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Future of Solid Organ Transplantation: Organ-Specific Tolerance

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Abstract. A transplant between two people who are not genetically identical is called an allotransplant and the process is called allotransplantation. Donor organs and tissues can be from people who are living, or people who have died because of a significant brain injury or lack of circulation. Allotransplantation can create a rejection process where the immune system of the recipient attacks the foreign donor organ or tissue and destroys it. The recipient may need to take immunosuppressive medication for the rest of their life to reduce the risk of rejection of the donated organ. In general, deliberately induced immunosuppression is performed to prevent the body from rejecting an organ transplant. The adverse effects associated with these agents and the risks of long-term immunosuppression present a number of challenges for the clinician. Immune tolerance, or immunological tolerance, or immunotolerance, is a state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response in a given organism.

Keywords: organ transplantation; immunosuppressive therapy; rejection; immune tolerance; regulatory cells; chimerism; review

Solid organ transplantation is a life-saving procedure for various end-stage diseases, but the inherent requirement for life-long immunosuppression for preventing graft rejection comes with many side effects, such as increased risk of infection, neoplasms as well as nephrotoxicity and diabetogenicity [1–4].

Long-term immunosuppressive therapy represents a huge burden on transplant recipients, but currently cannot be omitted. Research in tolerance has elucidated mechanistic pathways of rejection, T cell regulation and T cell activation previously unknown [4]. Diagnostic assays to identify tolerance and distinguish it from “non-tolerance” are needed, and progress continues in this area. The work by some groups suggest that both blood and liver tissue gene expression can predict the outcome of immunosuppression withdrawal [5]. It is important to notice that, the genetic signature of tolerance in liver transplantation may differ significantly from that of kidney transplantation for some reasons that are unknown at this time [6]. Of course the tolerogenic environment of the liver plays a very important role in this field.

So minimization or withdrawal of immunosuppressive drugs remains a major goal in transplantation, and may be achieved in patients who have developed tolerance towards their grafts.

In clinical practice, operational tolerance is defined as “a well-functioning graft lacking histological signs of rejection, in the absence of any immunosuppressive drugs in an immunocompetent host” [7, 8].

An animal is formally proven to be tolerant when in the absence of immunosuppression, a second graft from the same donor is accepted, while a graft from a third-party donor is rejected.

In general, operationally tolerant transplant recipient cannot be identified prospectively. Due to the lack of biomarkers to guide weaning or cessation of immunosuppressive drugs, the majority of recipients will rely on life-long immunosuppressive therapy. This situation is especially problematic in kidney transplantation where tolerance is a very rare event [9].

In general there are two kinds of tolerance; central (in-thymic) and peripheral (non-thymic).

Positive selection, also called thymic education, ensures that only clones with TCRs and moderate affinity for self-MHC are allowed to develop.

Negative selection by means of apoptosis occurs when T cells have extremely high affinity for the MHC-self-peptide complex.

Many potentially reactive T cells escape thymic selection; this reflects that many antigens are absent intrathymically.

cally or present at insufficient levels to induce tolerance in the thymus; so several non-thymic mechanisms prevent autoimmunity and are also capable of rendering peripheral T cell repertoires tolerant. These mechanisms are:

- sequestration of antigens into privileged sites;
- apoptosis of T cells caused by persistent activation or neglect;
- clonal anergy (lack of costimulation) (CD28-CD80/86, CD40-CD40L);
- regulatory T cells (Tregs, CD4+CD25+FoxP3+ T cells).

Clinical research to induce full or partial tolerance in transplant patients has been induced in allograft transplantation in many centers. A state of indefinite survival of a well-functioning allograft without the need for maintenance immunosuppression was the main target of the researchers. Rare cases of operational tolerance after transplantation with complete cessation of immunosuppressive therapy have been reported [10, 11].

Full tolerance was achieved with myeloablative therapy before organ transplantation in combination with induced donor chimerism in hematologic malignancies treated with bone marrow transplantation [12].

At present partial tolerance or minimal immunosuppression is possible. This partial or incomplete, donor-specific tolerance has been termed *prope tolerance* or *minimal immunosuppression tolerance* [13, 14].

Stable graft function for 1 year or more referred as functional or operational tolerance [15, 16].

The reasons for graft loss can be broadly classified into three categories:

- 1) inflammation induced reactions against graft tissues, specifically ischemia-reperfusion (I-R) injury;
- 2) immun-initiated reactions against graft tissues;
- 3) direct organ toxicity by immunosuppressive drugs.

When an alloantigen is recognized, the innate and adaptive immun systems respond synergistically to reject the allograft through non-exclusive pathways, including contact-dependent T cell cytotoxicity, granulocyte activation by either Th1- or Th2-derived cytokines, NK cell activation, alloantibody production and complement activation [17].

Improvements in the short term success of renal and extra-renal transplantation have had a minimal impact on long term success and the rate of late graft loss is essentially unchanged [18, 19]. The advantages associated with the avoidance of chronic immunosuppression continue to drive the enthusiasm for implementing approaches to induce tolerance to transplanted organ allografts as the term chronic rejection is mainly characterized by antibody-mediated rejection and a score to reflect interstitial fibrosis and tubular atrophy [20].

Strategies for inducing transplantation tolerance

There are two obligatory components to achieving transplantation tolerance: depletion of alloreactive Tconv and upregulation of alloreactive Treg cells. The balance between graft destruction and regulation can be shifted using strategies to inhibit the activity of Tconv cells and/or increase

the relative frequency or functional activity of alloantigen-reactive Treg cells.

Mixed chimeric and cellular tolerogenic therapies are being trialed where drug-based therapies have failed [21, 22].

Manipulating innate immune system

TLRs drive innate immune responses as part of I-R (ischemia-reperfusion) injury and this leads to the subsequent initiation of adaptive alloimmune responses; so deficiency in the TLR adaptor protein MyD88 leads to donor antigen-specific tolerance. MyD88 deficiency is associated with an altered balance of Tregs over Tconv cells promoting tolerance instead of rejection.

Lymphodepletional strategies

Lymphodepletion in the form of “induction therapy” is an effective strategy for addressing the precursor frequency of alloreactive Tconv cells at the time of organ transplantation and preventing acute allograft rejection. However, ongoing maintenance therapy during post-depletional cell repopulation is necessary to prevent T memory cells from driving rejection and alloantibody formation (mAb, radiation and cytotoxic drugs are necessary) [23].

Cellular therapy

A. In addition to CD4+ CD25+ FoxP3+ nTregs and iTregs; Tr1 cells produce large amounts of IL-10 [24]; Th3 cells produce TGFb [25]; Tr35 cells produce IL-35; CD8+ CD28-cells [26] and CD3+CD4-CD8-cells [27] and NKT cells [28] have all been reported to exert regulatory effect on alloimmune responses. Suppression of alloreactive T cells permits long-term graft survival and, at times, operational tolerance [29–31].

Using rabbit ATG and Rituximab (plus FK and Sirolimus) for tolerance induction in living-donor renal recipient [32].

Alemtuzumab (Campath-1H), mAb to CD 52, found densely distributed on T and B cells and NK cells [33]. Alemtuzumab in combination therapy with costimulation blockade, regulatory T cell infusion and donor stem cell transfusion are some of the novel approaches to tolerance induction currently in study [34–38].

B. B cells have also been shown to serve a regulatory role; unlike Tregs there are no validated molecular or phenotypic markers to define Bregs, so they are currently defined on the functional basis of their IL-10 production [39].

Particularly the role of transitional B cells is important; they represent a regulatory B cell population based on their increased IL-10 production; meanwhile it is noticed that no difference in B cell subsets (total, naive, transitional) or inhibitory cytokines (IL-10 and TGFb) was detected when compared to healthy controls [40]. On the other hand B cells play a major role in chronic rejection, as donor-specific alloantibodies have been linked to chronic rejection and long-term graft failure [41–44]. Long-term allograft acceptance has been achieved by augmenting traditional immunotherapy with B cell depleting antibodies [45]. BAFF (B cell activating factor) is involved in B cell survival, pro-

liferation, and maturation. It has been correlated with increased PRAs, DSA (donor specific alloantibodies), B cell repopulation and C4d+ renal allograft rejection [46–48]. Its blockade using human recombinant mAb Belimumab promoted tolerance in murine models by:

- depleting follicular and alloreactive B cells;
- promoting an immature/transitional B cell phenotype;
- abrogating the alloantibody response;
- sustaining a regulatory cytokine environment [49, 50].

C. Costimulation Blockade: alloreactive T cell activation requires signal 1 and signal 2 [51]. Blockade of costimulation effectively prevents T cell activation and allograft rejection. T cells become anergic and they express ICOS (inducible costimulator) and play a regulatory role. Costimulatory signals of the CD28 : B7 and CD40 : CD40L are the most studied and most important. CTLA-4 binds with 10–20 folds higher affinity than CD28 to B7 on APCs and inhibits the T cell. Also this ligation induces IDO promoting the suppressive functions in CTLA-4 regulatory CD4+ cells [52].

Abatacept and Belatacept, fusion proteins composed of CTLA-4 and IgG1, confer potent inhibition of alloreactive T cell responses. Belatacept is more effective compared to Abatacept [53]. However lymphoproliferative disorder in the belatacept-treated patients are more important than calcineurin blockers [54–56].

D. Tolerogenic DCs, macrophages, and MSCs (mesenchymal stromal cells).

The tolerogenic properties of DCs include the ability to acquire and present antigen, expand and respond to antigen-specific Tregs, constitutively express low levels of MHC and costimulatory molecules, produce high IL-10 and TGF β and low IL-12, resist activation by danger signals and CD40 ligation, resist killing by NK or T cells and promote apoptosis of effector T cells [57].

i. Tregs stimulated by Rapamycin-conditioned DCs suppress more effectively antigen-specific T cell proliferation [58].

ii. IL-10-generated human tolerogenic DCs were optimal in producing highly suppressive Tregs [59].

— TAIC (transplant acceptance-inducing cell) is an immunoregulatory macrophage. They are IFN γ -stimulated monocyte-derived cells (IFN γ -M ϕ C) described as a non-DC and more mature form of resting macrophage expressing F4/80, CD11, CD86, PDL-1. Their suppressive effect is through the enrichment of CD4+CD25+FoxP3 cells and cell contact- and caspase-dependent depletion of activated T cells [60].

— Mesenchymal stromal cells (MSCs) have immunomodulatory properties, they inhibit T cell activation and proliferation possibly due to the production of nitric oxide and IDO (indoleamine-2,3-dioxygenase) [61]. MSCs harvested from term fetal membranes have been shown to significantly suppress allogeneic lymphocyte proliferation in mixed lymphocyte reactions (MLR) by suppressing IFN γ and IL-17 production and increasing IL-10 production [62, 63].

E. Chimerism-based approaches.

Chimerism is the concept that cells of different donor origins can coexist in the same organism. It might be derived into “mixed” or “microchimerism” and “full” or “macrochimerism”.

Mixed is defined as the presence of both donor and recipient cell lineages coexisting in the recipient bone marrow.

Full chimerism implies complete elimination of recipient hematopoietic lineages and population of the recipient bone marrow by 100 % donor cells [64].

The main aim should be that donor cells that could attack the host and cause GVHD need to be eliminated while at the same time preserving the recipient’s ability to produce immune populations that can defend against infections [65]. This might be realised by partial irradiation of the recipient bone marrow with peripheral deletion of recipient T cells allowed for the development of both donor and recipient hematopoietic cells and induction of tolerance to donor tissue without the need for full myeloablation [66–68]. Lastly in kidney transplantation, as the tolerance has two components, central and peripheral, the induction strategy consists of thymic irradiation to allow for development of a donor T cell reservoir in these organ recipients [69–71].

Kidney Transplant Tolerance

1. CD20 gene expression was significantly increased in urinary sediments of operationally tolerant KTRs (Kidney tx recipients) [72].

2. An increase in the percentage or absolute number of B cells in the peripheral blood of operationally tolerant KTRs [73–76].

3. Enrichment of naive and transitional B cells at the expense of memory B cells [76].

4. Human CD24^{hi}CD38^{hi} B cells have recently been described as containing regulatory B cells (Bregs) [77].

5. Relative increase in the inhibitory Fc receptor Fc γ RIIb and an increase in the negative modulator BANK1 (B-cell scaffold protein with ankyrin repeats 1) [76].

6. An increase proportion of central memory cells and a decreased proportion of effector cells [78].

7. Upregulation of many TGF β regulated genes, as well as downregulation of costimulatory and T cell activation genes [79].

8. A high ratio of expression of FoxP3 to MAN1A2 (alpha-1,2-mannosidase) [73].

Conclusions

Limited data exist on the capacity of the currently defined biomarkers of tolerance to identify patients in which immunosuppressive drugs can be withdrawn.

Induction of chimerism in combination with kidney transplantation might provide development of central tolerance by deletion [80].

Alemtuzumab (Campath-1H) treatment is promising with minimal immunosuppression to create “Prope Tolerance” [81, 82].

The proteasome inhibitor Bortezomib in combination with donor specific transfusion (DST) might be suitable since Bortezomib induces apoptosis of highly activated lymphocyte including plasma cells, B cells and T cells [83, 84].

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Майбутнє трансплантації органів: органоспецифічна толерантність

Резюме. Трансплантація між двома особами, які не є генетично ідентичними, називається алотрансплантацією. Донорські органи та тканини можуть бути отримані від живих людей або від людей, які померли через серйозну травму мозку або порушення кровообігу. Алотрансплантація може призвести до процесу відторгнення, коли імунна система реципієнта атакує чужорідний донорський орган або тканину та руйнує їх. Реципієнту може знадобитися приймати імуносупресивні ліки протягом усього життя, щоб зменшити ризик відторгнення донорського органа. Як правило, медикаментозно індукована імуносупресія про-

водиться для запобігання відторгненню трансплантата. Побічні ефекти, пов'язані з цими препаратами, та ризики довготривалої імуносупресії представляють для клініциста серйозну проблему. Імунна толерантність, або імунологічна толерантність, або імунотолерантність, — це стан несприйнятливості імунної системи до впливу речовин або тканин, що здатні викликати імунну відповідь у даному організмі. Їй присвячена дана стаття.

Ключові слова: трансплантація органів; імуносупресивна терапія; відторгнення; імунна толерантність; регуляторні клітини; химеризм; огляд

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Будущее трансплантации органов: органная толерантность

Резюме. Трансплантация между двумя лицами, которые не являются генетически идентичными, называется аллотрансплантацией. Донорские органы и ткани могут быть от живых людей или людей, умерших из-за серьезной черепно-мозговой травмы или нарушения кровообращения. Аллотрансплантация может вызвать процесс отторжения, когда иммунная система реципиента атакует чужеродный донорский орган или ткань и разрушает их. Реципиенту может потребоваться принимать иммуносупрессивные средства на протяжении всей жизни, чтобы снизить риск отторжения донорского органа. Как правило, индуцированная иммуносупрессия назначается, чтобы не дать организму

отторгнуть трансплантат. Неблагоприятные эффекты, связанные с этим назначением иммунодепрессантов, и риски долгосрочной иммуносупрессии представляют для клиницистов серьезную проблему. Иммунная толерантность, или иммунологическая толерантность, или иммунотолерантность, — это состояние невосприимчивости иммунной системы к веществам или тканям, которые способны вызывать иммунный ответ в данном организме. Ей посвящена данная статья.

Ключевые слова: трансплантация органов; иммуносупрессивная терапия; отторжение; иммунная толерантность; регуляторные клетки; химеризм; обзор