAMatchmaker (www.epitopes.net).

Many studies have demonstrated correlations between eplet loads and post-transplant antibody responses and allograft survival [2]. Accordingly, HLA mismatches with low eplet loads

are associated with decreased rejection incidence and better transplant outcome. Such mismatches are comparable to HLA matches and this information seems useful in selecting more suitable donor-recipient mismatch combinations in protocols to achieve clinical transplant tolerance.

Immunological tolerance is epitope-specific and is induced through exposure to a tolerizing antigen expressing such epitope. By definition, a tolerized recipient can never have antibodies specific for a tolerizing epitope even after re-exposure to that epitope. Can tolerance be induced by mismatched HLA alleles with multiple mismatched eplets including those that are recognized as antibody-verified? Serum analysis with single allele panels have shown that most sensitized patients have antibodies specific for limited numbers of mismatched HLA epitopes whereas other epitopes on immunizing HLA alleles are non-reactive. Such antibody specificity information is being used in determining potential donor mismatch acceptability for sensitized patients even for eplet-expressing alleles that have not been tested in the assays.

We must raise the question why sera from sensitized patients so often lack antibodies to certain mismatched eplets including those that are antibody-verified. Are such antibodies undetectable in the circulation because they had been absorbed by the transplant? However, post-allograft nephrectomy serum samples have also shown restricted antibody specificities. Depending on the HLA type of the sensitized patient, some eplets on mismatched HLA alleles induce antibody responses whereas other eplets are not immunogenic. Moreover, serum antibody analysis has shown that certain donor alleles are completely non-reactive demonstrating that none of their mismatched eplets had elicited specific antibodies.

For each sensitized patient, the interpretation of negative serum reactivity with donor alleles and eplets is important for the identification of potential donors with acceptable mismatches. Since the patient had been exposed to such mismatches and did not show antibodies, does this reflect immunological tolerance? If so, can we call such acceptable mismatches “preferred” because upon re-exposure, they would be unable to elicit specific antibodies? Although highly sensitized patients have high re-transplant success rates with acceptable mismatches, I am unaware of any studies focusing on re-transplants with preferred acceptable mismatches.

HLA sensitization is a frequent event in thrombocytopenic patients who have become refractory to random donor platelet transfusions. Such patients have high serum HLA class I antibody reactivity but can be successfully be transfused with platelets from HLA matched donors. In my experience, certain highly sensitized patients continue to respond well to repeated platelet transfusions with selected HLA mismatches without becoming refractory to these mismatches. Can this be considered evidence for immunological tolerance?

The lack of antibodies specific for certain mismatched eplets can be explained in several ways. First, the patient might lack B-cells carrying B-cell receptors specific for these eplets; in other words, a selective B-cell depletion. B-cell differentiation occurs primarily during fetal life but continues throughout adulthood giving rise to new mature B-cells. Can this explain the emergence of de novo DSA several years following transplantation?

Second, the patient may lack T helper cells needed by epitope-activated B-cells for their transformation to antibody-producing cells. Instead, regulatory T-cells may specifically induce such B-cells to become anergic or undergo apoptosis. Does this B-cell anergy reflect an active state of epitope-specific immunological tolerance and how long can this be maintained?

The importance of HLA epitopes in the immune response to a transplant has led to the conclusion that "The Holy Grail to clinical transplant tolerance is paved with HLA epitopes". Depending on the relationship between the HLA types of donor and recipient one can expect differences in repertoires of epitopes including the more immunogenic, antibody-verified eplets.

HLAMatchmaker can readily determine eplet repertoires for each patient. Donor mismatches with high eplet numbers may represent immunological barriers that are difficult to overcome. Conversely, immunological tolerance might be more readily achieved with donor alleles with low numbers of mismatched eplets.

In tolerance inducing protocols, follow-up HLA antibody specificity analyses might differentiate between immunogenic and tolerizing eplets and this information would be useful to determine which eplets are significant barriers in preventing tolerance. Epitope specificity analyses following desensitization protocols may distinguish between eplets that remain antibody-reactive and eplets that have become non-reactive. Can the latter be considered tolerogenic?

In conclusion, since HLA epitope-based matching outperforms traditional HLA antigen matching, it makes sense to include epitopes in protocols designed to achieve clinical transplant tolerance. Eplet mismatch determinations of donor HLA mismatches and serum analyses of epitope-specific antibodies are easy ways to investigate this concept.

Author Contributions

The author has completed all the work.

Competing Interests

The author has declared that no competing interests exist.

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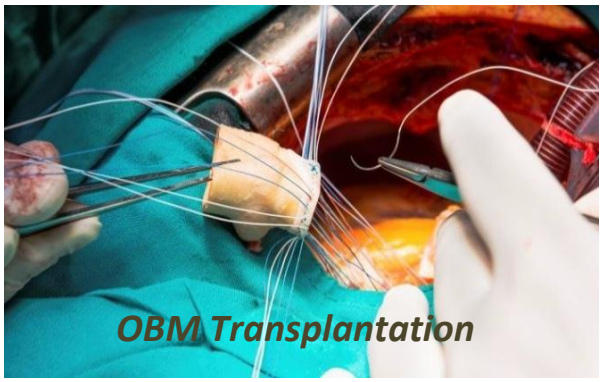

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