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Article · July 2013

DOI: 10.6002/ect.2013.0004 · Source: PubMed

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Regulatory T Cells as a Therapeutic Tool To Induce Solid-Organ Transplant Tolerance: Current Clinical Experiences

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Abstract

Long-term tolerance is potentially an ideal in organ transplant. Achieving this leads us to eliminate immunosuppressive therapies and their associated side effects. Although most succession in this field belongs to mixed chimerism methods of tolerance induction, regulatory T cells and (T-reg)–based methods also have been demonstrated to prevent organ rejection and lead to transplant tolerance through different mechanisms. In contrast to chimeric protocols (which require bone marrow transplant), T-reg–mediated protocols do not aggressively manipulate blood and the immune system. Most treatment has been done for graft-versus-host disease after hematopoietic stem cell transplant. This review describes different types and mechanisms of action and clinical strategies using T-regs to induce transplant tolerance.

Key words: *Kidney transplant, Regulatory T cells, Tolerance*

Introduction

Transplant tolerance is an active state of allograft-specific unresponsiveness without requiring long-term immunosuppression.[1-2] Two reasons have made this state the Holy Grail of transplant. First, although conventional immunosuppressive therapy and better surgical techniques have remarkably improved short-term outcomes (most centers report 1-year graft and patient survival rates of more than 95%), the final result of transplant in most cases is chronic graft rejection (which can be seen in 58% of kidney transplanted patients); and secondly, the nonspecific and lifelong use of immunosuppressive therapies cause severe complications (eg, life-threatening infections, secondary malignancies, transplanted organ dysfunction, significantly increased cardiovascular morbidity and mortality, and inhibiting developing immune tolerance to the graft).[1-5] Therefore, promoting and maintaining tolerance is a major challenge toward longer survival of transplanted organs.[3-4] Regulatory T cells (T-regs) have been shown to prevent acute and chronic rejection and to lead to transplant tolerance.[1,2,4] This is because of induction or promotion of tolerance while alleviating immunosuppressive therapy and its associated side effects.[1,4] To induce, promote, and maintain the tolerance, combining immunomodulating T-regs and a short course of immunosuppressive therapy are needed,[1] and then there needs to be a continuous supply of graft antigens to sustain T-cell–mediated regulation.[4]

Regulatory T cells and transplant tolerance

Regulatory T cells are a subset of T cells that involve peripheral self-tolerance via actively suppressing auto-reactive T cells ($CD4^+$, $CD8^+$), B cells, natural killer cells, natural killer T cells, mast cells, and dendritic cells.[5] Regulatory T cells down-regulate immunity to foreign antigens, and depletion of these cells leads to autoimmunity.[1]

Two main types of T-regs including naturally occurring $CD4^+CD25^+$ cells and inducible (adaptive) $CD4^+CD25^+$ cells, and some other subsets induce

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Acknowledgements: *The authors have no conflicts of interest to declare. This study was originated from the studies related to a research supported by Deputy of Research, Kashan University of Medical Sciences (kaums), Grant No. 9096.*

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Experimental and Clinical Transplantation (2013) 5: 379-387

DOI: 10.6002/ect.2013.0004

transplant tolerance.[1-2] It also should be considered that the $CD4^+CD25^+$ cells are essential to achieve[6] and maintain[7] transplant tolerance. Naturally occurring T-regs develop in the thymus through a high-affinity mode toward self antigen-MHC complex.[8] They consist of 1% to 3% of total peripheral $CD4^+$ cells and are based on the expression of the transcription factor Helios, 70% of all peripheral T-regs.[9] They constitutively express CD4, $CD25^{high}$ (IL-2Rα chain), TGF-β-LAP (transforming growth factor beta-latency–associated peptides [a component of the TGF-β receptor]), CTLA-4 (cytotoxic t-lymphocyte antigen 4), FR4, Foxp3, Helios (a member of the Ikaros transcription factor family), and inducible T-cell COStimulator. Although, they do not express CD127 (IL-7R α-chain) or CD49b (the α-chain of the integrin VLA-4), they are completely demethylated in the T-cell regulatory–specific demethylated region (TSDR) within the Foxp3 locus.[1-5] Among all above-mentioned markers, TSDR demethylation is the most reliable criterion for natural T-reg cells currently available.[10] It has been shown that the demethylated status of cytosine at cytosine-phosphate diester-guanine sites in the Foxp3 locus increases expression of the gene.[11] Maintenance of nT-regs in the periphery depends on some factors including IL-2 and TGF-β. IL-2 develops naturally occurring T-regs in the thymus, and causes their homeostasis and activation in the periphery.[12] Transforming growth factor-β induces T-regs to express Foxp3 and causes their homeostasis and activation in the periphery.[5] It is likely that INF-γ and IL-5 are needed to maintain the tolerance-transferring property of $CD4^+$ T-cells.[13] The central hemostatic function of naturally occurring T-regs is done through a cell-cell contact without any cytokine expression except for surface-bound TGF-β.[10]

$CD4^+$ T cells that are exposed to alloantigens in a tolerogenic environment induce the second type of T-regs that are less stable in maintaining self-tolerance in comparison to naturally occurring ones.[14] A case in point is when alloantigens are presented, either by immature dendritic cells or in the presence of immunosuppressive cytokines.[15] In specific inflammatory environments, the presence of these inducible T cells increases the number and potency of alloantigen reactive T-regs; therefore, peripheral tolerance is induced.[5] Inducible T-regs do not express transcription factor Helios, and according to this property, they consist of 30% of all the peripheral T-regs that are partially demethylated in the Foxp3 TSDR site.[5] They are expanded from $CD25^+CD4^+$ cells in the periphery[3] or derivate de novo peripherally from naïve $CD4^+CD25$-$CD45RA^+$ non–T-regs in an antigen-specific, Foxp3-dependent, Helios-independent, and thymus-independent manner, with the same structural and functional characteristics as natural $CD4^+CD25^+$ T-regs.[1,5]

Interleukine-10 secreting T-regs (Tr1 cells) have a phenotype of CD4+CD25-IL10+Foxp3- and are induced in the periphery by antigenic stimulation in limited costimulation conditions and under the inductive effects of IL-10, CD46 engagement, and immature dendritic cells.[1,2,4-5] Tr1 cells secrete large amounts of IL-10, TGF-β, and IL-5 to control inflammation in injured tissues[4-5] by inhibiting naïve and memory T-cell responses irrespective of their antigen specificity,[5] and the reticence of antigen presenting cells (APCs) to express costimulatory molecules or to secret proinflammatory cytokines.[16] Based on the antigen status, this kind of T-reg induces tolerance to organ transplants by producing IL-10 or TGF-β.[17] This is advantageous because there is less of a chance for systemic immunosuppression.

The other subset of T-regs is Th3 cells. These cells are induced from $CD4^+$ T cells after oral antigen administration, and secrete large amounts of TGF-β to control inflammation in injured tissues.[4,18]

The natural $CD8^+CD28$-$CD25^+Foxp3^+$ T-regs produce IL-10 and TGF-β, and have roles in tolerance induction by killing donor APCs,[19] tolerating recipient dendritic or endothelial cells,[20] and suppressing $CD4^+$ T cells with allospecificity.[19]

Double negative T-regs, derived from proliferating $CD4^+$T cells, compose 1% to 5% of TCR^+ cells in the periphery. Despite this low quantity, these cells can induce immune tolerance and are potent in inhibiting alloimmunity responses in an antigen-specific manner mediated by their Fas/FasL-dependent cytolysis.[10]

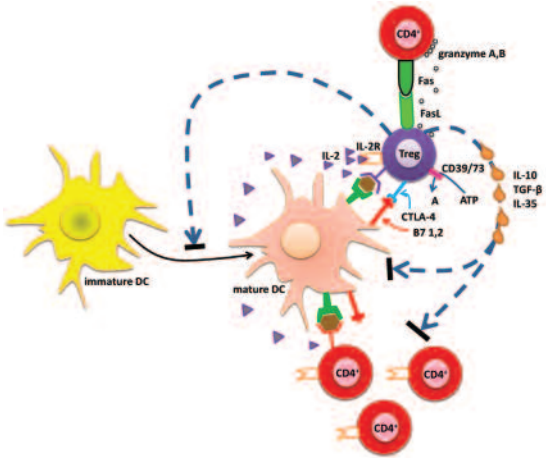
There are growing reports demonstrating that kidney-,[4] liver-,[21] lung-,[22] heart-,[23] and skin-transplanted patients[24] with chronic (and sometimes acute) rejection, have a diminished T-reg phenotype/function compared with tolerant or stable patients. Increased T-regs in some cases of acute rejection may be a response to high donor-activated effector T-cell activity.[5] It has been shown that decreased number of $CD4^+CD25^{high}$ $Foxp3^+$ cells during the first 6 months after a transplant reach

partial recovery by 1 year and increase over baseline levels by 2 years.[4] Taken together, these studies indicate that T-regs play a significant role in promoting transplant tolerance by effectively responding to antidonor effector T-cell activity.

General prospective of mechanisms used by regulatory T cells to induce tolerance

Regulatory T cells act through 4 general mechanisms, although combining these mechanisms could possibly explain a regulatory process for inducing the tolerance (Figure 1). The first mechanism is exerted through cell-cell contact, by expressing CTLA-4, surface TGF-β, ICAM-1, lymphocyte-activation gene 3, fibrinogenlike protein 2, and CD39/CD73. These T-regs indirectly inhibit target reactive T cells to decrease T-cell proliferation, antibody and cytokine production/secretion, costimulation/adhesion, and to induce their anergy/death and their conversion to T-regs.[5,10]

Figure 1. Histomorphometric Evaluation of Fully Allogeneic C57BL/6 Aortic Grafts



The second mechanism is applied by secreting inhibitory cytokines such as IL-10, TGF-β, and IL-35. These cytokines inhibit reactive T cells directly (by lowering secretion of IL-2, IL-5, and TNF-α) or indirectly (through antigen-presenting cells).[5,10]

The third mechanism is apoptosis that is induced by Galectin-1 expression on the surface of T-regs, perforin-dependent and perforin-independent granzyme A/B mechanisms, and IL-2 (as a T-cell growth factor) consumed by CD25 on T-regs.[5,10]

The final mechanism leading to a metabolic disruption in effector cell targets includes the suppressive second messenger cyclic adenosine monophosphate and the inhibitory CD39/CD73 pathway, which hydrolyze inflammatory extracellular adenosine triphosphate to anti-inflammatory adenosine.[10]

Regulatory T cells reside in lymphoid tissues[25] and block initiation of aggressive immune responses[26]; some migrate to graft sites to inhibit the aggressive cells that have escaped from the regulation.[26] Some factors known to mediate T-regs trafficking among peripheral blood, lymphoid tissues, and inflamed grafts include CD103 integrin,[27] CD62L,[4] CCR4,[28] CCR5,[29] and CCR8.[28]

The transcription factor Foxp3, originally identified in lethal human features called *immune dysregulation polyendocrinopathy enteropathy X-linked* and *X-linked autoimmunity-allergic dysregulation syndrome*, are critical to natural and inducible T-regs development, peripheral maintenance, function, and homeostasis.[1,4-5] It appears to be a necessary,[3] but not specific,[30] marker of T-regs. It has shown that acetylation of lysine residues at the amino terminus of the histone tail promotes an open chromatin structure that leads to binding of transcription factors, which induces Foxp3 expression.[31] In cases of transplant tolerance, acetylated histone protein and Foxp3-regulated miRNAs might be accurate markers for monitoring active immune tolerance in patients after transplant,[3] and histone deacetylase inhibitors dramatically could be effective in prolonging graft survival by enhancing of Foxp3 binding to the IL-2 promoter and down-modulation of IL-2 production.[31] Foxp3 gene expression may be the most accurate diagnostic, as well as prognostic, marker of renal acute rejection and graft loss.[32] Unexpectedly, expression of Foxp3 protein in renal tubules and the interstitium of patients with acute rejection is associated with poor graft survival than in those with low expression of Foxp3 protein.[30]

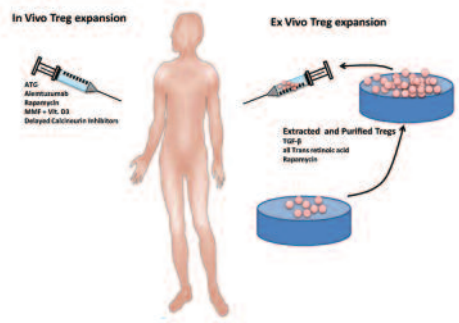
There is an association between Foxp3+ T-regs and inflammation.[33] Such association do not mean that $Foxp3^+$ T-regs induce inflammation by themselves, but rather, it seems that they are regulatory cells, generated by the inflammatory process of rejection to stabilize the inflammation by lowering the activity of effector T cells in a time-dependent manner to promote a state of transplant tolerance.[34] The role of $Foxp3^+$T-regs during graft rejection will be clearer if Foxp3 expression is normalized to the T-lymphocyte compartment that infiltrates the graft, and not the whole graft tissue sampling. Earlier approaches have considered Foxp3

expression as a contributory component of the lymphocyte infiltration, rather than an indicative of the extent of the inflammatory infiltrate. Such consideration may result in high Foxp3 expression that positively correlates with a better outcome, a lower inflammation grade, or a donor-specific hyporesponsiveness.[30] Moreover, in the context of rejection, Foxp3 can be expressed in recently activated effector T cells and bona fide T-regs.[30] Deoxyribonucleic acid demethylation in the Foxp3 locus discriminates regulatory T cells from activated Foxp3$^+$ conventional T cells.[35] This concept is confirmed by positively correlation of circulating CD127- CTLA-4 T-reg population with quantitative assessment of natural Foxp3 TSDR.[36]

Generation of regulatory T cells for clinical tolerance induction

There has been an increased interest in using T-regs as a biological therapy to preserve and restore tolerance toward alloantigens. Clinical strategies for the therapeutic use of T-regs can be divided into 2 types: *adoptive transfer of ex vivo expanded T-regs,* and *de novo regulatory T-cell induction or conversion of naive T cells into T-regs in vivo* (Figure 2).

Figure 2. Different Ways of T-regs Expansion



(1) Adoptive autologous T-regs therapy could induce organ transplant tolerance. To fulfill this induction, they should first be isolated from the patient's peripheral blood by magnetic cell sorting[37] and fluorescence-activated cell sorter[38] systems, and after expansion, re-infuse them. There is no risk of rejection of re-infused T-regs because they are autologous.[2] These systems gave a purity of up to 90%,[38] which could be achieved by using either a positive selection of cells having markers of CD4, CD25, CD45RA, and FR4, or a negative selection of cells having some markers of CD19, CD127, and CD49b cells.[1,2,5,14]

Because of the low frequency of T-regs in human peripheral blood, there are not enough to be sorted and transferred directly to patients. Therefore, ex vivo expansion is required.[2,14] Ex vivo expansion of T-regs could be achieved through nonspecific (which would render polyclonal T-regs) or specific pathways (which produce alloantigen-reactive T-regs).

Alloantigen-reactive T-regs are 10 to 100 times more potent than polyclonal T-regs[39] and can be produced through direct[2] and indirect[40] pathways. In direct pathways, autologous T-regs are stimulated by allogenic APCs, while in indirect pathways, they are stimulated by autologous APCs pulsed with alloantigens.[5] It is likely that autoimmunity can be induced by the indirect form of expansion. The reason for such autoimmunity is activation and proliferation of residual contaminating autologous effector T cells (which are present in the ex vivo media of T-regs) by autologous APCs expressing autologous antigens. Artificial antigen presenting cells expressing single HLA: allopeptide resolve this problem and also increase 4-fold expansion of naturally occurring T-regs.[14] Moreover, different strategies have been used to explain the ex vivo expansion of T-regs (reviewed in[14]). These strategies should conserve T-reg sufficiency (in both numbers and potency to dominate over effector T-cells),[2,9] purity (to resolve the problem of contaminating effector T-cells [which make the transfer of T-regs ineffective]),[2,14,] stability (to prevent their conversion to effector Th1/Th17 cells in the body under the influence of proinflammatory cytokine effects),[2,3] capacity (to provide their survival and appropriate migration),[2] consistency of Foxp3 expression,[14] and specificity (to induce a more-potent tolerating response than that of polyclonal ones and prevent pan-suppression, which results in increased risk on infections and cancers).[41]

Although the range of effective dosages of T-regs that will prevent rejection in humans is not known, a practical guide is a single infusion of 3 to 5 × 10^9 T-regs, which combined with thymoglobulin induction, can effectively increase T-reg percentage to more than 33%. After T-reg expansion, this dose can be produced readily from 1 U of blood.[39] Transforming growth factor-β, all-trans retinoic acid[42] and rapamycin[43] can induce human naïve CD4$^+$CD25-CD45RA$^+$ non–T-regs to acquire greater suppressive capacity than total CD25hi cells. Compared with inducible T-regs, expansion of naïve T-regs is therapeutically more

advantageous because of being more likely to remain in a Foxp3 positive state when transferred in vivo.[43] The other reason is more functioning T-regs expressing homing receptors that could concentrate them at lymphoid organs.[44] Therapeutic use of ex vivo expanded T-regs also could be approached by rapamycin, which provides a more-consistent suppressive cell functionally[45] and numerically.[46]

It is possible to generate T-regs by in vitro protocols too (reviewed in[3]). These in vitro generated T-regs could induce tolerance and already has been used in some trials.[47-48]

(2) In vivo generated T-regs could induce tolerance. The most actively investigated tolerance induction regimen is pretreatment of the patient using donor-specific transfusion with/without prepurified T-regs, and then examining the patient's administration with blocking monoclonal antibodies targeting CD4, CD154 (CD40L), lymphocyte function associated antigen-1, and ICAM-1 costimulation.[1] Antithymocyte globulin, monoclonal antibodies against CD3 and CD52 (each reviewed in[14]), and pharmacologic inhibition of histone deacetylase,[49] phosphodiesterase three[50] and mammalian target of rapamycin (mTOR) inhibitors[49] also could increase the number and function of T-regs in vivo and induce graft survival.

Trials using regulatory T-regs to induce transplant tolerance

Contradictory to chimeric protocols of tolerance induction in the field of organ transplantation, T-reg–mediated protocols do not aggressively manipulate the blood and immune systems.[1] The adoptive transfer of T-regs was established when it was found that T-regs with immunosuppressive effects can be isolated from peripheral blood and expanded in vitro.[51] Moreover, it has been shown that T-regs are expanded in tolerized animals and could be found in recipient's lymphoid tissue,[25] as well as tolerized grafts.[26] Interestingly, naïve animals administrated by T-regs isolated from tolerized animals showed a state of tolerance,[7] which would not be achieved without T-regs.[6] To test how T-regs induce transplant tolerance, Jiang and associates cultured T-regs with donor antigen-bearing APCs and surprisingly showed that these T-regs prevented rejection of mouse skin grafts, which are mismatched with the specific transplant antigen only, but not the rejection of an unrelated third party skin graft.[40] Such T-regs also have been shown inside the skin graft of tolerant mice.[52]

All these data represent a major advance toward the therapeutic use of T-regs in allograft tolerance. In clinical transplant, T-regs were capable at controlling graft-versus-host disease (GVHD) after allogeneic bone marrow transplant.[53] The advantage of isolating T-regs from healthy donors and successfully treating GVHD in animals provides proof for designing T-reg trials in hematopoietic stem cell transplant aiming at the prevention of GVHD.[54-56] In the first human study done in a hematopoietic stem cell transplant setting, Trzonkowski and associates used ex vivo expanded T-regs to treat GVHD after bone marrow transplant in 2 patients (1 had acute GVHD and the other had chronic GVHD). They reported neither unexpected adverse reactions nor alleviation of chronic symptoms despite the absence of pharmacologic immunosuppression in the patient with chronic GVHD, and the other 1 died despite initial and transitory improvements.[54]

In late 2010, Brunstein and associates used T-regs isolated from third-party cord blood samples with 4 to 6 HLA matches to treat 23 GVHD patients with advanced hematologic malignancies. They reported neither toxicity nor adverse events during up to 1 year of follow-up, and also they reported a reduced incidence of grade II to IV GVHD from 61% to 43%.[55] The first phase I/II clinical trial reporting on the efficacy of T-regs for preventing GVHD after haploidentical stem cell transplants in 28 patients (22 with acute myeloid leukemia, 5 with acute lymphoblastic leukemia, and 1 with high-grade non-Hodgkin lymphoma) showed that cliniMACS-selected T-regs allowed 26 patients to remain free of clinically relevant GVHD at all with a proper immune reconstitution, and just 2 patients developed grade II GVHD.[56] It also should be noted that in the absence of infused T-regs, all patients enrolled in these trials were prone to lethal GVHD after being given such a high-donor number of T effector cells. In these trials, 1×10^5 kg-1 to 30×10^5 kg-1 T-regs on 1 day after the transplant were infused, and some patients received a second dose on day +15. Overall results in these trials are promising with different degrees of immune system recovery and GVHD improvement in signs and symptoms, with no adverse side effects, such as infections or early mortality.

A multicenter phase I/II trial (the ONE study; www.onestudy.org) on living-donor kidney

recipients is taking place in different cities in Europe to evaluate safety and potential therapeutic benefits of infused T-reg cells.[14] The investigators are developing protocols that use different types of expanded recipient polyclonal T-regs in patients receiving a common immunosuppressive protocol based on the Symphony study (ie, daclizumab induction, mycophenolate mofetil, low-dose tacrolimus, and steroids). Each center will enroll 20 patients as a control arm, and 10 patients will be the case arm, receiving the same immunosuppressive regimen as controls (but without anti-CD25 induction) plus T-reg cell therapy. The experiences obtained by these studies on bone marrow transplants will present valuable details.

Effects of immunosuppressive drugs on T-regs

Inducing allospecific tolerance using T-regs, we need to use some elements of immunosuppression. Therefore, the effect of immunosuppressive drugs on T-regs is critical. This immunosuppressive therapy will be needed after transplant until the T-regs can establish themselves.[14]

Cyclosporine inhibits development,[57] frequency,[58] and function[59] of T-regs, and inhibits their conversion from naïve $CD4^+$ cells[60] in transplant recipients. Delaying administration of cyclosporine may not have such an effect.[3]

In contrast to cyclosporine, sirolimus and everolimus (mTOR inhibitors) selectively facilitate expansion of T-regs,[58,61] induce conversion of alloreactive $CD4^+$ Foxp3- T cells to $Foxp3^+$ T-regs,[61] and preserve suppressive activity of T-regs.[62] This suggests that mTOR inhibitors are ideal candidates for short-term immunosuppression therapy after depleting T cells after transplant.[3]

It seems that mycophenolate mofetil administration along with mTOR inhibitors favors expansion of the T-regs through induction of tolerogenic dendritic cells[63] and inhibiting expansion of memory T cells.[64] Mycophenolate mofetil increases frequency of T-regs and induces tolerance when combined with vitamin D3.[62-64]

Preferentially, antithymocyte globulin causes the expansion of T-regs and promotes their function in vivo.[65] The mechanism by which antithymocyte globulin induces expansion of T-regs is conversion of $CD4^+CD25^-$ cells to $CD4^+CD25^+$ cells.[66] Antithymocyte globulin in humans depletes T cells; thus, it may be useful for lymphodepletion before T-reg therapy where it can increase the T-reg/T effector ratio.

Corticosteroids promote survival and function of T-regs.[61] In animals, anti-CD3 monoclonal antibodies increase the frequency of T-regs; therefore, protecting the animal from diabetes.

B7 blockade may lead to T-reg depletion, but combining belatacept (CTLA4-Ig)—a blocker of CD28 costimulation—and anti-IL-2R, does not deplete T-regs after renal transplant, likely because the blockade is nonsaturating.[1] Alemtuzumab (humanized anti-CD52 mAb) also may favor T-reg survival especially when combined with rapamycin and costimulation blockade.[67]

Barriers in the use of T-regs to clinical practice

No demonstration has been shown of allospecific tolerance induction by infusing T-regs in an otherwise unmanipulated, fully MHC incompatible host.[1] The reasons for such unsuccessful treatment are technical limitations and the high frequency of contaminating alloreactive T cells. The low number of naturally occurring T-regs in circulation, and our lack of knowledge in specific markers makes it difficult to isolate pure populations of such cells. Furthermore, their low expansion potential continues to limit clinical application.[14]

Conversely, contaminating T cells in T-reg expansion culture causes an improper ratio of T-reg/T effector. One reason for several orders of nominal antigen-specific T cell response is mismatching. The more mismatching there is, the more T-reg is needed.[1] As a result, in the absence of effective deletion of substantial numbers of alloreactive T cells, more-rapid expansion of alloaggressive T cells overcomes the protective effects of T-regs across MHC mismatches.[68]

The other pitfall is direct versus indirect expansion of specific T-regs. These two T-regs do not act synergistically,[1] and because of the limited lifespan of donor antigen presenting cells, direct specific T-regs have less low-frequency in most patients with long-term grafts including those with chronic rejection.[69] Therefore, to induce transplant tolerance, T-regs with an indirect pathway specificity are required to expand a procedure that is problematic in deceased-donor transplants. In living-donation, there usually is enough time for the best immunodominant peptides and then, to expand specific T-regs for alloantigens.

The other significant pitfalls are innate immune responses in inflammatory conditions such as infections, autoimmunities, surgical trauma, and ischemia-reperfusion injury. The inflammatory signals of such conditions may spoil suppressive phenotype of T-reg. Therefore, minimizing such effects or delivering T-regs at a time far from tissue injury is a significant element of tolerance induction.[1,14]

Although not observed yet, occurrence or relapse of infections and tumors may be problematic in cases of large scale T-regs and should be considered in future clinical trials.

Taken together, transferred T-regs must first have appropriate trafficking and homing (reviewed in[70]); second, they must preserve stability for Foxp3 expression and not produce inflammatory cytokines,[71] despite the unavoidable inflammation during transplant; third they must either survive or impart their memory of tolerance to the host immune system; fourth, they must convert recipient alloantigen-specific T cells to a regulatory phenotype[72]—a process known as *infectious tolerance*—lastly, immunosuppression must not have side effects on the number and function of transferred T-regs.

It seems that stability of T-regs would be a challenging problem. Fortunately, there are ways that could improve these properties of T-regs. For example, retinoic acid increases stability of nT-regs expanded in rapamycin,[73] and IL-2[74] and rapamycin[43] can stabilize Foxp3 expression of nT-regs, and even promote demethylation of the Foxp3 TSDR.[74] It must be borne in mind that inflammatory cytokines such as IL-1[75] are associated with loss of T-reg stability and its conversion to T effector cells. Therefore, avoiding inflammatory signals is essential for surgical trauma as well as ischaemia-reperfusion injury.

Conclusions

The knowledge of immune tolerance in basic studies translated into clinical practice holds a promise of improved therapies in medicine. There is a great thanks to T-regs that possibly could be isolated, expanded, and transferred to the transplanted patient. Because of these results from clinical trials using human T-regs to treat GVHD after hematopoietic stem cell transplants, it seems that these cells eventually will emerge as a successful tool for solid-organ transplant tolerance.

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