Tregs and kidney: From diabetic nephropathy to renal transplantation

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Abstract

Kidney transplantation is recognised as the most effective treatment for patients with end-stage renal disease (ESRD). Kidney transplantation continues to face several challenges including long-term graft and patient survival, and the side effects of immunosuppressive therapy. The tendency in kidney transplantation is to avoid the side effects of immunosuppressants and induce immune tolerance. Regulatory T-cells (Tregs) contribute to self-tolerance, tolerance to alloantigen and transplant tolerance, mainly by suppressing the activation and function of reactive effector T-cells. Additionally, Tregs are implicated in the pathogenesis of diabetes, which is the leading cause of ESRD, suggesting that these cells play a role both in the pathogenesis of chronic kidney disease and the induction of transplant tolerance. Several strategies to achieve immunological tolerance to grafts have been tested experimentally, and include combinations of co-stimulatory blockade pathways, T-cell depletion, in vivo Treg-induction and/or infusion of ex vivo expanded Tregs. However, a successful regimen that induces transplant tolerance is not yet available for clinical application. This review brings together certain key studies on the role of Tregs in ESRD, diabetes and kidney transplantation, only to emphasize that many more studies are needed to elucidate the clinical significance and the therapeutic applications of Tregs.

Key words: Diabetes; Foxp3; Kidney transplantation; Regulatory T-cells

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Core tip: This review brings together certain key studies on the role of regulatory T-cells (Tregs) in end-stage renal disease, diabetes and kidney transplantation, only to emphasize that many more studies are needed to elucidate the clinical significance and the therapeutic applications of Tregs.
INTRODUCTION

Immunological self-tolerance in the periphery is achieved by the negative regulation exerted on the immune response by a variety of cells of which the best characterized populations are the regulatory T cells (Tregs)\(^1\). Tregs mediate self-tolerance and tolerance to alloantigens by suppressing the activation of effector T-cells (Teffs), and exerting anti-inflammatory activity\(^2\). Of Tregs the best characterized and studied cells are the CD4\(^+\)CD25\(^+\)Foxp3\(^+\) Tregs, especially in the context of autoimmune diseases and organ transplantation\(^3,4\).

Treg-induction and/or infusion of Tregs that were not only able and sufficient to mediate graft tolerance, but were also able to transfer long-term survival to naive recipients.

Tregs include natural (n)Tregs that are generated in the thymus and inducible (iTregs) that are generated in the periphery. nTregs arise in the thymus and express the forkhead/winged helix transcription factor Foxp3 that, in turn, controls nTreg differentiation\(^5\). iTregs arise in the periphery from memory and naive CD4\(^+\) Teffs following stimulation by self- or allo-antigens in the presence of IL-4, IL-10, TGF-\(\beta\) and IL-2. iTregs may or may not express the transcription factor Foxp3, and exert their suppressive activity mainly via the secretion of anti-inflammatory cytokines, mainly TGF-\(\beta\) and IL-10\(^6,17,18\). TGF-\(\beta\) induces the expression of Foxp3, converting CD4\(^+\)CD25\(^+\) naive Teffs to Tregs in the periphery. nTregs are antigen non-specific, while iTregs are usually antigen-specific\(^17,18\).

Tregs are further subdivided into Tr1 cells that mainly secrete IL-10 and Th3 cells that mainly secrete TGF-\(\beta\). Both iTreg types inhibit the maturation of dendritic cells (DCs) and the activation and proliferation of both memory and naive Teffs\(^18\).

Regulation of Tregs

A well-studied regulator of Tregs at the molecular level is the transcription factor Foxp3, the expression of which is critical for their development and function\(^19,20\). Data from animal studies have provided evidence that Foxp3 deficiency causes loss of Treg suppressive activity leading to the development of a lethal autoimmune syndrome\(^5\). In accordance, adoptive transfer of CD4\(^+\)CD25\(^+\)Foxp3\(^+\) T-cells from wild-type mice can prevent the development of severe autoimmune diseases observed in Foxp3-deficient mice\(^3\). In humans, Foxp3 deficiency has been associated with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome\(^22-24\).

Both DNA and histone protein modifications are implicated in the epigenetic regulation of Foxp3\(^25\). Regarding DNA modifications, the methylation status of cytosine at cytosine-phosphate diester-guanine sites in the locus of Foxp3 influences its expression\(^26\).

Histone modifications entail the acetylation of lysine residues at the amino terminus of the histone tail, inducing Foxp3 gene expression. Interestingly, these epigenetic regulators can be used to enhance the function and number of Tregs, for potential therapeutic applications\(^26\).
Suppressive mechanisms of Tregs

Tregs express the T-cell receptor and may suppress innate and adaptive immune responses. Tregs exert a cell-cell contact-dependent suppression, and they also exert suppressive activity mediated by cytokines, mainly IL-10 and TGF-β. Tregs can block Teffs at any stage of their activation, proliferation, differentiation, and effector functions.

Tregs suppress the activation of antigen presenting cells (APCs) through the expression of membrane-associated inhibitory molecules such as the cytotoxic T lymphocyte antigen 4 (CTLA4) and lymphocyte activation gene-3, a CD4-related trans-membrane protein that binds HLA II on APCs (DCs in particular) and inhibits their activation and the ensuing antigen presentation.

In addition, Tregs induce the apoptosis of target cells by producing several cytolitic molecules such as granzymes A and B, perforin, and galectin 1. Tregs also exert suppressive activity by causing metabolic disruption of Teffs through IL-2 consumption (IL-2 is an essential growth factor for naive Teffs), suppression of cyclic adenosine monophosphate synthesis, and inhibition of the CD39-CD73 pathway. Specifically, CD39 hydrolyzes ATP or ADP to AMP. CD39 is a dominant ectoenzyme expressed by Tregs. Catalytic inactivation of extracellular ATP by CD39 can be considered as an additional anti-inflammatory mechanism mediated by Tregs. Co-expression of CD39 and CD73 generates pericellular adenosine. Adenosine is an inhibitor of T-cell responses and exerts its effect via binding to the A2A receptor.

Wu et al. reported that the suppressive function of Tregs is mediated through a complex formed by the transcription factors NFAT and Foxp3, whereas in Teffs, NFAT forms a complex with the activator protein-1 (AP-1). The authors suggested that a strategy to induce tolerance is to inhibit the NFAT:AP-1 interaction by small molecules, without interfering with the NFAT:Foxp3 interaction.

The recent finding that NFAT is a common regulator for both Teffs and Tregs indicates that NFAT is an essential transcription factor for the functional integrity of both populations. Therefore, immunosuppressive drugs targeting NFAT activity in stimulated T-cells, such as calcineurin inhibitors, may also suppress the activity of Tregs.

Both nTregs and iTregs also suppress B cell activation and the ensuing antibody production. It has been reported that nTregs kill B cells directly by secreting perforin and granzyme B, whereas iTregs inhibit B-cell activation through the secretion of IL-10 and TGF-β.

Site of action of Tregs

In the setting of autoimmune diseases, Tregs are activated in the draining lymph nodes to prevent priming and clonal expansion of autoreactive Teffs; they then migrate to the inflamed tissues, exerting their suppressive activity in the periphery.

In the setting of transplantation, Treg migration to the graft is required to prevent graft rejection. Early trafficking of Tregs to the graft prevents the exit of donor-derived DCs to the drained lymph nodes, decreasing thus the extent of alloimmune priming.

TREGS AND DIABETIC NEPHROPATHY

Diabetes is one of the major causes of ESRD. Type 1 diabetes (TID) has been described as a chronic autoimmune disease due to T-cell mediated destruction of pancreatic β-islets leading to insulin deficiency. Data from experimental studies indicate that Treg cells are involved in the pathogenesis of TID.

It is not clear whether the peripheral blood count of CD4+CD25+Foxp3 Tregs is altered in TID patients. Jailwala et al. reported that the frequency of Tregs in TID patients is not altered but that these cells have an increased sensitivity to apoptosis. Studies in nonobese diabetic (NOD) mice showed that depletion of CD4+CD25+ T-cells, leads to TID development, in addition, abolishment of the CD28 and ICOS co-stimulatory pathways, that are critical for Treg homeostasis and function, exacerbate TID. Also in NOD mice, TID progression is linked with a reduction in Treg number and suppressive activity in the inflamed pancreatic islets, together with a diminished IL-2 production by Teffs. In addition, Tregs may lose Foxp3 expression with concomitant loss of their suppressive activity during TID progression.

Although type 2 diabetes is considered to be a metabolic disorder with no autoimmune etiology, recently an adiposity-associated chronic inflammation process mediated by immune mediators has been proposed as an underlying mechanism of this disease. Interactions between metabolic disorders, hemodynamic changes, oxidative stress, inflammation and genetic predisposition, seem to contribute to the pathogenesis of diabetes and diabetic nephropathy. Interestingly, an increased expression of CD4+CD25+Foxp3 cells has been revealed in type 2 diabetic patients with micro and macroalbuminuria. Potential link between Tregs and disease progression. However, the relationship between CD4+CD25+Foxp3 Tregs and type-2 diabetic nephropathy is not well studied. In the db/db mouse with type 2 diabetes, CD4+CD25+Foxp3 Treg depletion with anti-CD25 monoclonal antibody, enhanced insulin resistance, albuminuria and glomerular hyperfiltration. Adoptive transfer of CD4+CD25+Foxp3 Tregs increased Foxp3 mRNA synthesis in the recipients and improved insulin sensitivity and type 2 diabetic nephropathy.

TREGS AND KIDNEY TRANSPLANTATION

Tregs in transplantation tolerance and acute rejection

A large body of evidence supports the notion that CD4+CD25+Foxp3+ Tregs play a fundamental role in the establishment and maintenance of operational tolerance.
Table 1 Regulatory cells in humans

| Cell               | Phenotype          | Properties                                      | Ref. |
|--------------------|--------------------|-------------------------------------------------|------|
| T-cells (Treg)     | CD4+CD25-          | Secreting mainly IL-10 and TGF-β; some           | [1-4,17,77-79] |
|                    | CD4+CD25+Fox3+     | secrete IL-35 or IFN-γ                           |      |
|                    | CD4+CD25+CD127+/lo | IFN-γ                                           |      |
|                    | CD4+CD45RO-        | Secrete mainly IL-10-10 but also                 | [80] |
|                    | CD8-               | TGF-β, IFN-γ, CCL4, downregulate APC or DC maturation; direct killing of CD4+ T-effs and APCs |      |
|                    | CD28-              | IL-10 and IL-4                                  |      |
|                    | CD8-CD28 (Fox3+)   | Secrete IL-10, TGF-β, IL-4                      | [83] |
| CTLA-4             | CD4+CD8+TCRαβ+     | Suppress antigen-specific T-cells; secrete mainly IFN-γ but also IL-4 | [82] |
|                    | TCRβ6-             | Secrete IL-10, TGF-β, IL-4                      | [83] |
| T-cells or monocytes| HLA-G              | Secrete IL-10, IL-35, TGF-β, soluble             | [84,85] |
| iNKT               | CD3+CD16+CD56+     | Can secrete IL-4 ± IL-4 ± IL-10 ± TGF-γ, direct killing of target cells | [86] |
| B-cells (Breg)     | CD19+/20+, CD80/86+| Secrete IL-10 and IL-35, induce Tregs, downregulate DC maturation | [87] |
|                    | CD40+, TLR4, mainly IgG and IgA BCR | | |
| tDC                | PD-L1/L2+, FasL     | Secrete IL-10 and TGF-β; downregulate T-eff activation | [88] |

APC: Antigen presenting cell; DC: Dendritic cell; BCR: B-cell receptor; tDC: Tolerogenic dendritic cells; iNKT: Natural killer T regulatory cells; TGF: Transforming growth factor; IL: Interleukin; IFN: Interferon; HLA-G: Human leukocyte antigen-G; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4.

To renal allografts

In animal models of transplantation, Tregs were present in tolerant allografts and were shown to migrate to the allograft tissue. It was also shown that Tregs, induced in vitro, in vivo or expanded ex vivo after alloantigen stimulation, promoted transplant tolerance to the allograft.

Salama et al. were the first to demonstrate the existence of antigen-specific Tregs capable of suppressing alloresponses to donor HLA peptides in human kidney transplant recipients. In accordance, data from renal liver and lung transplantation in humans showed a high number of circulating and intragraft Tregs in tolerant stable recipients. On the other hand, recruitment of Tregs into the graft, as part of an allogeneic inflammatory response, suggests a role for Tregs in immune-mediated graft injury.

Reports on the clinical and prognostic significance of Foxp3+ cell infiltrates in renal allograft recipients with acute rejection are contradictory. Muthukumar et al. reported that renal transplant patients with an acute rejection episode expressed high levels of Foxp3 mRNA in the urine, and that the lower levels of Foxp3 were associated with a poorer response to anti-rejection therapy, postulating that this could be a future non-invasive marker for the level of renal graft function. Bunnag et al. reported that Foxp3 expression in human kidney biopsies was linked to rejection and did not correlate with a favourable outcome. In accordance, data from studies that used Foxp3 analysis from graft biopsy cores, have demonstrated a higher Foxp3 expression in the allografts with acute rejection in comparison with stable renal allografts or with those displaying antibody-mediated rejection. It should be emphasized that these studies did not report any potential benefit of Foxp3-enriched infiltrate on renal allografts outcome, or even associated the level of in situ Foxp3 expression with tubulitis, higher scarifying scores and worse prognosis of renal allografts survival.

Contrary, in the context of lower graft inflammation such us borderline changes and subclinical episodes of acute rejection, it seems that Treg-enriched graft infiltrate has a protective role in interstitial inflammation and graft function. Data from protocol biopsies in recipients with episodes of subclinical cellular rejection, reported a correlation of low Foxp3/CD3 ratio with a poor graft function up to five years post-transplantation.

Tregs in chronic allograft nephropathy

The number of CD4+CD25+Foxp3+ Tregs usually decreases after transplantation. Renal transplant recipients with chronic rejection have a lower number of peripheral CD4+CD25+Foxp3+ Tregs compared to those with stable renal graft function. In accordance, Al-Wedaie et al. reported a decreased count of CD4+CD25+ Tregs in the blood of renal allograft recipients with chronic rejection.

A decreased synthesis of Foxp3 mRNA in renal recipients with chronic rejection has been reported in comparison to stable or operationally tolerant renal allograft recipients or healthy controls. On the other hand, an increased frequency of infiltrating Foxp3+ T-cells in renal grafts with chronic rejection and poor graft function has been reported. It can be hypothesized that higher numbers of Tregs reflect an effort to suppress the immune response at the site of inflammation.

Interestingly, Ashton-Chess et al. reported that the expression of Foxp3 both in blood and renal graft did not distinguish rejecting from non-rejecting renal recipients. The authors suggested that Foxp3 expression does not correlate with rejection but it depends on the time post-transplantation and the age of the patients.

An important issue that needs to be addressed is whether Tregs in renal allograft recipients have a normal suppressive capacity. Data from several studies on the development of chronic rejection have shown a quantitative defect of Tregs whereas data from other studies a functional deficit of Tregs. Given that...
immunosuppressive drugs can have detrimental effects on the number\(^2\) induction, function and survival of Tregs, the answer to this question is difficult because all the renal allograft recipients enrolled in these studies were on double or triple immunosuppressive regimens. Thus it could be assumed that the decreased number of Tregs or their functional deficit reported in recipients with chronic rejection was partially due to the effect of immunosuppression.

In addition, Tregs may contribute to chronic allograft nephropathy through new onset post-transplant diabetes, hypertension\(^2\) and hyperlipidemia\(^2\), but these hypotheses need to be explored in experimental models and in the clinic.

CONCLUSION

Regarding the entire spectrum of studies on chronic kidney disease and renal transplantation, Tregs are clearly implicated both in the pathogenesis of diabetic nephropathy and in the induction of transplant tolerance. Nevertheless, up to date, a relatively small number of clinical and experimental studies have explored the mechanism of Treg involvement in diabetic nephropathy. In addition, although a large body of evidence implicates Tregs in the immune mechanisms of acute and chronic rejection, their exact role remains unclear. The therapeutic potential of Tregs in kidney transplantation is promising but challenging for human patients. More studies are needed to elucidate the clinical significance and the therapeutic applications of Tregs and, also, of all the emerging types of regulatory and tolerogenic cells (Table 1) in kidney diseases and transplantation.

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