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Th17 Cells and Transplant Acceptance¹

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Abstract

The discovery of Th17 cells has revealed a novel pathway of T cell maturation. As with Th1 and Th2 lineages, Th17 cells promote graft pathology. However, a growing body of evidence indicates that Th17 cells may exhibit resistance to current methods of immunosuppression. Identification of this lineage provides an additional and challenging target for promoting graft acceptance.

Keywords

Th17; Transplantation; Tolerance

Introduction

CD4⁺ and CD8⁺ T cells can function as helper subsets, polarizing to produce select profiles of cytokines and resulting in graft damage. The Th1/Th2 paradigm (1) has been studied extensively in the context of transplantation yet the role of Th1/Th2 polarization in determining allograft acceptance or rejection remains controversial (2). More recently, the two-lineage model has been expanded to include a subset of regulatory T cells (Treg), follicular T helper cells (Tfh), Th22 cells, and Th17 cells (reviewed in (3, 4)). Whether these lineages represent stable phenotypes (3) or are malleable is an open question. Indeed, recent evidence suggests that while Th2 cells are more limited in their plasticity, Th1, Th17 and Treg cells have an increasingly greater potential for change (3). The discovery of these subsequent lineages and their potential flexibility has added an additional layer of complexity to identifying effector mechanisms of graft rejection.

The induction of Th17 cells, defined as CD4⁺ or CD8⁺ cells producing IL-17 (5), is highly dependent upon signals from cytokines produced by other T cells and dendritic cells. The cytokines TGF β and IL-6 induce the signature Th17 transcription factor, ROR γ T, resulting in IL-17 production (6). The Th17 response is propagated by the cytokines IL-23 and IL-21 (7, 8), and IL-17 production is antagonized by the Th1 transcription factor T-bet (9, 10) and the cytokines IFN γ (11), IL-4 (11), IL-2 (12). CD8⁺ Th17 cells may also be inhibited by the CXCR3-binding chemokines that can costimulate Th1 responses to alloantigen (13).

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Th17 cells are unique in that T cell receptor (TCR) cross-linking rapidly induces IL-17 secretion and this secretion is minimally enhanced by engagement of traditional costimulatory molecules (i.e. CD28, ICOS, 4-1BB, and CD40L) (14, 15). Indeed, IL-17 production by CD8⁺ T cells occurs independently of CD40-CD40L costimulation (10). As an example of lineage plasticity, it should be noted that Tim-1 costimulation can “de-program” CD4⁺Foxp3⁺ regulatory cells resulting in proliferation and Th17 differentiation (16). While the role of costimulation in Th17 differentiation warrants further study, *in vitro* differentiated CD4⁺ Th17 cells have been shown to express many costimulatory and inhibitory molecules (17).

Implication of Th17 in rejection

As is the case with other chronic inflammatory diseases (6, 11, 18–20), Th17 have also been associated with allograft rejection (reviewed in (18, 21)). In clinical transplantation, IL-23 and IL-17 serum levels are elevated during acute hepatic rejection (22), and IL-17 production is implicated in graft versus host disease (23). IL-17 is also detected in the bronchoalveolar lavages of lung transplant patients with acute rejection episodes (24) and the urine of patients undergoing subclinical renal rejection (25). In addition, chronic rejection in lung transplantation correlates with the development of PBMC IL-17 responses to collagen V, a normally cryptic fibrillar collagen (26).

Th17 cells have also been implicated in acute and chronic rejection in animal models of transplantation. In rat lung transplantation, ischemia/reperfusion injury can locally release typically cryptic collagen V fragments and these fragments result in T cell priming and graft pathology (27). This collagen V reactivity is associated with elevated levels of IL-17 and IL-23 within lung isografts (28) and can be controlled by transfer of CD4⁺ T cells from collagen V tolerant rats (29). Antonysamy et al. reported that IL-17 promoted cardiac allograft rejection in mice via inducing maturation, antigen presentation, and costimulatory capabilities of dendritic cells (30). In a mouse model of human artery rejection, IL-1 α from endothelial cells induced CD4⁺ T cell production of IL-17, resulting in the recruitment of CCR6⁺ T cells to the graft and graft pathology (31). Further, IL-17 neutralization in mice can inhibit acute, but not chronic, vascular rejection (32). In addition, IL-17 producing CD4⁺ cells acutely reject class II MHC mismatched cardiac allografts in mice deficient in the Th1 transcription factor T-bet (33, 34).

In contrast to other lineages, pathologic Th17 cells are resistant to CD40-CD40L costimulatory blockade. In the absence of T-bet, IL-17 produced by CD8⁺ T cells is necessary for CD40-CD40L costimulatory blockade resistant allograft rejection and intragraft IL-17 is readily detectable (10). Only when CD8⁺ T cells are depleted, or following IL-17 or IL-6 neutralization, does CD40-CD40L costimulatory blockade result in protection of the graft (10). Similarly, TLR9 stimulation can overcome the graft-protective effects of CD40-CD40L costimulatory blockade (35) by inducing IL-17 upregulation (36). In this model, neutralizing IL-6 and IL-17 again results in graft acceptance (36). Whether the Th17 response in graft rejection is a default response, a contribution to graft pathology, or an alternative response when other pathways are inhibited remains to be elucidated.

Regarding chronic rejection, Faust et al. have reported that fibrosis is inhibited in the absence of TGF β receptor signaling and IL-17 expression (37). As both IL-6 and IL-17 induce collagen production (38–40), IL-17 may also serve as a target for inhibiting chronic graft rejection.

Variable resistance of Th17 to immunosuppression

Early graft loss due to acute rejection was greatly reduced following the advent of immunosuppressive therapies. However, despite immunosuppression, episodes of acute rejection can predispose patients to later allograft rejection (reviewed in (41)) and recent research has revealed inconsistent Th17 cell resistance to these therapies. The IL-17 promoter is NFAT-dependent (42), and the calcineurin inhibitor cyclosporine A (CsA) can inhibit IL-17 transcription. *In vitro*, CsA inhibits IL-17 mRNA and protein expression in PBMC from donors with rheumatoid arthritis (43). In psoriasis patients, CsA down-regulates genes for IL-17 and related proteins (44). In contrast, others have reported CsA and FK506 do not inhibit IL-17 production in activated human PBMC (45, 46).

The anti-proliferative mycophenolic acid (MPA) reduces Th17 cell differentiation of human PBMC correlating with inhibition of IL-1 β production by monocytes and Tim-1 expression by CD4⁺ T cells (46). Also *in vitro*, the anti-proliferative mTOR inhibitor rapamycin inhibits IL-17 production and increases TGF β -induced Treg differentiation (47). However, others found that MPA does not inhibit human PBMC IL-17 production (45).

Patients treated with glucocorticoids for giant cell arteritis have suppressed Th17 responses, including a reduction in the Th17-inducing and maintenance cytokines IL-6, IL-1 β , and IL-23 (48). When stimulating PBMC from healthy donors *in vitro*, dexamethasone inhibits IL-17 production (45). Another group reported that in mice, cells skewed towards the Th17 phenotype *in vitro* induce airway hyperresponsiveness that is not inhibited by dexamethasone (49).

The conflicting nature of these reports suggests that the method of cell priming may affect susceptibility to immunosuppression. Further, more research is needed to determine if and how currently used immunosuppressive drugs affect and control Th17 cell differentiation. Indeed, many of these studies were performed *in vitro* with exogenous cytokines and drugs added directly to the cell culture. These additions may be present in concentrations that do not occur physiologically, and this consideration must be taken into account when interpreting these data. Further, current immunosuppressive protocols following transplantation rarely rely on a sole form of immunosuppression. Additional studies are needed to follow the effects of immunosuppression on Th17 cell development and function, with an experimental emphasis on *in vivo* systems and with a combination of drugs.

Th17 cell resistance to regulation

Another barrier to controlling graft-reactive Th17 cell responses is the finding that Th17 cells are poorly suppressed by Treg. In a model of autoimmune gastroenteritis (AIG), Stummvoll et al. reported that Treg effectively controlled Th1 cells, moderately controlled Th2 cells, and controlled Th17 cells only at early time points (50). It has also been shown that only induced regulatory cells (iTreg, (51)) or natural regulatory cells (nTreg, (52)) that are antigen-specific, not polyclonal iTreg or nTreg (51), are capable of reversing Th17 cell-induced pathology. One issue with Th17 cell control by Treg may be that while TGF β inhibits Th1 and Th2 cell development, it has no effect on the proliferation of Th17 cells. Indeed, TGF β induces Bcl-2 in Th17 cells, resulting in a survival advantage of Th17 cells relative to Th1 cells (53). Further, in inflammatory environments nTreg, but not iTreg can actually convert to Th17 cells in the presence of IL-6 (54). This difference has been attributed to the fact that iTreg have been recently exposed to IL-2, which inhibits the Th17 response (12) and induces the down-regulation of the IL-6 receptor, perhaps rendering the iTreg more resistant to Th17 cell conversion (54). Indeed, in humans, IL-21 can induce resistance of Th17 cells to Treg suppression (55, 56). As Th17 also produce IL-21 (55), this

cytokine may contribute to the refractive nature of Th17 cells to Treg regulation. In contrast, a specific subset of Treg may suppress Th17 cells in humans. Foxp3+CD39+ Treg can suppress Th17 cells *in vitro* (57), suggesting that the pro-inflammatory extracellular ATP cleaved by CD39 and converted into immunosuppressive adenosine by CD73 (58) may be an important step in limiting the Th17 cell response (57).

Conclusions

Taken together, these findings suggest that conventional methods of immunosuppression may be insufficient in controlling Th17 cells and preventing graft pathology. Further, Th17 cells can produce IL-22 and IL-21 (8, 39, 55); additional cytokines also expressed in instances of Th17 cell mediated rejection. In addition, Th17 cells and their cytokines can have various deleterious effects on graft survival (Figure 1). Hence, the contributions of these Th17 cytokines to allograft pathology remain to be elucidated and addressed in developing new therapies targeting Th17 cell responses in transplantation. Understanding the *in vivo* actions and differentiation of Th17 cells may unlock new therapeutic targets to prolong graft survival.

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Figure 1.

Th17 cells produce the cytokines IL-17, IL-22, and IL-21. These cytokines can act on a variety of cell types and induce a variety of immune responses. Adapted and compiled from (8, 39, 55).