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The Effect of Chronic Kidney Disease on T Cell Alloimmunity

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Abstract

Purpose of review—Altered differentiation and activation of T cell subsets occur in patients with CKD, but the impact on graft rejection and protective immunity during transplantation are not fully understood.

Recent findings—Patients with CKD have decreased frequency of naïve T cells, accumulation of activated, terminally differentiated memory cells, and skewed regulatory versus T helper 17 ratio. Naïve and memory T cell subsets do not appear to improve following kidney transplantation. Retained thymic output is associated with acute rejection, while naïve lymphopenia and accumulation of CD8⁺T_{EMRA} cells correlate with long-term graft dysfunction. CD28^{null} memory cells accumulate during CKD and appear to confer protection against acute rejection under standard immunosuppression and possibly co-stimulation blockade. T cells bearing CD57 are also increased in patients with CKD and may underlie rejection during co-stimulation blockade.

Summary—The mechanisms by which CKD alters the differentiation and activation status of T cell subsets is poorly understood. Further research is also needed to understand which cell populations mediate rejection under various immunosuppressive regimens. To date, there is little use of animal models of organ failure in transplant immunology research. CKD mouse models may help identify novel pathways and targets to better control alloimmunity in post-transplant.

Keywords

chronic kidney disease; T cell; kidney transplant; rejection

INTRODUCTION

Chronic kidney disease (CKD) is life-long condition resulting in premature death due to the systemic complications that arise with the progressive loss of kidney function. Patients with end-stage renal disease (ESRD), at the extreme end of the CKD spectrum, have long been recognized to have signs of immune dysfunction evidenced by increased susceptibility to

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infections [1,2], increased risk of cancer [1,3], and impaired response to vaccination [4,5]. It has become increasingly recognized that CKD results in impaired interaction between the innate and adaptive arms of the immune system [6]. ESRD is widely considered to be a chronic state of oxidative stress [7] and inflammation which likely contributes to these alterations.

Alterations in T cells during ESRD may have implications for kidney transplant outcome. It has long been appreciated that prolonged wait time on dialysis is associated with increasing risk of death-censored renal allograft loss [8,9]. There is also evidence to suggest that increasing time on dialysis promotes accumulation of alloreactive T cells and the frequency of donor-reactivity on ELISPOT is strongly correlated with early acute rejection following kidney transplant [10,11]. Recent studies are beginning to provide new insight into the impact of specific T cell alterations on renal transplant outcomes. However, much remains to be understood in order to translate this knowledge into clinical practice for personalization of immunosuppression treatment to maximize allograft survival while minimizing consequences of excessive immunosuppression.

With advancements in multi-parameter flow cytometry, there have been a number of studies describing differences in specific T cell phenotypes among patients with CKD and ESRD. The potential for reversibility of these changes with improved renal function and reduced inflammation following kidney transplant [12] are starting to be explored. The full impact of these immune system disturbances on kidney transplant outcomes and on protective immunity during transplantation, however, are not fully understood.

Lymphopenia and loss of naïve T cells

T cell lymphopenia during renal failure has been appreciated for some time [13]. Data suggest that the global T cell lymphopenia is primarily due to selective loss of circulating naïve CD4⁺ and CD8⁺ T cells [14,15] (Figure 1) and central memory CD4⁺ T cells attributed to increased activation-induced apoptosis [8,14,16] and possibly decreased circulating interleukin 7 (IL-7) [15]. The number of naïve and central memory cells significantly correlates with serum urea, creatinine, and phosphorus levels indicating worsening T cell lymphopenia with increasing severity of renal dysfunction [14]. Furthermore, the dialysis procedure itself appears to exacerbate activation-induced apoptosis [14,16] and reduces proliferative capacity [17] of T cells. Thymic output, as measured by the frequency of CD31⁺ T cells (recent thymic emigrants) and detection of T-cell receptor excision circles (TREC), is also impaired in dialysis patients compared to similar-aged healthy individuals [18]. Remaining naïve T cells have higher frequency expression of the IL-2 receptor (CD25), the activation marker, CD69 [16], and inflammatory chemokine receptors, CXCR3 and CCR5 [15], suggesting an aberrant state of activation. Taken together, ESRD is associated with a T cell lymphopenia resulting from markedly reduced numbers of naïve cells likely due to a combination of cell loss via activation-induced apoptosis, reduced IL-7 homeostatic signals, and impaired thymic output. Remaining T cells appear to have an aberrant activation status.

It is becoming clear that despite restoration of kidney function and therefore decreased oxidative stress/inflammation [12], many of the T cell populations are not normalized

following kidney transplantation. A recent prospective, longitudinal study from the Netherlands suggests that naïve T cell counts and thymic output do not improve following kidney transplantation [19*]. However, interpretation of these findings is confounded by the use of immunosuppression following transplantation. For example, recent evidence suggests that induction therapy with antithymoglobulin (ATG) may impair thymic output up to 12 months post-transplant [20**] compared to basiliximab induction. A retrospective study from France found approximately 5% of patients had long-term CD4⁺ T-cell lymphopenia (absolute counts < 300/mm³) at 10 years following kidney transplantation which was associated with reduced thymic emigration [21*]. Interestingly, dialysis duration prior to transplant, but not the use of depletion induction agents or recipient age, was the only significant risk factor for long-term lymphopenia in this cohort. In summary, data reported to date suggests thymic output does not improve post-transplant in many patients. At this time, it is unclear whether these observations represent a permanent change in thymic function, stable imprinting in T cells themselves, alterations in bone marrow precursor cells, or an effect of standard immunosuppression (CNI, steroids, cell-cycle inhibitor) or depletion induction.

There is also some evidence that impaired thymic output correlates with renal allograft outcomes. Long-term T-cell lymphopenia was significantly and independently associated with an accelerated decline in renal allograft function, despite similar rate of biopsy-proven acute rejection and comparable immunosuppression with date-matched non-lymphopenic transplant recipients [21*]. Conversely, there is recent evidence to suggest that retained thymic output, measured by absolute or relative frequency of recent thymic emigrants (CD45RA+CD31+CD4⁺ T cells) is associated with increased risk for acute rejection following depletion induction [22*].

Accumulation of effector memory subsets

There is growing interest in identifying and understanding the role of pre-formed, allogenic cross-reactive memory cells in mediating transplant rejection. ESRD patients display increased frequency of circulating effector memory T cells, particularly of CD8⁺ T_{EMRA} cells which are negative for CD45RA and CCR7, in excess of that expected from normal aging [15,18]. We have also recently reported that children with CKD display similar skewing of T cell memory subsets [23*], despite the assumption that they should have limited antigenic experience and retained thymic function given their young age.

Furthermore, peripheral T cells isolated from ESRD patients have been shown to display markers of acute and chronic activation, such as HLA-DR [24], CD57 [18,23*], and CD69 [8,16] with increased frequency compared to similar-aged healthy individuals (Figure 1). Many of these activated cells appear in the effector memory subsets. For example, ancillary data from a clinical trial of Rituximab induction, suggests that T_{EMRA} population frequencies and counts remain stable up to 24 months post-transplant regardless of Rituximab induction [25*]. Similarly, CD8⁺T_{EMRA} cells remained elevated at 1-year post-transplant in the prospective study mentioned earlier by Meijers, et al [19*]. However, the functionality of the accumulated memory cells is less clear and may be illuminated by studies geared toward defining the subsets on the basis of their expression of co-stimulatory and co-inhibitory receptors (see below) in addition to memory status.

A recent study in the Netherlands found that patients that had not experienced biopsy-proven acute rejection within the first two years had higher pre-transplant frequencies of CD8⁺ T_{EMRA} frequencies than those that did experience rejection [26]. Furthermore, patients with high pre-transplant frequencies of CD8⁺ T_{EMRA} cells had increased rates of cancer during immunosuppression, suggesting a state of relative immune-senescence. A separate study found accumulation of CD8⁺ T_{EMRA} cells with cytokine expression profile (granzyme B⁺, Perforin^{hi}) suggestive of cytotoxic and effector function in patients with limited T-cell receptor (TCR) Vβ repertoire diversity detected at an average of 6 years post-transplant [27*]. These patients were also more likely to have long-term allograft dysfunction a median of 6 years following TCR typing, raising the possibility that terminally differentiated cells can contribute to chronic rejection.

Defining alloaggressive T cells in the context of CKD: Loss of CD28 and expression of CD57

The frequency of total memory cells alone is unlikely to be sufficient to predict the risk of transplant rejection or to help personalize immunosuppression regimens. Additional markers within terminally differentiated memory subsets of patients with ESRD have promise for improved prediction of rejection and long-term graft function. One marker of increasing interest is the loss of CD28 given its role in the co-stimulation pathways targeted by the latest immunosuppressive medication approved for kidney transplant, belatacept.

Several studies have described accumulation of CD4⁺CD28^{null} cells within T_{EMRA} subsets in ESRD patients [28,29,30]. We also found children with CKD [23*] have variable accumulation of CD28^{null} cells. Again, CD28^{null} counts (both CD4⁺ and CD8⁺) do not appear to improve and remained elevated compared to healthy peers at 12-months post-transplant [19*] in the absence of induction therapy.

There are several studies suggesting accumulation of CD28^{null} cells results in immune-senescence and lower risk of rejection. For example, CD28^{null} populations within the CD4⁺ subset are expanded in kidney transplant recipients on CNI immunosuppression with long graft survival [31]. Furthermore, patients with the highest tertile of pre-transplant CD8⁺CD28^{null} frequencies have recently been shown to have the lowest rates of acute-rejection at 1 year following basiliximab induction and standard triple-therapy immunosuppression, even after taking into account the number of HLA mismatches [26]. However, increased frequency of CD8⁺T_{EMRA} CD27⁻CD28⁻ cells detected in stable transplant recipients was associated with a 2-fold increased risk for long-term graft dysfunction (up to 15 years of follow-up from time of phenotyping) [27*] (Figure 1). These cells expressed high levels of perforin, granzyme B, and T-bet. This phenotype (CD8⁺CD45RA⁺CCR7⁻CD27⁻CD28⁻) also correlated with frequencies of CD57⁺ cells and the ability of CD8⁺ T cells to secrete TNFα and IFNγ *in vitro*. Patients in this study underwent T cell phenotyping on average 6 years post-transplant during stable graft function, raising the question whether pre-transplant frequencies of these populations may also predict long-term graft dysfunction or possible chronic rejection.

Effector memory cells, which accumulate in patients with renal failure, appear to be inherently resistant to co-stimulation blockade (e.g. belatacept). Interestingly, one possible

explanation is that TEM cells down-regulate CD28 expression during allo-stimulation in the presence of CTLA4-Ig [32*]. We have similar unpublished observations that PBMCs isolated from patients pre-transplant that subsequently experienced rejection during belatacept treatment exhibited larger increased frequency of CD4⁺CD28^{null} cells induced during ex vivo stimulation with PMA/Ionomycin (Ford, unpublished). Furthermore, we have recently published evidence that low pre-transplant frequency of CD28^{null} cells within the CD4⁺T_{EM} subset (similar to healthy individuals) was associated with early rejection during belatacept immunosuppression at our center [33*].

CD57, which is often expressed in a subset of CD28^{null} cells, has been another marker of interest to identify pre-existing memory cell populations that can mediate allograft rejection under various immunosuppressive regimens. There is less information about the frequency of CD57⁺ cells in CKD and ESRD patients. However, increasing frequency of CD28⁻CD57⁺CD4⁺ T cells at the time of transplant has been associated with acute rejection in patients receiving ATG induction, but did not predict rejection in patients receiving basiliximab induction [20**]. There is also a recent evidence that CD57⁺CD4⁺ cells retain cytolytic capacity despite expression of markers associated with terminal differentiation, and may contribute to rejection under belatacept treatment [34**].

Alterations in regulatory and Th17 T cells during CKD

In addition to the observed increase in frequency and activation status of memory T cells, CKD has been shown to be associated with alterations in both T helper 17 (Th17) and regulatory T cell populations (Figure 1). These two CD4⁺ T cell subsets possess distinct functions (Th17 are inflammatory while Treg are suppressive), but seminal studies have revealed that their differentiation pathways are related: the presence of TGF-beta alone results in Treg polarization, while TGF-beta in the presence of IL-6 results in Th17 polarization. Further, Treg and Th17 cells are capable of transdifferentiating into one another. Intriguingly, in one study patients with CKD/ESRD were shown to have decreased CD4⁺CD25⁺ Treg cells with impaired regulator function [35], and in another dialysis patients were noted to possess an increased effector T cell: regulatory T cell ratio [36]. Furthermore, low pre-transplant frequencies of suppressive Treg populations characterized as CD4⁺CD25⁺CD127^{lo} bearing TNFR2 has been associated with delayed graft function [37*].

However, all of these studies were limited by the fact that they did not include FOXP3 as a marker of Treg populations and by the fact that they were small, single center studies that used different staining definitions to identify Treg populations. More recently, however, a multi-center study in Europe performed a longitudinal analysis of Treg populations in 75 kidney transplant recipients found decreased absolute number and relative frequencies of both natural Tregs (CD4⁺CD25^{high}CD127^{low}FOXP3⁺) and activated Tregs (CD4⁺CD25^{high}CD62L⁺CD45RO⁺) following transplantation [38*]. Patients experiencing acute rejection within the first year of transplant (n=6) had higher pre-transplant frequency of activated regulatory T cells. Though a limited sample size, this study raises interesting questions about Treg subset frequencies in the prediction of post-transplant outcomes that deserves further investigation.

In contrast to the generally observed decrease in FOXP3⁺ Treg in CKD patients, most studies have observed that CKD results in an increase in Th17 cells. Specifically, one study noted an increase in IL-17-secreting CD4⁺ effector memory T cells in patients with ESRD [39]. A separate study noted increased Th17 differentiation in chronic hemodialysis CKD patients, and interestingly noted that this increase in Th17 frequency correlated with higher phosphate and iPTH levels [40], suggesting that the presence of these metabolites during CKD may promote Th17 differentiation in these patients.

Mechanisms by which CKD induce immunologic derangements

The mechanisms by which CKD results in altered differentiation and activation status of many T cell subsets is poorly understood. One hypothesis is that alterations in the Vitamin D/ Ca²⁺/ phosphorous axis directly impacts T cell differentiation [41] (Figure 2). Evidence that exists to support this idea include the fact that the number of naïve T cells significantly correlated with phosphorus levels, indicating worsening T cell lymphopenia with increasing severity of hyperparathyroidism [14], though no direct relationship with PTH has been born out, and the fact that Vitamin D deficiency at time of kidney transplant was an independent risk factor for acute cellular rejection in series of 351 adult kidney transplant recipients [42]. Furthermore, a randomized controlled trial of Vitamin D3 supplementation to normalize vitamin D stores in hemodialysis patients resulted in decreased time-dependent increase in cellular alloimmunity as measured by ELISPOT, but without changes in T cell memory subsets [43*]. Also in support of the idea that vitamin D deficiency in CKD patients could underlie altered alloimmunity are *in vitro* studies suggesting that activated vitamin D [1,25(OH)₂D₃] enhances the suppressive effect of abatacept on T cell proliferation and cytokine production and can reduce resistance to co-stimulation blockade during strong TCR stimulus [44*], suggesting that CKD-related derangements in the vitamin D-PTH axis may contribute co-stimulation blockade resistance.

A separate, non-mutually exclusive hypothesis to explain the altered immunity in CKD patients is centered on the role of erythropoietin on the immune system (Figure 2). Recent studies have revealed that, compellingly, erythropoietin receptor signaling inhibits human T cell proliferation and cytokine secretion and decreased allogeneic CD4⁺ T cell proliferation during *in vitro* MLR in a dose-dependent manner [45*]. In a separate analysis, erythropoietin-induced T cell suppression was found to function indirectly through its effect on macrophages[46*]. Because EPO levels are significantly decreased during CKD, this could result in dysregulated immune responses to infections and a transplanted organ. In support of this hypothesis, an open-label, multicenter, randomized controlled trial of epoetin-beta treatment in transplant recipients with anemia (Hgb <11.5), demonstrated improved death-censored graft survival and graft function for those patients treated for normalization of anemia (Hgb >13) [47].

CONCLUSION

In summary, CKD is associated with decreasing naïve T cell populations with an aberrant state of activation, accumulation of terminally-differentiated memory cells some which have lost the expression of CD28 or gained CD57, and an imbalance between suppressive

regulatory T cells in and T helper 17 cells (Figure 1). With improving recognition that certain T cell populations present prior to transplant impart increased risk for allograft rejection or dysfunction, one area that needs further exploration is to understand mechanisms underlying accumulation of these populations during CKD and to develop therapeutic approaches to mitigate this risk. In addition, further research is needed to understand how the aforementioned cell populations mediate rejection under various immunosuppressive regimens. In an ideal world, comprehensive immune-phenotyping prior to transplant can identify an individual's optimal regimen to prevent rejection and subsequent monitoring can identify patients at risk for complications (rejection, infection, cancer) prior to being symptomatic. In order to develop these prognostic tools and personalized immunotherapy, we must first better understand the mechanisms by which a patient's pre-existing immune disturbances break through immunosuppression to reject an allograft. While studies of human biology can identify novel targets via correlation, confirming causation in animal models using young, naïve animals without organ failure are unlikely to recapitulate the critical components of the human condition pre- and post-transplant. To date, there is little use of animal models of organ failure in transplant immunology research. We posit that the use of CKD mouse models will illuminate new pathways and targets to better control alloimmunity in CKD patients following transplantation.

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Key points: (3–5 bullet points that summarize your article)

- Patients with renal failure have signs of immune dysfunction with increased risk for infection, cancer, and impaired vaccine response
- The composition of T cell memory subsets and activation status are altered during chronic kidney disease and in many cases appear to mimic immunologic changes associated with aging
- Patients with CKD exhibit variable accumulation of memory T cell subsets and CD28^{null} T cells
- More data are needed describing longitudinal changes in T cell subset frequencies and function during the entire spectrum of CKD and following transplant, the mechanisms underlying these
- Future studies should be aimed at understanding whether uremia-induced changes in T cell function are reversible, how they affect transplant outcomes, and the mechanisms underlying these disturbances.

T cell alterations in CKD

Figure 1. CKD-associated T cell disturbances

Patients with CKD have been characterized to have variable loss of naïve T cell numbers with remaining naïve T cells bearing markers of activation, accumulation of memory T cells, including terminally-differentiated T_{EMRA} cells with loss of CD28 and/or expression of CD57, and finally a relative loss of suppressive regulatory T cells (Treg) with a gain of T helper 17 (T_H17) cells. These particular T cell populations have been associated with transplant outcomes.

Chronic Kidney Disease (CKD)

Metabolic Derangements

Glomerular/Tubular Dysfunction

Figure 2. Uremia-induced immune dysfunction

Chronic kidney disease results in a pro-inflammatory “uremic milieu” which is postulated to cause immune dysfunction. Metabolic derangements include iron deficiency and/or erythropoietin deficiency or resistance, alterations in the calcium-phosphorus-vitamin D-PTH axis, and activation of the renin-angiotensin system and some of these have been shown to directly impact T cells. Glomerular and tubular dysfunction results in accumulation of cytokines and uremic toxins can promote oxidative stress and inflammation. EPO, erythropoietin; Vit D, vitamin D; PTH, parathyroid hormone; Phos, phosphate. Figure is adapted from Cohen, G. and Hörl W. H. Immune Dysfunction in Uremia—An Update; *Toxins* 2012; 4(11): 962–90 [48].