Tolerance: Is It Achievable in Pediatric Solid Organ Transplantation?

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KEYWORDS

• Pediatric solid organ transplantation • Allo-immune response
• Tolerance • Immunosuppression withdrawal

In 1956, John Murray performed the first successful kidney transplant. A kidney from one identical twin was transplanted into the other.[1] Four years previously, the first attempt at pediatric kidney transplantation occurred in France.[2] In this case, a 16-year-old boy received a kidney from his mother after a nephrectomy of his right kidney and subsequent discovery that his left kidney was missing. Although the mother was ABO compatible, the outcome, rejection after 21 days and death of the boy, demonstrated the powerful effects of the immune system's allorecognition, a factor not at work in genetically identical transplants. At this point in history, the mechanisms underlying allorecognition were poorly understood, but 1 year later, in 1953, Peter Medawar performed the seminal experiment demonstrating the potential to overcome the alloimmune response and induce a state of immunologic tolerance.[3] Although much progress has been made in controlling alloimmunity through the use of ever-improving immunosuppressive therapies, the discoveries of Medawar still have yet to be translated such that tolerance can be successfully achieved routinely in the clinical transplant setting.

Therefore, in the clinical arena of transplantation, tolerance remains, for the most part, a concept rather than a reality. As delineated in many of the organ-specific articles in this issue, the current paradigm of lifelong immunosuppression leaves a lot to be desired, particularly for children who face a lifelong burden. Although modern immunosuppression regimens have effectively handled acute rejection, nearly all organs

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except the liver commonly suffer chronic immunologic damage that impairs organ function, threatening patient and allograft survival. In addition to the imperfect control of the donor-directed immune response, there are additional costs. First, there is the burden of mortality from infection and malignancy that can be directly attributed to a crippled immune system. Second, there are insidious effects on renal function, cardiovascular profile (hypertension, hyperglycemia, and dyslipidemia), bone health, growth, psychological and neurocognitive development, and overall quality of life. It is likely that the full consequences of lifelong immunosuppression on pediatric transplant recipients will not be fully appreciated until survival routinely extends beyond 1 or 2 decades after transplantation. Therefore, it can be argued that the holy grail of transplantation tolerance is of the utmost importance to children who undergo solid organ transplantation.[4,5]

THE ALLOIMMUNE RESPONSE

Responses to alloantigens are primarily mediated by host T cells. As naive alloreactive T cells must be activated to cause rejection, they require antigen to be presented on antigen-presenting cells (APCs). Antigen presentation can occur via direct or indirect antigen presentation. In direct antigen presentation, donor APCs leave the graft, migrate to regional lymph nodes, and activate host cells that recognize donor major histocompatibility complex (MHC). Indirect antigen presentation involves recipient APCs presenting peptides derived from donor MHC or other donor-specific proteins, and presenting them to host T cells. Direct allorecognition is believed to be largely responsible for mediating acute rejection. However, chronic rejection is more likely mediated via the indirect pathway, because self-APCs are resident and donor APCs eventually die out. Current strategies for suppressing the immune response to transplanted organs attempt to address both pathways of antigen presentation by suppressing the activation of T cells. However, it is not clear whether tolerance-induction strategies will adequately address both pathways, as protocols that affect direct presentation may not prevent slowly developing chronic rejection mediated by self-APCs continuing to present donor organ antigens.

DEFINITION OF TOLERANCE

Tolerance, a state of normal allograft function without histologic evidence of immunologic damage in the complete absence of immunosuppression, can be induced or occur spontaneously. Tolerance induction strategies refer to treatment regimens specifically designed to achieve the tolerant state that is typically delivered around the time of transplantation. In contrast, spontaneous or operational tolerance most often refers to achievement of the tolerant state without an induction regimen that is uncovered through successful withdrawal of immunosuppression. As such, biomarkers capable of identifying and/or monitoring the tolerant state are much needed to enhance the success and decrease the risk of discontinuation of immunosuppression.

MECHANISMS OF TOLERANCE

Immunologic tolerance is based on the fundamental premise of immunity, namely self- versus non-self discrimination. Because productive immune responses rely on the immune system's ability to recognize foreign antigens to protect the host, an elaborate process for ensuring proper recognition of foreign from self-antigens has evolved. To prevent one from responding to one's own cells and proteins, the immune system uses several mechanisms to induce self-tolerance. These mechanisms are mediated centrally and in the periphery, and are depicted in **Fig. 1**.