Th17/Treg Imbalance in Lung Inflammatory Diseases

Subjects: Immunology

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Regulatory T cells (Tregs) and T helper 17 cells (Th17) are two $CD4^+$ T cell subsets with antagonist effects. Th17 cells promote inflammation, whereas Tregs are crucial in maintaining immune homeostasis. Th17 cells and Treg cells are the foremost players in several inflammatory diseases.

Th17 cells Treg cells inflammation lung

1. Introduction

The immune system acts as the guardian of the host and functions to defend against foreign antigens, induce self-tolerance, and promote immunological memory. However, it is not protective or beneficial all the time. The individual's tissue components may be attacked by the immunological reaction resulting in autoimmune diseases in specific settings. It is certain that a single theory or mechanism cannot explain autoimmune diseases. As proposed by Shoenfeld and Isenberg, autoimmune diseases are caused by various factors, including immunological, genetic, hormonal, and environmental factors [1]. Non-genetic components rather than inherent components play a dominant role in determining disease susceptibility and severity, which has been demonstrated by the discordance of autoimmune diseases in identical twins [2]. Immunological factors play a vital role in the initiation, progression, and regression of autoimmune diseases. In a typical setting, T cells are tolerant to physiological levels of self-antigen. However, this state of tolerance breaks down in some individuals, resulting in autoimmune/inflammatory diseases. One of the critical features of inflammatory diseases is the deregulated Th1/T helper 17 cells (Th17) responses, frequently accompanied by a reduction and/or alteration of regulatory T (Treg) cells. Th17 cells serve as inflammatory cells, which in excess, promote inflammatory diseases. On the other hand, Treg cells show suppressor function, which, when in failure, contributes to the same disease [3].

1.1. Th17 Cells

Initial studies by Infante-Duarte et al. identified $CD4^+$ T cells producing IL-17A as a T helper cell subset distinct from Th1 and Th2 cell subsets [4]. This subset, called Th17 cells, predominantly produces interleukin-17A (IL-17A), IL-17F, IL-21, and IL-22 [5]. IL-17A, originally named CTLA8, was cloned and described by Rouvier et al. [6]. It is a homodimeric glycoprotein with 155 amino acids linked by disulfide bonds. IL-17F, also produced by Th17 cells, shows 55% similarity with IL-17A, and they form IL-17F homodimers, IL-17A homodimers, or IL-17A-IL-17F heterodimers [7]. IL-17 binds to its receptor (IL-17R), a transmembrane protein, highly expressed in rats and mice's spleen, kidneys, liver, and lungs [8]. Th17 cells require the transcription factor, RORγt, and cytokine IL-6 in

combination with transforming growth factor-β (TGF-β) for their differentiation [9]. IL-6 acts as a major factor guiding the differentiation of T cells into Th17 cells or Treg cells [9]. IL-21, together with TGF-β, also functions as an alternative pathway to generate Th17 cells [10]. Once they reach the site of inflammation, IL-17 released by Th17 cells stimulates the expression of pro-inflammatory cytokines like granulocyte-macrophage colony-stimulating factor, Granulocyte-colony stimulating factor, IL-6 and tumor necrosis factor-alpha (TNF-α) [11]. In addition, IL-17 also promotes the secretion of CXC chemokines, which attracts neutrophils in vivo [11]. Moreover, IL-17 stimulates the production of antimicrobial peptides, such as β-defensin and S100 proteins, providing defense against a wide range of microorganisms [12][13].

1.2. Treg Cells

As the bias towards pro-inflammatory cytokines and cells induces the development and perpetuation of autoimmunity, immunoregulatory factors are thought to straighten out the laterality. Regulatory T cells are crucial members of the family of immunoregulatory cells that preserve self-tolerance and fine-tune the immune response. Treg cells suppress inflammation by cell-cell contact or releasing cytokines, such as IL-10 or TGF-β, and they require the transcription factor FoxP3 for their differentiation [3][14]. In recent years, research has identified two types of Treg cells called natural Treg cells (nTreg) and inducible Treg cells (iTreg). nTreg cells develop in the thymus, and when entering peripheral tissues, they suppress self-reactive T cells. Studies in both mice and humans found that nTreg cells constitute around 10% of CD4 T cells in the periphery [15]. They express FoxP3 before they are released from the thymus, and the expression of TGF-β helps in their maintenance of inhibitory function after they migrate from the thymus [3][14]. Inducible Treg cells develop from naive T cells in the secondary lymphoid organ upon antigen exposure. Following interaction with TCR, TGF-β induce the FoxP3 expression in $CD4^+$ $CD25^-$ cells, thereby, converting them to $FoxP3^+$ $CD4^+$ $CD25^+$ cells [16]. These iTreg cells mediate their inhibitory activities by secretion of IL-10 or TGF-β, which is crucial for inhibiting overexuberant immune response [17] (**Figure 1**).

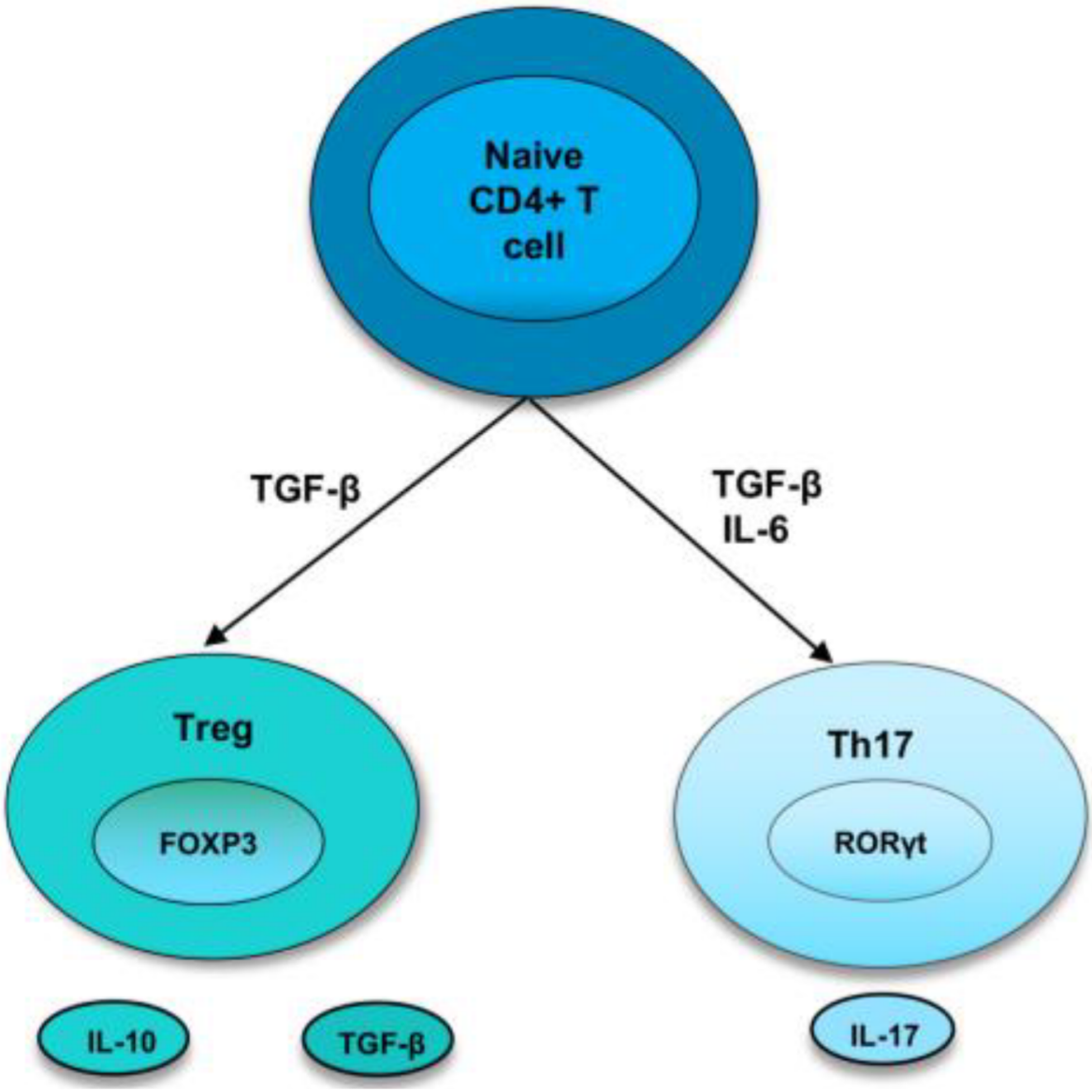

Figure 1. Differentiation of naive T cells into Th17 and Treg cells. In naive $CD4^+$ T cells, TGF-β induce the development of Tregs by promoting Foxp3 expression. Treg cells express cytokines, IL-10 and TGF-β. However, in the presence of IL-6 and TGFβ, RORγt is induced, leading to a Th17 phenotype.

2. Th17/Treg Cells in Lung Inflammatory Diseases

2.1. Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory lung disease characterized by airway and/or alveolar abnormalities that cause obstructed airflow from the lungs [18]. Studies over the last decade highlighted the relevance of maintaining the balance between Th17 cells and Treg cells to control the inflammatory response in COPD. An increased Th17 response is involved in the progression of Chronic Obstructive Pulmonary Disease (COPD) in both clinical and experimental studies [18]. Th17 cytokine, IL-17A, levels were higher in the sputum of patients with COPD stages 3 and 4 compared to non-smokers and healthy smokers [19]. Reduced numbers of Treg cells were observed in the

bronchial epithelium of severe/very severe COPD patients than in those with mild and moderate COPD and healthy smokers [20].

2.2. Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is an important cause of acute pulmonary failure with severe disease and mortality [21]. The most common cause of ARDS is bacterial or viral pneumonia [21]. ARDS is characterized by dysregulated inflammation, increased permeability of microvascular barriers, and uncontrolled activation of coagulation pathways [21]. Activation of several immune cells, including neutrophils, macrophages, and dendritic cells, plays an important role in the development of ARDS [22]. The involvement of $CD4^+$ T cells has been revealed recently for the pathogenesis of ARDS. ARDS patients show a higher frequency of Th17 cells and IL-17 compared to the control group [22]. The Th17/Treg ratio is higher in the peripheral blood of ARDS patients compared with the healthy controls [22]. A higher Th17/Treg ratio is associated with more adverse outcomes in ARDS patients. Mechanistically, recent studies demonstrated that secreted phosphoprotein 1 (SPP1) exacerbated lung inflammation in ARDS by modulating Th17/Treg balance [23]. SPP1 reduces the ubiquitination and degradation of HIF-1α, which, in turn, leads to a higher Th1/Treg ratio. IL-33 production in LPS-induced ARDS is reported to increase the Th17/Treg ratio [24]. IL-33 deficiency inhibits the differentiation of T cells into Th17 cells and restores Th17/Treg balance. Consequently, IL-33 deficiency significantly reduces inflammation in LPS-induced ARDS, whereas recombinant IL-33 treatment exacerbates lung inflammation [24].

2.3. Sarcoidosis

Sarcoidosis is an inflammatory disorder characterized by granulomatous inflammation that affects multiple organs, mostly the lungs and mediastinal lymph nodes [25]. Emerging studies suggest the pleiotropic functions of Th17 and Treg cells in the pathogenesis of sarcoidosis. Higher IL-17A cytokine production is observed in the BALF of patients with pulmonary sarcoidosis [25]. Moreover, a higher Th17/Treg ratio was observed in peripheral blood and BAL of patients with active and progressive sarcoidosis [26]. After treatment with corticosteroids, the level of Foxp3 mRNA was elevated in the peripheral blood, and expression of RORγt mRNA was reduced [26].

2.4. Asthma

Asthma is a chronic inflammatory disease of the airways involving inflammatory cells such as mast cells, eosinophils, neutrophils, macrophages, and T lymphocytes [27]. Typically, asthmatic inflammation is mediated by excessively activated Th2 cells eosinophilia [27], but recent studies showed the involvement of cytokine IL-17A in multiple asthma pathogenesis, including neutrophilic inflammation, steroid insensitivity, activation of epithelial cells, and airway remodeling [28]. A large number of cells positive for IL-17 are reported in the sputum and bronchioalveolar fluids (BALFs) of asthmatic patients [29]. In addition, many reports identified that levels of IL-17A are correlated positively with the severity of asthma [30][31][32]. Inhibition of IL-17 in a model of LPS-induced asthma exacerbation aid in controlling Th2 and Th17 responses and signaling pathways associated with inflammation and remodeling [33].

2.5. Pulmonary Infectious Diseases

In addition to their role in non-infectious inflammatory lung diseases, maintaining Th17 /Treg balance is important for protective immunity against lung infections. Human IL-17A and IL-17F are crucial for protective immunity against mucocutaneous candidiasis [34]. Treg cells prevent the differentiation of naïve T cells into Th17 cells and prevent the clearance of *Candida albicans* infection [35]. IL-17 is identified as a critical factor required for protective immunity to *Pneumocystis* infection. Administration of anti-IL-17 neutralizing antibody to wild-type mice infected with *P. carinii* resulted in severe fungal infection [36]. Similarly, regulatory T cells are recruited to the lung during the course of *Pneumocystis* infection in mice [37]. Depletion of the Treg population results in increased levels of IL-1β and IL-6, leading to increased lung injury [37]. Th17/Treg balance also acts as a critical factor for controlling lung inflammation during chlamydial infection. IL-17A produced by Th17 cells during chlamydial lung infection has a significant impact on the development of protective type 1 immunity [38][39][40]. Chlamydial lung infection of mice induced IL-17 production in lung and lymph nodes at earlier and later stages of infection [41]. Neutralization of IL-17 in mice resulted in higher body weight loss, bacterial burden, and more severe pathological changes in the lung compared with sham-treated control mice [41]. IL-17 neutralized mice exhibit reduced Th1 responses, increased Th2 responses, and altered DC phenotype. Moreover, the adoptive transfer of DC isolated from IL-17-neutralized mice failed to protect the recipients against challenge infection compared to DC from sham-treated mice [41].

On the other hand, higher Treg responses contribute to tissue pathology after chlamydial lung infection [39][40]. Treg cells are observed in the chlamydial infection site of both humans and mice [42][43][44]. Recent studies suggested that NK cells provide protective immunity to chlamydial lung infection by maintaining Th17/Treg balance [45][46]. During *Chlamydophila pneumoniae (Cpn)* lung infection, NK cell depletion increased the number of Treg cells and IL-10-producing $CD4^+$ T cells. The changes in T cell responses were associated with severe disease and bacterial load in the lung. Adoptive transfer of DCs from NK cell-deficient mice induced Treg cells in the recipient mice, which promotes pathological response [45]. In the mice model of *Chlamydia muridarum* lung infection, NK cell depletion resulted in lower IL-17 cytokine production and Th17 cells [46].

3. Conclusions

The importance of the balance between pro-inflammatory and anti-inflammatory cytokines and cells in maintaining immune homeostasis is widely acknowledged. Th17 cells promote inflammation and pathology, whereas Treg cells maintain self-tolerance. The balance between inflammation and self-tolerance is disrupted, leading to inflammation.

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