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Significance of Th17 Immunity in Transplantation

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Abstract

Purpose of Review—The aim of this review is to provide an overview of significance of Th17 immunity in acute, chronic and antibody mediated allograft rejection. The role of Th17 immunity in development of *de novo* autoimmunity following transplantation is outlined. It will also consider the impact of Th17 immunity on transplantation tolerance. Potential therapies to target Th17 immunity are discussed.

Recent Findings—IL-17 is produced by a wide variety of immune and non-immune cells in response to injury. IL-17 production by tubular epithelial cells in response to complement activation in acute antibody-mediated rejection may perpetuate immune injury. Th17 dependent *de novo* autoimmunity contributes to chronic allograft rejection. Targeting IL-17 not only inhibits Th17 immunity but also attenuates Th1 immunity by affecting the initial recruitment of immune cells to sites of inflammation and modulates innate and adaptive immune responses that ultimately lead to tissue destruction.

Summary—Th17 immunity is now beginning to be appreciated as a set of responses mediated not only by CD4 Th17 cells but a variety of immune cells and a plethora of cytokines that collaborate to mediate immune pathology, including transplant rejection. Development and contribution of *de novo* autoimmunity to chronic rejection is increasingly appreciated. The developmental plasticity of Tregs and Th17 cells is a major hurdle to Treg-based cellular therapies for transplantation. Several biologics targeting Th17 immunity are under evaluation for autoimmune disease. It remains to be determined if these can be used in transplantation to improve outcomes.

Keywords

IL-17; acute allograft rejection; chronic allograft rejection; antibody-mediated rejection; transplantation tolerance

INTRODUCTION

T cells have long been known to play a central role in mediating allograft rejection(1, 2). CD4 T helper cells play a critical role in orchestrating the alloimmune response. Classically, naïve CD4 T cells, upon stimulation, were believed to undergo dichotomous differentiation into T helper-1 (Th1) or T helper-2 (Th2) cell lineages with their own set of cytokines and functional properties(3). In the year 2005, a distinct lineage of CD4 T helper cells, termed Th17 cells was described as playing an important role in inflammation(4, 5). However, in

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the last decade, with the discovery of induced regulatory T cells (iTregs), description of the novel T helper-17 (Th17) cells and the plasticity among these subsets has sparked debate on the accuracy of defining CD4 T cell subsets as fixed T cell lineages(6–8). Nevertheless, it is clear that many diseases manifest a particular type of immune response, where the predominant cell types are either of Th1, Th2 or Th17 type. Th17 immunity is characterized by a set of immune responses including CD4 Th17 cells producing IL-17A, IL-17F, IL-21 and IL-22, and release of a host of proinflammatory cytokines (IL-1 β , IL-6, IL-8, TNF α , IL-23, G-CSF, GM-CSF)(9), and chemokines (CXCL1, CXCL2, CCL2, CCL20)(10) by a variety of tissues and cell types(11). This leads to recruitment of other inflammatory cells including neutrophils and monocytes to the site of inflammation(12–14). In addition to CD4 Th17 cells, CD8 T cells, $\gamma\delta$ T cells, neutrophils, macrophages and a variety of epithelial and parenchymal cells produce IL-17 family of cytokines.

Th17 Immunity in Acute Allograft Rejection

Well before Th17 cells were described, several investigators suggested a possible role of IL-17 in acute allograft rejection. In the very first report in transplantation, IL-17 transcripts were solely, but not reliably, observed in renal transplant biopsy specimens from patients experiencing a rejection(15). Next, IL-17 producing graft-infiltrating T cells were detected in renal allografts undergoing rejection. Further, IL-17 induced primary human proximal tubular epithelial cells to secrete IL-6, IL-8 and CCL2 and production of C3 *in vitro*(16). In keeping with this, IL-17 mRNA expression preceded that of IL-6 and IL-8 in rejecting rat renal allografts suggesting that initial IL-17 production early after transplantation could be playing important part in initiating innate immune responses and ischemia reperfusion injury (IRI). Furthermore, IL-17 mRNA-positive mononuclear cells (MNC) were consistently seen in the urinary sediment of kidney transplant recipients with biopsy appearance of early rejection, compared to none from recipients with urinary tract infection or with normal biopsy(17). More recently, increased CD4⁺IL-17⁺ cells have been described in renal biopsies from patients undergoing acute T cell mediated rejection(18). Increased serum IL-6, IL-17 and IL-23 levels along with increased expression of IL-6, IL-8, IL-17, TGF β and myeloperoxidase in the grafts have been reported in acute rejection of liver and kidney allografts(19–21). In acute cardiac allograft rejection, IL-17 is produced by neutrophils, CD4 and CD8 T cells and the frequency of Th17 cells in recipients experiencing acute allograft rejection is increased whilst the ratio of Th17/Treg decreases over time, suggesting that a disequilibrium of Th17/Treg balance toward a Th17 inflammatory response may be responsible for progression of acute rejection(22). Interestingly, there was minimal IL-17 mRNA expression in the wild-type allografts transplanted into IL-17 deficient recipients suggesting that the main source of intra-graft IL-17 are the infiltrating cells of the recipient(23). IL-17 deficiency in the recipient was associated with reduced intra-graft CXCL1 and CCL2 leading to reduced infiltration of leukocytes in the allograft early after transplantation. Notably, IFN γ production was also reduced in IL-17 deficient recipients. However, this did not translate into prolonged graft survival except in the case where CD8 T cells were depleted and rejection was mediated by CD4 T cells. Adoptively transferred alloantigen-primed CD4 T cell recruitment to the allograft was also reduced in IL-17 deficient recipients. In keeping with this, IL-17 deficiency was associated with prolonged graft survival and reduced infiltration of allografts, whilst a primary mixed leukocyte reaction did not show difference in alloantigen-specific proliferative response(24). Thus, IL-17 in the early phase of the alloimmune response appears to primarily facilitate the recruitment of leukocytes into the graft and contribute to acute rejection.

Th17 Immunity in Chronic Allograft Rejection

Our studies have highlighted the role of IL-17 in mediating accelerated rejection in a model of chronic allograft vasculopathy (CAV) in the absence of Th1 immunity(25). In this model,

T-bet deficient CD4 Th17 cells were the primary mediators of rejection. Neutralization of IL-17 led to prolongation of graft survival. These data were confirmed in IL-17 deficient recipients with intact Th1/Th2 immunity(26). In a model of TGF β -signaling dependent fibrosis and chronic rejection, IL-17 was critical for development of allograft fibrosis(27). In lung transplantation, IL-17A mRNA was increased in the spleens of recipients with obliterative bronchiolitis (OB) whilst IL-10 mRNA was increased in recipients without OB(28). In patients with kidney transplant failure, increased number of Th17 cells within the explanted kidney allografts correlated with faster progression of chronic rejection. Interestingly, the increased infiltration of Th17 cells was associated with increased IL-21 and activation-induced cytidine deaminase (AID) expression(29). AID is the key enzyme that controls Ig class switching and somatic hypermutation(30), suggesting that the deleterious effects of Th17 cells could also be mediated by their production of IL-21, a cytokine able to promote intra-graft lymphoid neogenesis and support the development of humoral immune responses contributing to chronic rejection. In another study, an increased IL-17⁺ total cell count in the renal transplant biopsies was predictive of late graft dysfunction, independent of time of biopsy after transplantation and C4d positivity. Thus, IL-17 immunostaining of renal transplant biopsies could serve as a surrogate marker for chronic rejection or worse renal allograft outcome(31). However, prospective studies are needed to validate the predictive value of intra-graft IL-17⁺ infiltrates.

Alloimmunity Induced Th17 Autoimmunity and Chronic Allograft Rejection

Development and contribution of *de novo* autoimmunity to chronic rejection is increasingly appreciated(32). Burlingham and colleagues in a prospective study of lung transplant recipients demonstrated that strong collagen V (Col-V)-specific responses were associated with increased incidence and severity of bronchiolitis obliterans syndrome (BOS)(33). The Col-V-specific responses were dependent on both CD4 T cells and monocytes and required IL-17, TNF α and IL-1 β . In another study, Abs to self-antigens K- α 1 tubulin (K- α 1T) and Col-V correlated strongly with development of BOS(34). PBMCs from lung transplant recipients with BOS compared to those without BOS contain lower number of IL-10 and higher number of IL-17 and IFN γ producing cells in response to these self-antigens. Binding of anti-K- α 1T Abs to airway epithelial cells leads to upregulation of transcription factors (TCF5 and c-Myc), cell cycle signaling, increased expression of fibrogenic growth factors and fibroproliferation(35). In another model of chronic rejection where anti-MHC class I Abs instilled intrabronchially into native lungs lead to changes similar to chronic rejection, anti-IL-17 therapy led to reduction of autoantibodies and lesions of chronic rejection(36). Similarly, heart transplant recipients with CAV demonstrate increased frequency of IL-17 and decreased frequency of IL-10 producing CD4 T cells specific to myosin, vimentin, Col-V and K- α 1T(37, 38). Anti-vimentin Abs are also reported in chronic kidney transplant rejection(39). Interestingly, development of DSA preceded the development of Abs to self-antigens which in-turn appeared prior to BOS and persisted when DSA were undetectable(34). These data suggest that epitope spreading is likely responsible for emergence of self-antigens as targets for autoimmune responses after transplantation.

Th17 Immunity in Antibody Mediated Rejection

IL-17 deficient mice exhibit impaired T-dependent antibody production(40). Th17 cells can function as B-cell helpers in that they not only induce a strong proliferative response of B cells *in vitro* but also induce germinal center formation and trigger antibody production with class switch recombination *in vivo*(41, 42). Further, IL-17 alone or in combination with B cell-activating factor control the survival and proliferation of human B cells and their differentiation into immunoglobulin-secreting cells. This effect was mediated mainly through the nuclear factor- κ B-regulated transcription factor Twist-1(43). In line with these

studies, B cell nodular aggregates were found in the interstitium of chronically rejected kidneys and at the center of these aggregates, a core of B cells expressed AID, suggesting that these nodules were functional intra-graft germinal centers(29). Interestingly, immunofluorescence staining for the membrane attack complex (C5b9), was principally seen in the failed grafts with high levels of Th17 cell infiltration. More recently, IL-17 expression by tubular epithelial cells in renal transplant recipients with acute antibody-mediated rejection (ABMR) has been reported(18). In cultured proximal tubular cells, C3a induced IL-17 gene and protein expression suggesting that tubular cells represent a significant source of IL-17 in ABMR in response to complement activation. These data reveal an intriguing relationship between Th17 immunity and B cell responses and warrant further exploration to develop novel therapies for ABMR.

Th17 Immunity, Tregs and Transplantation Tolerance

Tregs and Th17 cells share a differentiation pathway involving TGF β with IL-6 serving as a switch favoring Th17 differentiation. IL-17 deficiency was associated with reduced IL-6 level in the allograft and reduced IL-6 production *in vitro* by non-T/B cells in response to IL-17, IL-1 β and TNF α . Consequently, the proportion of CD4⁺CD25⁺Foxp3⁺ Tregs was increased in the allografts from IL-17-deficient recipients with prolonged survival(24). Further, TLR9 signaling by exogenous CpG at the time of transplantation abrogates co-stimulation blockade induced tolerance by inhibiting regulatory T cells and promoting Th1 and Th17 type immune responses(44). Thus, proinflammatory signals at the time of transplantation can change the type of the effector immune response. The identification and characterization of Tregs that control alloimmune responses has opened up opportunities to induce tolerance by Treg cell therapy(45). However, the disquieting prospect of Treg conversion to Th17 cells has tempered enthusiasm for such an approach(46–50). Direct evidence for such a concern in transplantation is provided by a study where Tregs adoptively co-transferred with minor alloantigen-specific T cells converted to Th17 cells *in vivo* and promoted neutrophil-mediated rejection of skin allografts(51). On the other hand, there is evidence that such IL-17-producing human peripheral regulatory T cells retain suppressive function(52). Further, although Th17 cells in autoimmune settings may be less susceptible to suppression by Tregs(53, 54), Th17-mediated acute rejection after lung transplantation can be controlled by CD4⁺ col(V)-specific regulatory T cells(55). However, in a corneal transplant model, paradoxically, IL-17A was noted to be essential for CD4⁺CD25⁺ Tregs to mediate a contact-dependent suppression and survival of corneal allografts(56). If these data are confirmed, this establishes a new paradigm whereby interplay between Tregs and Th17 cells is necessary for induction of tolerance.

Therapy Against Th17 Alloimmunity

Direct neutralization of IL-17—Blocking the action of IL-17 with soluble IL-17 receptor (R):Fc fusion protein inhibited alloantigen-induced T cell proliferation and prevented maturation of DCs *in vitro* and prolonged graft survival in a model of acute cardiac allograft rejection(57) and inhibited MNC infiltration in the intima and media with preservation of endothelium in an aortic allograft model(58). Local expression of soluble IL-17 receptor-immunoglobulin (IL-17R-Ig), by gene targeting, attenuated intra-graft cytokine mRNA expression and leukocyte infiltration in rat cardiac allografts, thereby mediating prolonged graft survival(59). These results suggest that IL-17R-Ig may act by down-regulating early-phase cytokines such as TNF α and IL-1 β induced by IRI. Neutralizing IL-17 with anti-IL-17 mAb, upregulated systemic IL-10, reduced acute rejection and prevented OB in a minor histocompatibility antigen incompatible lung transplant model(28) and inhibited corneal allograft rejection(60).

Novel approaches to target Th17 Immunity—IL-23, which is upstream of the IL-17 effector pathway and important in stabilization of Th17 differentiation, would be an ideal target for ameliorating Th17 mediated pathology(61). There have been numerous studies targeting IL-23 for autoimmune conditions(62) but only one to-date in a model of OB in tracheal transplantation with protection from development of chronic OB(63). Treatment with IL-12/23p40 antibody has been tried and it attenuates acute cardiac allograft rejection by reducing infiltration of grafts by inflammatory cells and by inhibiting allospecific production of IFN γ and IL-17 by splenocytes(64).

Increased T-bet and IL-17 protein expression was seen in renal allograft biopsies from recipients experiencing delayed graft function which is mostly seen in cases with increased cold-ischemia time(65). In keeping with this, high mobility group box-1 (HMGB1), an innate alarmin released in local tissue inflammation after IRI was noted to promote the development of alloreactive Th17 cells by inducing the secretion of IL-6 by DCs. Neutralization of HMGB1 decreased splenic alloreactive Th17 cells and IFN γ -producing CD8 T cells in the recipients, leading to less infiltration of neutrophils along with lower IL-6 and IL-17 expression levels in the grafts as well as prolongation of cardiac allograft survival(66).

We have used a Th17-biased model of allograft tolerance resistance to study the impact of targeting a T cell co-stimulatory pathway, and demonstrated that targeting T cell Ig and mucin domain-1 (Tim-1) with anti-Tim-1 overcomes this resistance by specifically inhibiting the pathogenic IL-17-producing CD8 T17 cells(67).

Similarly, CD28 and ICOS signaling appears to be important for Th17 differentiation(5, 68). However, CTL4Ig enhanced Th17 differentiation *in vitro*(69). These unexpected results are in line with recent studies showing higher incidence of acute rejection in patients treated with more intense regimen of belatacept in renal transplantation(70). Similarly, ICOS signaling may be important for Treg function. Therefore caution should be exercised in targeting the CD28/B7 and ICOS pathways for prophylaxis against Th17 immunity and transplant rejection.

Immunosuppressive regimens and Th17 Immunity—Corticosteroids inhibit production of a wide variety of cytokines including IFN γ , IL-4 and IL-17(71). Th17 responses could be effectively suppressed with glucocorticoids in patients with giant cell arteritis(72). With regards to calcineurin inhibitors (CNIs - Cyclosporine and Tacrolimus), suppression of IL-17 production by PBMCs in the presence of CNIs is not observed consistently(71, 73–75). On the other hand, mycophenolic acid (MPA) inhibits polarization of human CD4 T cells into Th17 cells *in vitro*(76) and although both MPA and tacrolimus (TAC) inhibit Th17 and Th1 responses upon T cell activation, MPA exerted a stronger inhibitory effect on IL-17 production than TAC(77). In keeping with this, renal transplant recipients treated with MPA in combination with minimized dose of TAC tended to have lower circulating IL-17 levels than patients treated with TAC alone given at conventional dose. Sirolimus (SRL) has been shown to inhibit IL-17 production and increase TGF β -induced Treg generation(78). In line with these studies, renal transplant recipients treated with alemtuzumab induction and conversion to SRL monotherapy 6 months after transplantation followed by MPA withdrawal at 12 months had higher numbers of Th17 and Treg cells at 3 years compared to those who had to be put back on MPA in addition to SRL(79). These Tregs could suppress the Th17 cells, however, Treg-mediated suppression of IFN γ production was much more effective than inhibition of IL-17A production.

CONCLUSION

The literature reviewed here indicates that Th17 immunity is associated with and contributes to all forms of allograft rejection including acute, chronic and antibody-mediated rejection. Th17 immunity however is not apparent prominently as a feature of unmodified alloimmune response, where Th1 immunity generally predominates. The impact of IL-17 appears to stem from its capacity to initiate an immune response, by recruitment of immune cells to sites of injury, maturation of antigen presenting cells, T helper differentiation and ultimately shaping the type of alloimmune response that prevails which may include a combined Th17/Th1 type response. The development and contribution of *de novo* autoimmunity to chronic rejection following transplantation is increasingly appreciated. Th17 immunity appears to play an important role in this as seen in primary autoimmune diseases. The developmental relationship between Th17 cells and Tregs mandates careful evaluation of Treg plasticity in Treg cell therapy regimens for transplantation tolerance. Continued work is required to further characterize the role of Th17 immunity in transplantation and development of novel strategies to target Th17 immunity and prevent adverse transplant outcomes.

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Abbreviations

IRI	ischemia reperfusion injury
MNC	Mononuclear cells
CAV	chronic allograft vasculopathy
OB	obliterative bronchiolitis
AID	activation-induced cytidine deaminase
BOS	bronchiolitis obliterans syndrome
DSA	donor-specific antibody
ABMR	antibody-mediated rejection
HMGB1	high mobility group box-1
Tim-1	T cell Ig and mucin domain-1
MPA	mycophenolic acid
TAC	tacrolimus
SRL	sirolimus

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KEY POINTS

- Th17 immunity is characterized by a set of immune responses, including secretion of IL-17 family of cytokines, IL-21, IL-22, IL-23 and chemokines that collectively mediate immune pathology.
- Th17 immunity contributes to allograft rejection by recruitment of immune cells to sites of inflammation and maturation of antigen presenting cells.
- Th17 immunity is particularly likely to emerge when other types of immune responses are effectively suppressed by conventional immunosuppression.
- Tregs may convert to Th17 cells in inflammatory environment and as such limit the utility of Treg cellular therapies that do not address prevention of such conversion.