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Editorial

Tolerance in Renal Transplantation - ②

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The transplant of organs is one of the greatest therapeutic achievements of the twentieth-century. In organ transplantation, the adaptive immunity is considered the main response exerted to the transplanted tissue, since the principal target of the immune response are the MHC (major histocompatibility complex) molecules expressed on the surface of donor cells [1]. However, we should not forget that the innate and adaptive immunity are closely interrelated, and should be viewed as complementary and cooperating. When a human transplant is performed, HLA (Human Leukocyte Antigens) molecules from a donor are recognized by the recipient's immune system triggering an alloimmune response. Matching of donor and recipient for MHC antigens has been shown to have a significant positive effect on graft acceptance.

When a human renal transplant is performed, HLA molecules (Human Leukocyte Antigens) from a donor are recognized by the recipient's immune system triggering an alloimmune response [2]. This could happen by three recognizing mechanisms: First, an indirect recognition: this type of mechanism has a dominant role in chronic rejection; second, a direct recognition: this mechanism determines a strong immune response in the acute rejection; and third mechanism, a "semi-direct" recognition: that could be mediated by immunoglobulin-like receptors of natural killer (NK) cells and can mediate potent acute rejection.

On the other hand there are two mechanisms for tolerance: the central and peripheral. In the central mechanism of tolerance the events occur in T cells in the thymus and this is based on clonal deletion and energy of cells (APCs). In the peripheral mechanism of tolerance an inactivation of T lymphocytes in peripheral tissues such as lymph nodes and spleen may be involved.

Tolerance in renal transplantation is an important issue for physicians and researchers who have attempted different strategies to promote tolerance in renal transplantation, including implementation of protocols in which tolerance induction have been a planned objective before the transplant, and also several surgical procedures for ABO-incompatible living kidney transplantation.

Tolerance in human transplantation can be defined in two ways. Clinical tolerance (also referred to as clinical operational tolerance) is the survival of a foreign organ or tissue (allogeneic or xenogeneic) in a normal recipient in the absence of immunosuppression. Immune tolerance is the absence of a detectable immune response against a functional organ or tissue in the absence of immunosuppression [3].

Early evidence demonstrating that adult mice could be tolerant of skin grafts after the induction of neonatal tolerance by the introduction of splenocytes intraperitoneally was shown by Brent and Medawar [4], in 1953. The central role of the thymus in mediating cellular immunity and graft rejection was established by JFAP Miller, who showed that nude mice [5] tolerated skin allografts because of a marked deficiency of lymphocytes. Conversely, there have been recent studies that show that spleen transplantation in pigs or dogs has a tolerogenic effect on renal transplantation [6].

In our study [7], the splenosis and splenectomy resulted in the induction of clinical tolerance to renal transplantation. Indicators of tolerance included improved renal function (in the case of splenosis) and higher recipient survival (in the case of splenectomy), relative to controls receiving only transplantation. When splenosis was performed, microchimerism is hypothesized as a tolerance mechanism, while in the case of splenectomy the suggested mechanism is a decrease in IgM and CD4⁺CD25⁺ T lymphocytes. The spleen is involved in the production of B lymphocytes and IgM, and splenectomy thus can result in decreased antibody content and increased tolerance. This effect could be considered analogous to the effect of rituximab (anti-CD20⁺ monoclonal antibody), which avoids acute rejection mediated by antibodies, resulting in a tolerogenic effect. On the other hand, recent studies show the important role of the spleen for the induction and maintenance of regulatory CD4⁺CD25⁺ T cells which are important for self-tolerance. This immune regulatory mechanism is known as non-specific suppression of activation and differentiation, through the release of anti-inflammatory cytokines. So, upon splenectomy, the activity of the regulatory T cells is presumably affected, and this may simulate the mechanisms of action of some currently used immunosuppressant drugs, such as basiliximab and daclizumab (chimeric monoclonal antibodies that selectively affect T lymphocytes).

On the basis of the promising results obtained in these animal models, several tolerogenic protocols have been attempted in humans, but most have failed to achieve robust and stable tolerance after renal transplantation. This is due to that the transplantation immunobiology is very complex, because of the involvement of several components such as antibodies, antigen presenting cells, helper and cytotoxic T cell subsets, immune cell, surface molecules, signaling mechanisms and cytokines; which play a role in the alloimmune response.

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