

Tolerance in Organ Transplantation: Evolution of Strategies

Editorial

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The primary objectives of prolonging survival of transplanted organs and their recipients are compromised by cell-mediated and antibody-mediated rejections, infections, side-effects of immunosuppressive agents, malignancies and non-adherence [1]. Strategies to eliminate the need of long-term immunosuppressive agents and induction of tolerance have been the goal of research for 60 years. Transplantation tolerance is defined as induced modification of the host immune system which leads to indefinite, drug-free, transplant survival with maintenance of full incompetence [2].

Peter Medawar et al., pioneered in inducing tolerance in experimental animals 60 years ago. They demonstrated that prenatal or neonatal mice inoculated with allogeneic splenocytes were tolerant as adults to skin grafts from same donor strains resulting in drug-free indefinite graft survival, devoid of complications, including chronic rejection [3]. Since then several strategies of tolerance including heart, liver, kidney, bone marrow transplants have been developed in laboratory rodent models [4]. In 1999, Spitzer et al., demonstrated successful induction of tolerance in human renal transplant recipients through development of mixed lymphohaemopoietic chimerism or observed sustained allograft tolerance [5].

Tolerance of one's own tissues and elimination of autoimmunity are achieved by central and peripheral mechanisms. Central tolerance is generated within the thymus where immature autoreactive T cells with a high affinity for self-major histocompatibility complex molecules are subjected to apoptosis, a process referred to as negative selection or deletional tolerance [6]. The peripheral tolerance involves extrathymic mechanisms, whereby the activated T cells, which have escaped negative selection and emigrated from thymus, are suppressed by specialised T cells, termed as regulatory T cells (Tregs) [7]. Combination of both central and peripheral mechanisms are essential for the elimination of autoreactive cells and induction of self-tolerance.

Thymic-derived, regulatory Treg cells represent a subset of CD4⁺

T cells (Foxp3⁺CD4⁺CD25⁺ regulatory T cells), which suppress unwanted responses against self-antigens and prevent autoimmunity. Tregs can suppress a whole range of immune cells including B cells, NK cells, CD4⁺ or CD8⁺ T cells, and both monocytes and dendritic cells. Emerging evidence suggest that the presence of regulatory B cells (Breg) in the spleen and blood of patients that spontaneously develop graft tolerance, bearing the phenotype CD24^{int}CD38⁺CD27⁺IgD⁺IgM^{+/low}, can transfer donor-specific tolerance via IL-10 and TGF-beta1-dependent mechanisms and to suppress *in vitro* TNF-alpha secretion [8, 9].

Based upon the experience of animal models and human studies, in transplant recipients, central deletional tolerance provides the most robust and long-lasting state of unresponsiveness. Mixed haemopoietic chimerism and donor thymic transplantation are two strategies aimed at harnessing the potential of central tolerance in humans. Co-stimulation blockade using cytotoxic T cell lymphocyte associated antigen-4 immunoglobulin (CTLA4Ig) which blocks the CD28:CD80/86 costimulatory pathway has been used to develop peripheral tolerance.

Mixed haemopoietic chimerism strategy involves a bone marrow or stem cell transplant in addition to the organ transplant. Historically, the experimental transplant recipients were subjected to whole body irradiation to eliminate mature alloreactive T cells. This was followed by transfusion of donor haemopoietic stem cells. The donor alloreactive T cells in the recipient were subsequently eliminated by the thymus leaving behind the newly developed T-cell repertoire of mixed chimeras tolerant toward the donor organs [10].

Subsequently, a T-cell depleting and non-myeloablative conditioning regimens were introduced for induction of mixed chimerism, which included limited body irradiation, splenectomy, anti-thymocyte globulin, donor bone marrow cell infusion and course of cyclosporine [11]. To avoid the risk of non-myeloablative irradiation, less toxic protocols of co-stimulation blockade led to mixed chimerism animals. The most frequently used co-stimula-

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tion blockers interfere with CD28/CTLA4-CD80/CD86 or the CD40L(CD154)-CD40 pathways [12, 13]. Following administration of anti-CD154 and CTLA4Ig leads to a significant increase of Foxp3⁺ regulatory T cells in tolerant animals [14].

To enhance central deletional tolerance, co-transplant of vascularised donor thymus at the time of organ transplantation were performed using composite organs called “thymokidneys” and “thymohearts” in thymectomised animals, which showed prolonged allograft survival and diminished development of chronic vascular lesions [15, 16].

Nobel laureate Rolf Zinkernagel and Starzl had proposed that all outcomes of organ or bone marrow transplantation are determined by the balance between the number of leukocytes that travel to lymphoid organs and the number of donor-specific T cells produced at those sites [17]. Recipients of organ allografts usually receive large doses of immunosuppressive therapy during the early period of maximal leukocyte migration. These large doses may erode the mechanism of tolerance by clonal exhaustion–deletion [18].

Currently available immunosuppressive agents impact Treg cells in the alloimmune milieu with both beneficial and deleterious interactions to the allograft. Basiliximab, an IL-2 receptor blocker decreases Tregs, while lymphocyte depleting agents such as anti-thymocyte globulin and alemtuzumab increase Tregs. Calcineurin inhibitors, a mainstay maintenance immunosuppression since the mid-1980s, suppresses Tregs, while mammalian target of rapamycin inhibitors expands Tregs [19, 20].

Significant progress has been made in the development of biomarkers those can uncover mechanisms and act as tools for identifying and monitoring recipients who develop a state of operational tolerance, during accidental immunosuppression withdrawal secondary to problems of over-immunosuppression or toxicity [21]. Operationally tolerant kidney, liver and heart allograft recipients have been reported [22]. In addition to Tregs, other immune cells, such as dendritic cells, monocyte/macrophages or natural killer cells, have been described as part of the process operational tolerance [23-25].

A joint meeting organized by the European Society of Organ Transplantation and The Transplantation Society for basic science research was organized in Paris in 2013, recommended to establish a registry of results of patients enrolled in tolerance trials, establish protocols, biomarkers, include children 12 years and older and establish a task force to manage the logistics of the trials [26, 27].

In conclusion, induction of transplant tolerance and acceptance of organ without the perils of immunosuppression remain the holy grail, which depends on successful implementation of tolerance strategies in nonhuman primates. Although costimulatory blockade and mixed chimerism have been successful in inducing tolerance in nonhuman primates, the transfer of tolerogenic cell populations such as Tregs and mesenchymal stem cells are important advances, which are under investigation [28].

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