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Immunogenicity of Shared Molecular Epitopes in the Humoral Response as Biomarker of the Rupture of Immune Tolerance in Transplantation

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The true role of donor-specific human leukocyte antigen (HLA) antibody (DSA) response to a solid allograft is not fully understood [1]. Recently, new serum-screening assays (mainly based in the luminex technology) have strongly increased and defined the detection and specificity analysis of DSA in allosensitized patients in waiting list of transplantation or in transplanted recipients. HLA antibodies are usually epitope-specific and not antigen-specific. Recipients who lost a allograft develop cross-reactive (CREG) antibody patterns that are specific for the HLA molecules that usually share the organ donors mismatched epitopes or eplets. In general, the involved eplets or epitopes are easily visible on the top of the HLA molecules adjacent to the bound peptide. Immunizing antigens have mismatched eplets that can form antibody-reactive epitopes with self-configurations on the molecular surface.

The main problem is to assign as positive all those antigens showing some CREG reactivity with all mismatched antigens and clarify their role with respect to clinical significance, permitting that the transplant staff member's on-call can completely be sure of discard or accept a patient in waiting list of transplant as candidate recipient. The accurate assumption of determined and prohibited antigens and permitted antigens will get to stratify the risk of antibody-mediated rejection (AMR) and transplant outcome. In addition to this, luminex median fluorescence intensity (MFI) levels are playing a very important role to prevent and treat humoral rejection episodes in pre- and post-transplantation, respectively [2,3]. However, it is important to take into account that the solid phase HLA antibody detection assays were not originally designed to provide quantifiable data and the results of this determination should be taken with precaution.

In this sense, the differential immunogenicity of HLA epitopes and their cross-reactivity complicates the exact determination of the true risk of complications after solid organ transplantation. The problems of the HLA cross-reactivity, the shared molecular eplets and the establishment of an exact limit of cut-off point in luminex technology are seen in almost all HLA class I and class II loci, as reported [2-6].

Finally, the union of cellular (i.e. ELIspot, cross-matching, flow cytometry, cytotoxic precursors frequency, regulatory cells evaluation, between others), serological (i.e. definition of fixing complement capability of DSA, type of immunoglobulin subclasses, soluble molecules and cytokine profiles, definition of other non-HLA alloantigens, between other), molecular (i.e. definition of molecular epitopes and eplets, high resolution typing, and expression assays, between others) and clinical (i.e. incorporation of parameters of organ function, serum creatinine or C4d deposits, between others) informative assays can help to clear and define these facts in the future [1-7]. However, majority of these criteria are based on consensus of transplant experts and are without strong evidence behind them in any case. This is due to lack of objective criteria or biomarkers of rupture of immune tolerance to distinguish an immune responsive recipient and a non-responsive recipient. There seems to be light at the end of tunnel with hope of ability to appropriately discern the suitable biomarkers, with optimal utilization of donor organs, which are already in real scarcity. More and, retrospective and prospective data are needed with well-discussed and well-designed studies to define whether these immune tolerance biomarkers would be useful in accurate prediction of organ function outcome after transplantation.

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