IL-26 in asthma and COPD

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**ABSTRACT**

**Introduction:** New targets are needed to enable more accurate diagnosis, monitoring and effective therapy in uncontrolled asthma and chronic obstructive pulmonary disease (COPD), two disorders characterized by pathogenetic alterations in the innate immune response. Interestingly, the IL-10-related cytokine IL-26 has been found to be abundantly expressed in human airways and alterations in its expression have been linked to reduced lung function and markers of neutrophilic inflammation in patients with uncontrolled asthma or COPD.

**Areas covered:** Literature search was conducted on PubMed to identify articles in the field of IL-26 immunology, as well as clinical studies on IL-26 in asthma and COPD, published between 2000 and 2021. We outline the main sources of IL-26 in human airways, as well as the effect of this cytokine on relevant immune and structural cells. Finally, we discuss the potential involvement of IL-26 in the pathophysiology of uncontrolled asthma and COPD.

**Expert opinion:** IL-26 constitutes a potential target for diagnostic purposes and therapeutic modulation of the innate immune response in the airways of patients with asthma and COPD. It seems reasonable to expect more conclusive evidence of its clinical utility for personalized medicine within the coming 5-year period.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are heterogenous, chronic, and highly prevalent inflammatory lung diseases in need of new therapeutic targets. Corticosteroids have long been used to successfully treat mild-to-moderate cases of eosinophilic asthma, and the recently developed biological therapies targeting IgE and Th2 cytokines (i.e. IL-4, IL-5, and IL-13) have proven highly effective at reducing symptoms and exacerbations in severe Th2-high endotypes [1,2]. However, up to 60% of patients with severe asthma [3] do not benefit from corticosteroid treatment or anti-Th2 approaches. Similarly, COPD patients do not benefit from corticosteroid treatment in the absence of exacerbations and, most likely, neither do they from anti-Th2 therapy [4]. This is because patients with severe uncontrolled asthma or COPD present an endotype characterized by neutrophil accumulation [5,6] and increased expression of Th1 and Th17 cytokines (e.g. IFN-γ and IL-17) [7–11].

Biological therapies targeting IL-17 have proven beneficial for the clinical treatment of certain chronic inflammatory diseases, namely psoriasis and two of its associated manifestations: psoriatic arthritis and ankylosing spondylitis [12]. Nevertheless, according to the first phase 2a trials for each condition, anti-IL-17 therapy does not yield any effect on lung function in patients with moderate-to-severe asthma [13] or COPD [14]. However, it should be kept in mind that the recruitment criteria in these studies did not specify endotypes displaying airway neutrophilia or high IL-17 levels for the selection of patients. The same reservation can be made against an even more recent phase 2a trial, which forwarded evidence that biological therapy targeting IL-23 (the master Th17 regulator) yields no effect on lung function in patients with severe asthma, even among those with airway neutrophilia [15]. Because of this, it seems necessary to continue to improve our understanding of the cellular and molecular mechanisms that underlie relevant endotypes of asthma and COPD.

Interestingly, the cytokine IL-26 is co-expressed with IFN-γ in Th1 cells [16–18] and with IL-17 and IL-22 in Th17 cells [16,19,20]. IL-26 has potentially important antimicrobial properties and is abundantly expressed in human airways by several cell types. Moreover, alterations in the expression of IL-26 have been associated with reduced lung function and neutrophil accumulation in patients with uncontrolled asthma [21–24] or COPD [25,26]. In this article, we summarize the cellular immunology of IL-26 and review its potential involvement in the pathophysiology of uncontrolled asthma and COPD. We conclude our review by discussing the clinical relevance of these findings.
IL-26 is a homodimeric protein (36 kDa) originally termed AK155 following its discovery in human T cells transformed with herpesvirus saimiri [27]. Given its 25% homology and 47% similarity to IL-10, it is generally considered a member of the IL-10 family of cytokines [27], specifically the IL-20 subfamily. The IL26 gene is flanked by the genes encoding IFNγ and IL22 on chromosome 12q15 [27,28], and to date, expression of IL-26 has been reported in several immune and structural cell types from both healthy and ill individuals. IL-26 has important antimicrobial properties that have been reviewed in detail elsewhere [29,30]. Namely, IL-26 can kill extracellular bacteria via membrane-pore formation [31], reduce the viability of intracellular bacteria [32], form complexes with extracellular DNA (bacterial and self) that can be recognized by Toll-like receptors (TLRs) [31], and modulate viral infectivity [33]. In addition, IL-26 can play more traditional ‘cytokine-like’ roles via the heterodimeric (IL-10R2/IL-20R1) IL-26 receptor complex, which results in activation of the transcription factors STAT1 and STAT3 [34]. Although the expression of IL-10R2 is broad, IL-20R1 is mostly expressed by non-hematopoietic cells [17]. This limited expression pattern should restrict the action of IL-26 but this cytokine can paradoxically act on cells that do not express the archetypical IL-26 receptor complex (discussed below).

2.1. IL-26 expression in human airways

Constitutive expression of IL-26 has been reported in bronchial epithelial cells [35], lung fibroblasts [36], alveolar macrophages, and CD4+ and CD8+ T cells [37] isolated from human airways, as well as neutrophils isolated from blood [38], of healthy donors (Figure 1). Expression of IL-26 has also been detected in NK and NKT cells found in tuberculous pleural effusion [39], but whether they represent important sources of IL-26 in the airways in the absence of infection has not been investigated. Consistent with its postulated role in host defense, in vitro stimulation with endotoxin increased the expression of IL-26 in alveolar macrophages [37], lung fibroblasts [36], bronchial epithelial cells (preliminary data) [40] and blood neutrophils [38]. A similar response was observed when bronchial epithelial cells and lung fibroblasts were stimulated with several other TLR agonists (preliminary data) [40], when CD4+ T cells isolated from tuberculous pleural effusion were incubated with ESAT-6/CFP-10 (an M. tuberculosis antigen) [39], and when blood neutrophils were exposed to K. pneumoniae [38]. Furthermore, co-stimulation with a TLR3 agonist (poly-IC) and IL-17A synergistically increased the release of IL-26 in bronchial epithelial cells, which was further enhanced in the presence of the Th17 cytokine IL-22 [35]. Monocytes, which like neutrophils rapidly mobilize to the airway lumen upon infection, have been shown to express IL-26 only when stimulated with a combination of endotoxin, IFNγ, and an anti-IL-10 antibody [17], or on-going tuberculosis infection [41] (Figure 1). However, expression of IL-26 can also be enhanced in response to noninfectious compounds, as in the case of Th17 cells exposed to IL-1β [42], bronchial epithelial cells exposed to IL-17A [35], and alveolar macrophages exposed to water-soluble tobacco smoke components [25]. Finally, it should be kept in mind that TLRs can also be activated by damage-associated molecular patterns (DAMPs), as in the case of histones (TLR2 and 4) or mitochondrial RNA (TLR3) released by dying cells, and thus DAMPs can likely trigger and/or enhance IL-26 expression. Nonetheless, further research into the role of DAMPs in IL-26 expression is warranted.

So far, the expression of the IL-26 receptor complex in human airways has been reported in bronchial epithelial cells [35] and alveolar macrophages only [25], though it has also been identified in blood neutrophils from healthy donors [37] and in CD4+ T cells isolated from tuberculous pleural effusion [39]. Previous studies found that IL-26 induced the expression of TNFα, IL-8, and IL-10 in different human epithelial cell lines and primary keratinocytes via the IL-26 receptor complex [43,44]. Intriguingly, in vitro stimulation with IL-26 increased the transcription of pro-inflammatory mediators (e.g. TNFα, IL-1β, and IL-8) in alveolar macrophages [25] but inhibited the production of these same mediators in bronchial epithelial cells [37], all cells being of human origin. Moreover, bronchial epithelial cells responded to IL-26 stimulation by upregulating the expression of the IL-26 receptor complex and its associated transcription factors STAT1 and STAT3 [37]. In CD4+ T cells from tuberculous pleural effusion, exposure to IL-26 resulted in increased IL-22, TNFα, and IL-6 release [39]. Blood neutrophils, on the other hand, showed enhanced IL-8- and fMLP-dependent chemotaxis, reduced chemokines, decreased myeloperoxidase and elastase secretion, as well as...
downregulation of the IL-26 receptor complex, STAT1, and STAT3 in vitro in response to IL-26 [37,38]. These varied outcomes highlight the cell type- and tissue-specific effects of IL-26 (Figure 1).

Nevertheless, the results from several studies suggest that IL-26 has important effects on immune cells that do not express the IL-26 receptor complex. Unlike alveolar macrophages, human monocytes do not seem to express the IL-26 receptor complex under homeostatic conditions, but they still upregulate pro-inflammatory mediators in response to IL-26 [45]. Furthermore, IL-26-primed monocytes induced differentiation of naive CD4+ T cells to Th17 cells in vitro [45]. IL-26 was also shown to inhibit the production of IgA and IgG in anti-CD40-treated B cells [46] and induce the expression of inflammatory cytokines and interferons in NK cells [47] independently of the IL-26 receptor. Although these studies suggest the existence of a hitherto unidentified IL-26 receptor, it is also possible that IL-26 acts on these cells via an altogether different mechanism. For instance, IL-26 was shown to bind and shuttle extracellular DNA (bacterial and self) into the cytoplasm of human myeloid cells, and IL-26/DNA complexes were shown to activate plasmacytoid dendritic cells (pDCs) and monocytes via the TLR9, stimulator of interferon genes (STING), and inflammasome pathways [31,48]. Although different mechanisms have been put forward to explain how IL-26 might enter the cytoplasm [29], it remains to be determined whether IL-26 could shuttle other DAMPs besides extracellular DNA and whether internalized IL-26 could have effects by itself even in the absence of DAMPs.

2.3. In vivo studies

IL-26 is constitutively expressed in human airways, and intra-bronchial exposure to endotoxin increased the concentration of IL-26 in bronchoalveolar lavage (BAL) fluid from healthy human subjects [37]. Given that mice lack the IL26 gene [28], mechanistic studies regarding the function of this cytokine in health and disease have been hampered substantially. Nonetheless, the archetypical IL-26 receptor complex is expressed in mouse airways [49,50] and the effect of human IL-26 on mice has been investigated. Intranasal instillation of recombinant human IL-26 (rhIL-26) enhanced the endotoxin-mediated accumulation of leukocytes (mainly neutrophils and macrophages) and expression of pro-inflammatory mediators in the airway lumen of wildtype mice [49]. This confirms in vivo the enhanced chemotaxis of neutrophils observed in vitro [37]. However, a single instillation of rhIL-26 alone exerted no clear effect on wildtype mice in the first 72 hours post-
administration. In a model of transplant-related obliterative bronchiolitis, mice engineered to express human IL-26 showed increased IL-26 expression and collagen deposition in airway tissue 4 weeks after transplantation, which was inhibited by neutralizing anti-IL-26 antibodies [50]. These studies suggest that while IL-26 might not have any substantial short-term effects in vivo by itself, the long-term upregulation of IL-26 can lead to airway remodeling. Despite these findings, most animal models of disease have not been used to investigate whether IL-26 may play a role in asthma or COPD.

2.3.1. IL-26 in asthma

Among patients with asthma, distinct inflammatory profiles (i.e. endotypes) are associated with specific levels of disease control and response to treatment (i.e. phenotype). The endotype with high eosinophil counts (> 3%) in induced sputum can present mild-to-severe disease but responds well to corticosteroids and more specific anti-Th2 therapies [51]. However, up to 50% of all patients with asthma have a non-eosinophilic endotype [52–54], displaying neutrophilic or paucigranulocytic inflammation. The neutrophilic endotype of asthma (defined as > 61 or 76% neutrophils [depending on the study] in induced sputum) accounts for 18–25% of all cases [53,54], does not respond to available treatments [55], and is associated with more severe and poorly controlled disease (asthma control test (ACT) < 20) [56,57]. The paucigranulocytic endotype of asthma, on the other hand, shows no sputum eosinophilia or neutrophilia and manifests milder symptoms and better lung function than the eosinophilic and neutrophilic endotypes [58]. Given that IL-26 can be involved in neutrophil mobilization and Th17-mediated inflammation, key features of certain endotypes, this cytokine harbors therapeutic potential for the phenotype of uncontrolled asthma.

To date, the role of IL-26 in asthma has been the subject of four observational studies. A large case-control study showed that the concentration of IL-26 is higher in serum from adults with asthma than in healthy subjects regardless of disease severity, degree of control, or atopic status [24]. Another study focused exclusively on women with severe uncontrolled asthma and found that the concentration of IL-26 is increased not only in blood, but also in induced sputum (i.e. proximal airways) [23]. In contrast, our group has shown that the concentration of IL-26 is downregulated in BAL fluid (i.e. distal airways) of adult patients with mild-to-moderate asthma [22]. This discrepancy might be explained by the fact that each study probed different airway compartments and focused on populations with distinct disease severity. It is known that proximal and distal airways have unique immune and structural cell microenvironments [59,60], which might present different alterations in IL-26 expression during a complex inflammatory disease such as asthma. In addition, the down-regulation of IL-26 observed in BAL fluid from patients with mild-to-moderate asthma might be associated with a better response to glucocorticoid therapy, which has been shown to inhibit IL-26 production in vitro [36]. Severe and uncontrolled cases of asthma are resistant to glucocorticoid therapy and might favor IL-26 production. Indeed, when comparing the protein concentration of IL-26 in patients with controlled (ACT ≥ 20) versus uncontrolled (ACT < 20) asthma, IL-26 was found to be upregulated in sputum from children with severe uncontrolled non-eosinophilic asthma [21] and in BAL fluid from adults with mild-to-moderate uncontrolled asthma [22]. In summary, while changes in the expression of IL-26 appear to be compartment-specific and dependent on disease severity in asthma in general, evidence suggests that IL-26 is always higher in the airways of patients with uncontrolled asthma, particularly in non-eosinophilic endotypes (Figure 2).

Although the role of IL-26 in asthma has not been verified in interventional studies, some important correlations have been identified (Figure 2). Thus, IL-26 in induced sputum [23] and BAL fluid [22] correlated with reduced lung function (i.e. FEV₁% or FEV₁/FVC ratio) in adult patients with asthma. IL-26 also correlated with increased IL-8 in BAL fluid from adults with asthma [22], and with increased blood neutrophils in children with asthma [21]. Among adults with uncontrolled asthma, IL-26 correlated with increased IL-17A and neutrophil counts in sputum [23] and reduced eosinophils and lymphocytes in BAL samples [22]. Of note, adult patients with uncontrolled asthma who had low expression of IL-26 (< median) also had worse asthma control (i.e. lower ACT score) [22]. Finally, the inclusion of IL-26 in a predictive disease model resulted in higher accuracy when discriminating severe asthma from other inflammatory airway diseases [61]. Taken together, the evidence put forward by these studies suggests that IL-26 is linked to uncontrolled asthma, but it is unclear whether IL-26 is a causative factor, a consequence, or even a natural defense mechanism against disease progression. Notably, a recently identified IL26 gene polymorphism (rs7134599 A) was shown to reduce the risk of developing severe asthma, while another (rs2870946 CC) was shown to increase the risk of asthma in patients who smoke [24]. Although this study forwards IL-26 as a potential causative factor in asthma development, the underlying mechanisms are yet to be defined.

3. IL-26 in COPD

Although available therapies can reduce exacerbations and certain symptoms, COPD remains a deadly disease, in fact the third deadliest according to the World Health Organization (WHO) [62]. Long-term smoking is the predominant risk factor associated with COPD development, which often coincides with the development of its two major comorbidities: chronic bronchitis and/or emphysema. Besides tobacco smoking, COPD may also develop due to long-term inhalation of biomass smoke from indoors cooking [63] or occupational exposure to noxious particles (e.g. silica, asbestos, and asphalt) [64–66]. The clearest genetic predisposition for COPD is found in patients deficient in α₁-antitrypsin, a potent inhibitor of neutrophil elastase, which affects approximately 1% of all COPD patients [67]. It seems feasible that the causative factor may relate to immunological endotypes and clinical phenotypes of COPD. For instance, exposure to biomass smoke has been linked to more chronic bronchitis [68], less emphysema [69], and more serum IgE than exposure to cigarette smoke [70]. To date, the role of IL-26 in COPD has only been addressed in relation to COPD among long-term
smokers. Just like in uncontrolled asthma, IL-26 represents a potential therapeutical target for COPD among patients with the endotypes displaying neutrophilic airway inflammation and/or enhanced Th17 signaling.

Two independent studies recently showed that the concentration of IL-26 is increased in the airways of COPD patients and that this increase correlated with reduced lung function (i.e. FEV1% and FEV1/FVC ratio), increased neutrophil mobilization, enhanced expression of pro-inflammatory mediators, and higher body mass index (BMI) [25,26] (Figure 3). Nevertheless, from a statistical point-of-view, the increase in IL-26 seemed to be a consequence of long-term smoking rather than the disease itself. When all smokers with and without COPD were grouped together, it became apparent that increased IL-26 levels were associated with chronic bronchitis and colonization by pathogenic bacteria [25]. However, it is important to consider that these analyses were carried out in samples obtained during stable clinical conditions. During exacerbations, long-term smokers with COPD displayed even higher IL-26 levels in induced sputum. In fact, a detectable increase in IL-26 preceded the exacerbations by an average of 17 days [25]. This finding suggests that IL-26 is involved in the actual course of COPD and, potentially, that it may even bear potential as a biomarker of exacerbations. Intriguingly, inflammatory cells isolated from the airways of smokers with and without COPD expressed less IL-26 receptor complex and its associated transcription factors STAT1 and STAT3 [25]. It is still unclear whether this finding represents a protective mechanism.
against the pro-inflammatory activity of IL-26 or a defect that drives an increase in IL-26 production.

4. Conclusion
IL-26 has both direct and indirect antimicrobial functions and is constitutively expressed by many different immune and structural cell types in human airways. The local expression of IL-26 is upregulated in response to pathogen-associated molecular patterns, and IL-26 may enhance neutrophil mobilization to sites of infection. Interestingly, this IL-10-related cytokine exerts different inhibitory and pro-inflammatory effects on epithelial and immune cells from human airways, which highlights the importance of improving our understanding of its complete receptor biology. Based on a limited number of clinical studies on asthma and COPD, it can be concluded that local IL-26 is enhanced in the airways of patients with uncontrolled asthma, long-term smokers without COPD, and in long-term smokers with COPD who are undergoing exacerbations or have chronic bronchitis. Notably, these clinical studies have linked the upregulation of IL-26 with reduced lung function and markers of neutrophilic inflammation in patients with uncontrolled asthma and in patients with COPD and chronic bronchitis or exacerbations.

5. Expert opinion
From an immunological point of view, IL-26 emerges as a somewhat unique cytokine, given its capacity to kill bacteria directly, through a bactericidal effect, and indirectly, by promoting the mobilization of neutrophils. Clearly, due to its strong mechanistic link to the innate immune response in the airways, this ‘antimicrobial cytokine’ is interesting for asthma and COPD, two airway disorders in which the clinical course is impaired by bacterial colonization and infection. Moreover, the proven involvement of IL-26 in uncontrolled asthma, in COPD with chronic bronchitis or exacerbations, as well as its association with impaired lung function in these disorders, forwards it as a target of interest. Because IL-26 is abundantly expressed in human airways, this protein is also an accessible target for diagnostic purposes. However, it remains unclear whether the alterations in local IL-26 found in asthma and COPD represent a reactive and protective response or
a truly pathogenic one, a player that contributes to the progress of the referred airway diseases.

6. Five-year view

It seems both important and feasible that the intriguing receptor biology behind the dualistic effects of IL-26 can be dissected and better understood within the coming five-year period. We think that this will be necessary to determine how IL-26 should be targeted for clinical utility, whether in asthma or COPD. Likewise, it will be important to improve the understanding of which specific phenotypes of these two disorders may benefit from targeting IL-26. Notably, this key area of ‘target research’ will require extensive and costly clinical studies, combining a careful in-depth characterization of immunology, bacteriology, virology, and critical clinical features such as impaired lung function, symptoms, and exacerbation frequency in the coming years. In addition, it will be important to improve the understanding of how existing pharmacotherapy, including corticosteroids, affect immune signaling via IL-26 in the airways. Hopefully, this type of clinical research, with a stringent biological focus, can teach us how IL-26 can be utilized as a biomarker for diagnosis and monitoring or even as therapeutic target in two of the most prevalent and costly airway diseases at the global level.

Acknowledgments

The free-of-charge and non-copyright support of “smart.servier.com” in the processing of figures is gratefully acknowledged.

Funding

This manuscript was funded by the Swedish Asthma Allergy Foundation (AL: #F2019-0031), Heart-Lung Foundation (AL: #2010286), the Swedish Research Council (AL: #2021-01527) and Region Stockholm (AL: ALF #2018-0088).

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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