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Role of Th17 cells and IL-17 in lung transplant rejection

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Abstract

In the past decade, advances in immunology have led to the recognition that T cell differentiation is not simply Th1 or Th2 but involves differentiation to other subsets, such as T regulatory cells, T follicular helper cells, and Th17 cells. Th17 cells, characterized by production of IL-17, IL-22, and IL-21, have been implicated in the pathogenesis of autoimmune diseases, like rheumatoid arthritis and multiple sclerosis, but also play an important role in host defense and mucosal immunity. IL-17, with its pleiotropic effects on stromal cells, as well as hematopoietic cells, has long been recognized as a possible mediator of rejection after lung transplantation. Recent data have implicated IL-17 and Th17 cells in the development of autoimmunity and chronic rejection after lung transplantation in both animal models and humans. In this review, we will discuss the current data on Th17 and the prospects for the future for lung transplantation.

Keywords

Lung transplantation; Obliterative bronchiolitis; Bronchiolitis obliterans syndrome; Alloimmunity; Autoimmunity; IL-17; T cells; Rejection

Introduction

Since Mosmann and Coffman introduced the paradigm of Th1 and Th2 cells, it has long been recognized that not all immune responses easily fit into these designations [1]. The early paradigm suggested that Th1 cells were primarily involved in cellular immune responses, and Th2 cells were linked to humoral immunity. In organ transplantation, Th1 cells were associated with rejection whereas Th2 cells were considered to be protective. However, over the years, this simplistic characterization of cellular immunity did not fully explain the immunopathogenesis of the rejection response. Indeed, Th1 cells, as well as Th2 cells, were involved in rejection of organs after transplantation [2]. Now, the Th1/Th2 hypothesis has been expanded to include the newly described Th17 subset defined by secretion of IL-17, as well as T regulatory cells, T follicular helper cells, and other T helper subsets. Th17 cells are not only important for host defense but also play a role in the pathogenesis of autoimmunity and allotransplantation [3, 4]. Since Th17 cells are involved in the maintenance of mucosal immunity, it is not completely surprising that Th17 cells and their cytokines have been implicated in rejection after lung transplantation [5].

IL-17 was first identified in 1993 from a cDNA library and was initially named CTLA-8 [6]. In 1995, Yao and colleagues renamed the protein IL-17, presumably for its molecular weight as an unmodified protein of 17kDa and also cloned the receptor IL-17R [7]. IL-17, also called IL-17A, is the original member of what is now the IL-17 family of cytokines characterized by disulfide-linked homodimeric glycoproteins (reviewed in [8]). However, it was not until the discovery of another cytokine that the recognition of a distinct T helper subset termed Th17 was found. In 2000, investigators discovered the novel cytokine chain p19 which formed heterodimers with the IL-12 p40 chain and was named IL-23 [9]. Researchers had known that IL-12 p40^{-/-} animals were not susceptible to experimental allergic encephalomyelitis (EAE), suggesting that IL-12 and Th1 cells, induced by IL-12, played a critical role in pathogenesis, but that mice deficient for IFN γ (IFN γ ^{-/-} or IFN γ R^{-/-}) had increased susceptibility to EAE [10]. With the discovery of IL-23, an explanation for these contradictory findings was found. Further studies demonstrated that IL-23 could induce memory or activated T cells to produce IL-17 in vitro and induce EAE in vivo [11, 12]. While IL-23 was found to be able to induce IL-17 from T cells, it did not seem to have a large effect on naïve T cells and was unlikely to be inducing differentiation in vivo. Nevertheless, investigators determined that IL-17 producing Th cells were distinct from Th1, Th2, and T regulatory cells in vivo, and the term Th17 was coined by Harrington and colleagues [13, 14]. Th17 cells have their own distinct lineage specific transcription factors similar to Tbet for Th1 and GATA3 for Th2. ROR γ t, in particular, as well as ROR α , are two nuclear receptors critical for Th17 differentiation [15, 16]. However, other transcription factors, Stat3, IRF4, the aryl hydrocarbon receptor, and recently, BATF, have been found to be important for Th17 differentiation (reviewed in [17]). More recent studies have called into question the importance of Th17 cells for EAE and have highlighted the differences between effects from Th17 cells and IL-17 itself [18]. These effects may be due to the fact that IL-17 and its family members are made by non-CD4⁺ T cells, and the contribution of other cell types, such as $\gamma\delta$ T cells, NK cells, CD8⁺ T cells, NK T cells, and neutrophils is only beginning to be understood.

Initially, several cytokines were found to promote development and maintenance of Th17 cells including IL-1 β , TGF- β , IL-6, IL-23, and IL-21 (reviewed in [4]). Subsequent studies by three groups established that TGF- β was required for Th17 differentiation of mouse T cells [19–21]. TGF- β and IL-6 were found to be sufficient to induce Th17, but IL-23 was important for maintenance. If T cells cannot respond to TGF- β , they cannot differentiate to Th17 [21]. Studies in humans were initially somewhat controversial regarding the role of TGF- β , with some studies suggesting TGF- β as dispensable for development of human Th17 [22, 23]. Eventually, careful examinations determined that human serum was being used in these initial studies and was sufficient to provide the TGF- β necessary for Th17 differentiation [24–26]. Thus, TGF- β was thought to be essential for Th17 differentiation from naïve T cells in both mice and humans until a recent study challenged this conclusion. O'Shea and colleagues found that IL-23 in combination with IL-1 β induced Th17 in vitro independent of TGF- β signaling [27]. Furthermore, Th17 cells generated without TGF- β 1 were pathogenic in vivo in EAE, suggesting that alternative routes of Th17 differentiation may be active in vivo. This study and an earlier report also emphasized the increased inflammatory potential of IL-23-induced Th17 cells in contrast to when TGF- β is available [27, 28]. Low levels of TGF- β may promote Th17 differentiation but dampen the pathogenicity of Th17 by inducing IL-10 [28]. However, high levels of TGF- β can inhibit Th17 differentiation and promote T regulatory cell development [4].

While many studies have determined the cytokines important for Th17 differentiation in vitro, as well as those essential for in vivo differentiation, the precise response in vivo that would give rise to Th17 differentiation was not known. Recent insight into the initiation of Th17 responses in vivo has come from Blander and colleagues [29]. Infected apoptotic

neutrophils or B cells phagocytosed by dendritic cells were sufficient to induce Th17. Further inhibition of apoptosis in vivo in a mouse model of *Citrobacter rodentium* infection decreased the Th17 response in the gut. With these findings, the authors have linked the innate immune response to infected apoptotic cells with the development of Th17. In organ transplantation, including the lung, ischemia–reperfusion injury induces pathologic lesions that promote apoptosis along with the release of endogenous TLR ligands and may be the initial insult to induce differentiation of alloreactive Th17 cells.

Th17 cells produce multiple cytokines in addition to IL-17 (IL-17A): IL-17F, IL-22, IL-21, GM-CSF, and TNF α , as well as chemokines and growth factors. IL-17A can target stromal cells, endothelium, epithelium, and monocytes to induce IL-8, CXCL1, TNF α , and G-CSF and recruit neutrophils. In the lung, Kolls and colleagues have shown an essential role for IL-17 and IL-17R in protection from *Klebsiella pneumoniae* [30, 31]. Transgenic mice overexpressing IL-17(A) or IL-17F in the lung epithelium have similar phenotypes, with mucus hyperplasia and peribronchial and perivascular infiltrates consisting of T and B cells [13, 32]. But IL-17F-deficient mice, in contrast to IL-17A-deficient mice, had reduced neutrophilia and increased Th2 responses to allergens, suggesting that IL-17A and IL-17F are not redundant in their effector functions [32]. IL-22, an IL-10 family cytokine member found to be important for host defense and mucosal immunity, has been implicated in autoimmune diseases, particularly psoriasis [33]. Interestingly, IL-22 has also been shown to play an important role in epithelial barrier function as mice treated with anti-IL-22 are highly susceptible to *K. pneumoniae* infection, and bacteria rapidly disseminate from the lungs to the spleen [34]. IL-17 has also been demonstrated to protect the gut epithelium from ulceration in a mouse model of colitis and other studies [18, 35]. The biological impacts of the cytokines produced by Th17, as well as other cell types, are only beginning to be elucidated. Nevertheless, these cytokines clearly play an important role in mucosal immunity and maintenance of epithelial homeostasis, and the role of IL-17 in maintaining epithelial integrity in lung epithelium is an area in need of additional study.

IL-17, Th17, and allotransplantation

Since IL-17 induces stromal cells and monocytes to produce cytokines and promote granulopoiesis, it has long been recognized as a possible target for therapy during transplantation. In 1998, investigators demonstrated that IL-17 induced primary human kidney proximal tubular epithelial cells to produce IL-6, IL-8, and the chemokine MCP-1 in vitro and correlated the presence of IL-17 in renal allografts with acute rejection in humans in vivo [36]. IL-17 blockade was later found to prolong cardiac allograft survival in a mouse model, and the authors suggested that IL-17 promoted dendritic cell maturation leading to accelerated rejection [3]. In cardiac allografts, deficiency of IL-17 has also been shown to be protective from fibrosis related to chronic vasculopathy [37]. The authors suggested that Th17 differentiation and T cell-derived IL-17 production downstream of TGF- β signaling to T cells was responsible for chronic rejection of cardiac allografts. However, others have suggested that the source of IL-17 in cardiac allograft rejection is not Th17 cells but rather $\gamma\delta$ T cells highlighting the necessity of understanding the biology of IL-17 distinct from CD4⁺ T cells [38]. Others have also found that $\gamma\delta$ T cells are an innate source of IL-17 in the lung [39].

While studies have implicated IL-17 in chronic fibrosis and rejection, the precise role of Th17 in acute rejection of allografts is still controversial. Studies from Tbet^{-/-} mice deficient in Th1 responses demonstrate a role for both CD4⁺- and CD8⁺ IL-17-producing T cells in either rejection or resistance to tolerance, respectively, but the relevance in humans or Tbet sufficient mice is not clear [40, 41]. Interestingly, studies in tolerant grafts find that IL-6 and IL-17 induced by CpG ligands cooperate to break established tolerance, suggesting

that Th17 cells may play a role in episodes of rejection triggered by infections [42]. Innate immune activation secondary to microbial or environmental stimuli is highly likely to be playing a role in the immune response after transplantation in the lung, but further studies are needed to determine the relevance of IL-17 and Th17 to rejection after lung transplantation.

Th17 and lung transplantation

IL-17- and Th17-associated cytokines have been linked to the development of acute and chronic rejection after lung transplantation in both animal models and humans. Verleden and colleagues found that increased IL-17 in bronchoalveolar lavage (BAL) was associated with an increase in BAL lymphocytes and neutrophils during acute rejection on transbronchial biopsies from lung transplant patients [43]. The levels of IL-17 also correlated with increased severity of rejection [43]. However, another study found that while IL-17-positive cells were increased in endobronchial biopsies early after lung transplantation, no correlation was found between IL-17-positive cells and the severity of acute rejection [44]. The differences may be due to differences in sampling BAL compared to endobronchial biopsies but suggest that the early events after transplantation may be the most critical for inducing IL-17 production.

Lung transplant recipients with bronchiolitis obliterans syndrome (BOS) have been found to have increased BAL levels of IL-1 β and IL-6 and increased mRNA for TGF- β , IL-17, IL-23, and IL-8 compared to controls [45]. IL-8, the major chemokine for neutrophils, has previously been associated with BOS, but it was not known whether neutrophils were a marker of inflammation or a key mediator of obliterative bronchiolitis (OB) [46]. Since IL-17 promotes neutrophil chemotaxis, the presence of neutrophils may be secondary to a Th17-mediated alloimmune or autoimmune response. In a mouse model, increased levels of IL-6 and IL-17 also correlated with tracheal obliteration, and blockade of IL-6 decreased both allograft fibrosis and IL-17 transcripts [47]. IL-17 has also been shown to be an inducer of fibroblast cytokine secretion and proliferation, as well as stromal cell differentiation, making it an attractive target for mediating chronic rejection [48–50]. Several studies have now linked IL-17 to fibrosis in the lung in mouse models of pulmonary fibrosis and idiopathic pulmonary fibrosis in humans [49, 51, 52]. IL-17 and Th17 cells may be key regulators of the airway fibrotic response driving the development of OB.

Similar to other autoimmune diseases, Th17 cells have been implicated in the autoimmune response linked to the pathogenesis of OB/BOS. The development of type V collagen (col(V))-reactive CD4⁺ T cells was associated with a nearly tenfold increased risk for BOS in clinical lung transplantation, which was a greater risk than that associated with acute rejection episodes, HLA mismatch, or anti-HLA antibodies [5]. Cellular immune responses to col(V) were mediated by IL-17A, TNF α , and IL-1 β , but not IFN γ . Further, col(V) reactivity was dependent on monocytes (CD14⁺) [5]. These data suggest that autoreactive Th17 cells are mediators of BOS in humans. Autoantibodies to the epithelial-specific protein, K- α 1 tubulin, have also been found to be present in a significant number of patients with BOS [53]. In a mouse model, an alloimmune response in the lung was found to promote the development of col(V) and K- α 1 tubulin autoreactivity [54]. Both autoreactive T cells and autoantibodies were induced by the administration of Class I MHC alloantibodies in the airways of mice. Blocking IL-17 diminished the severity of the observed airway injury and fibrosis [54]. Interestingly, the macrolide, azithromycin, an important treatment for a subset of patients with BOS, has previously been found to suppress IL-17-induced IL-8 production from human smooth muscle cells, providing further support for IL-17 playing a role in BOS [55]. Since OB/BOS has been linked to local neutrophilic infiltration and IL-17 promotes recruitment and differentiation of neutrophils, it is

interesting to speculate that IL-17 derived from autoreactive T cells may in part explain the pathogenesis of BAL neutrophilia observed in BOS.

Tregs and Th17

A correlation between decreased Tregs and the incidence of BOS has been reported in lung transplantation recipients [56]. In addition to Tregs being decreased or suppressed post transplantation, inflammatory conditions such as infection, acute rejection, or other insults may suppress the regulatory activity of Tregs. An indirect relationship exists between Foxp3, the transcription factor that determines function of natural and induced Tregs, and ROR γ t, the transcription factor expressed in Th17 cells. Both Foxp3 and ROR γ t are critically dependent on TGF- β for expression and differentiation of Treg and Th17, respectively (reviewed in [4]). In vitro, IL-6 can redirect Foxp3⁺ T cells to express IL-17, and investigators have reported that this transition may occur in vivo during an inflammatory response in experimental autoimmune encephalitis [4, 57]. Since IL-6 and IL-1 β have previously been associated with BOS and are known mediators of Th17 development, an intriguing hypothesis is that Tregs with autoreactive T cell receptors convert to pathogenic T cells in the presence of these cytokines [4, 45]. Alternatively, cytokines secreted by autoreactive Th17 cells may inhibit Treg function in vivo. However, data on the reciprocal development between the Treg and Th17 lineage in vivo in humans are not established, and further studies are required to investigate these hypotheses.

Conclusions

In conclusion, Th17 cells and the cytokines they produce are only beginning to be understood, but their relevance for lung transplantation is manifold. The biology of IL-17 and Th17 cells is complex, and the lung has unique antigen-presenting cell populations with varied dendritic cells and alveolar macrophages likely to play distinct roles in the development of Th17 cells. Future studies are needed to determine the mechanisms by which ischemia and reperfusion injury, primary graft dysfunction, and environmental and microbial responses may promote the development of Th17 cells and the production of IL-17 from non-T cells. IL-17 may also play a role in alloantibody and autoantibody production, as IL-17 has been implicated in the development of germinal centers and autoantibody production in autoimmune disease [58]. Studies linking IL-17 to the development of fibrosis in humans and in patients with chronic rejection after lung transplantation suggest that IL-17 may be a critical mediator of obliterative fibrosis of the airways [5, 51]. Neutralizing IL-17 beyond the effects of azithromycin may one day be a promising therapy for patients. Treatments to block IL-17 or its receptor are currently in trials for autoimmune diseases and hold promise for complications of lung transplantation [59]. The pleiotropic effects of IL-17 and Th17 cells on stromal and hematopoietic cells provide compelling reasons for further research and underlie the current focus on targeting this pathway to affect outcomes after lung transplantation.

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