MINI-REVIEW

A Brief Overview of the Involvement of Il-26 In Asthma: Utility in Targeting Il-26

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ABSTRACT

Asthma is characterized by respiratory tract injury caused by immunocompetent cells, in particular $CD4^+$ T lymphocytes, that are involved via the production of distinctive sets of cytokines.Cytokines constitute one of the means of communication between cells through their ability to break down the different types of barriers (BBB, EBB).Variations in the secretion of these mediators in situ is a major indicator of an inflammatory situation associated with pathologies. The involvement of these cytokines in various pathologies has made it possible to draw up remedies for a large number of diseases. The dimeric cytokine interleukin (IL)-26 belong to the IL-10 family. It originally was perceived as a T-helper (Th) 17 cytokine. Subsequent studies have shown that IL-26 is produced by several populations of leukocytes and structural cells. This cytokine binds to a heterodimeric receptor complex including IL-10R2 and -20R1 (IL-26R) and signals through STAT 1 and STAT 3 to induce the release of chemokines and growth factors. Remarkably, IL-26 directly kills bacteria and inhibits viral replication. However, a duality of IL-26 appears between its inflammatory and protective role. Recent studies on human confirm multiple cellular sources in this critical interphase of host defence and demonstrate that stimulation of toll-like receptors (TLR) trigger the release of IL-26. Once released, it exerts a dualistic effect on cytokine production and up-regulates gene expression of IL-26R. IL-26 emerges as an important mediator, providing direct and indirect actions on microbes, actions that are essential for host defence and inflammation and bears potential as a biomarker of disease.The high level of IL-26 in asthma is altered and most often correlated with biological laboratory markers. It is hoped that further examination of IL-26 in the context of asthma could introduce new approaches allowing its use as a treatment, especially since IL-26 is produced by a multitude of inflammatory ones.

Key words: Asthma, IL-26, Biologic, Immunity, Cytokines.

INTRODUCTION

IL-26, also known as AK155, is a member of the IL-10 cytokine family that includes IL-10, interferon (IFN)-ds (IL-28A/B and IL-29), and the IL-20 subfamily (IL-19, IL-20, IL-22, IL-24, and IL-26).[1-3] IL-26 was first described as a gene whose expression is upregulated inherpesvirus saimiri-transformed T cells.[4]The expression of IL-26 is restricted to some T cell and natural killer (NK) cell subsets. The protein IL-26 has been evidenced in some Th17. [5] IL-26 has been reported to signal via the IL-10R2/IL-20R1 heterodimeric receptor. [6] While IL-10R2 is broadly expressed, IL-20R1 is expressed by many epithelial cell types, but not by hematopoietic cell. The only biological activity of IL-26reported so far is the upregulation of IL-8, IL-10, TNF-a, and/or CD54 expression by intestinal epithelial cell lines. Associated to a phosphorylation of STAT3 (and/or STAT1). [7-8]IL26 gene (*IL-26*) is located on chromosome 12q15, between *INFg* and *IL22*.[3]Here, we review the recent knowledge about IL-26 in asthma. IL-26 bears the potential to be an important mediator and effector molecule in host defence and inflammation in human airways.

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Utility in Targeting Cytokines: Biologic in Asthma

Biologics are an integral part of modern strategies for treatment of inflammatory diseases. Biologicals are proteins produced by biotechnology that have inhibitory effects on the mediators responsible for inflammation during an imbalance between lymphocyte populations. Treatment with biologics should follow the principle of suppressing inflammation and bringing the immune system to a state of homeostasis. Treatment for asthma should aim for remission or at least mild or minimal severity. Those biological treatments affect crucial points of bronchial inflammation. Among the mechanisms explored, there were IgE (Omalizumab), interleukin 5 (Mepolizumab and Reslizumab), interleukin 5 receptor alpha (Benralizumab) and interleukin 4/13 receptor (Dupilumab). Under investigation and expected to be soon commercialized is the monoclonal antibody blocking the thymic stromal lymphopoietin (Tezepelumab). Seemingly under study and promising, are anti-interleukin-33 (itepekimab) and anti-suppressor of tumorigenicity-2 (astegolimab).[9-12]Given these examples of therapeutic utility in the clinic, it seems imperative to improve the mechanistic understanding of additional types of cytokines and their signaling in inflammatory disorders in humans. It is imperative to understand the host's defence mechanisms against infections, which would facilitate the development of therapeutic alternatives to antibiotics.

Here we review current data on IL-26, a cytokine that was recently depicted in asthma. IL-26 bears the potential to bean important mediator and effector molecule in inflammation in human airways. There are a large number of resident (fibroblast, epithelial cell, endothelial cell….) and inflammatory cells (Th cells, NK cells, NKT cells, alveolar macrophages) in the human airways which are sources of IL-26 secretions. These cells also express IL-26R and interact with IL-26. Table 1 shows the state of recent knowledge on IL-26 in key immunological cells in the respiratory tracts. These data trace the various studies relating to the involvement of IL-26 as an inflammatory mediator.

Is IL-26 having a potential biomarker of disease severity in asthma?

Since IL-26 has been considered a pro-inflammatory cytokine, it is concluded that this cytokine can play pivotal roles in inflammatory diseases. Therefore, we aimed to discuss IL-26 expression and functions in asthma. IL-26 exerts a pivotal role in asthma pathogenesis [Table 1]. It has been confirmed that IL-26 levels were increased in peripheral blood (PBMC), bronchoalveolar lavage (BAL), induced sputum and asthmatic lung. In asthma, severalcytokines and chemokines such as IL-4, IL-13and IL-19 contribute to its pathogenesis. [13-16]Serum and Sputum IL-26 level were found increased in asthmatic patients compared to non-asthmatic controls. This study revealed a significant association of IL-26 gene polymorphisms with asthma for the first time which can serve as biomarkers for asthma. The significant increase of IL-26 serum protein levels in asthma patients suggested a major role of IL-26 in asthma phenotypes. [17-18]A study of single nucleotide polymorphisms (SNPs) in 440 adult asthmatics investigated the distribution of three IL-26 single nucleotide polymorphisms (rs7134599, rs2870946 & rs1558744).The presence of rs7134599 and rs1558744 polymorphisms considerably reduced the risk of developing asthma while the rs7134599 AA and AG genotypes protected against the asthma risk. The rs7134599 A allele was correlated with a lower risk of developing severe asthma while that of the rs2870946 CC genotype was associated with a higher risk of developing asthma in smoking patients ($p < 0.001$).[17]

Another study reported elevated level of IL-26 in asthmatic patients and was negatively correlated with lung function parameters (FEV1% and FEV1/FVCratio]. Conversely, the IL-26 level was linked to neutrophil accumulation in the lung. In vitro stimulation ofT helper (Th) $CD4^+$cells with recombinant IL-26 (rIL-26) has led to the generation of inflammatory cytokines (IL-1β, IL-6, IL-17Aand TNF-α) -producing $RORgt^+$ $IL-17^+$T cells. These mediators were known to promote the inflammatory process in severe asthma. [18]

The quantifying of airway IL-26 protein was investigated by Tufvesson*et al*. in 32 asthmatic patients. IL-26 was investigated in the BAL and transbronchial biopsiesof asthmatic patients. [19]The authors compared the level of IL-26 protein and IL-26 mRNA in uncontrolled asthmatics compared to controlled asthma and non-asthmatic participant. The concentration of IL-26 protein in cell-free BAL fluid was markedly lower in the pooled group of all patients with asthma than in healthy volunteers. In the subgroup with uncontrolled asthma, IL-26 concentration was higher than in the subgroup with controlled asthma, whereas it still tended to be lower than that in healthy volunteers.What is interesting to note that among all BAL-cell subsets, there was a clear trend toward a difference between controlled and uncontrolled asthma. In terms of BAL-cell counts, the IL-26 protein in cell-free BAL fluid displayed a negative correlation with lymphocytes, in the pooled group of all patients and particularly in the subgroup with uncontrolled asthma. There were strong similar trends for total leukocytes in these groups. Moreover, there was a corresponding correlation for macrophages in the pooled group of all patients with asthma. For eosinophils there was a corresponding correlation in uncontrolled asthma but there was no such correlation for neutrophils. At the gene level, IL-26 mRNA in BAL cells was higher in the subgroup with uncontrolled asthma compared with the subgroup with controlled asthma. What seems incomprehensible, the referred mRNA did not display any correlation with IL-26 protein in cell-free BAL fluid. The most interesting data was the detection of IL-26 positive cells in bronchial mucosa and alveolar lung parenchyma

from all asthmatic subjects. In alveolar lung parenchyma, the pooled group of patients with asthma (controlled and uncontrolled) displayed clearly immunoreactivity for IL-26 protein compared with healthy volunteers. In the subgroup with uncontrolled asthma, the referred immunoreactivity in alveolar lung parenchyma tended to be higher than that in the subgroup with controlled asthma, although lower than that in healthy volunteers. This shows above all that the treatment received by asthmatics would have a suppressive effect on the production of IL-26. This work is thought provoking that the data sets on IL-26 mRNA in BAL leukocytes, as well as protein in alveolar parenchymal tissue, support the idea that there is more gene expression leading to higher protein production of IL-26 in uncontrolled compared with controlled asthma, and that there is less IL-26 protein in the peripheral airways of adult patients with asthma than in healthy volunteers. [19]

One of the factors contributing to the severity of asthma is obesity. A recent study reports that exhaled IL-26 might be a perspective biomarker in non-obese and obese asthmatics. This theme is interesting because obese patients most often present with a more severe inflammatory process than non-obese patients. Avramenko et al. reported that exhaled IL-26 is elevated in obese and non-obese moderate-to-severe asthmatic patients. Exhaled IL-26 might be a perspective biomarker in non-obese and obese asthmatics. [20]

Adel-Patient *et al*. reported an analysis of a large set of immune constituents which may allow the identification of a biological immune signature of severe asthma. Such an approach may provide new leads for delineating the pathogenesis of severe asthma in children and identifying new targets for its diagnosis, prediction, and personalized treatment.[21]IL-26 was considered by the authors as a very important parameter depicting the complexity of immunological profile of severe asthmatics.

A pilot study from Konradsenet al. suggested that sputum IL-26 in severe asthma could be considered asa potent biomarkers of Th2-mediated inflammation. Sputum IL-26 protein bears a potential as a biomarker of disease severity in a clinical phenotype of pediatric asthma.[22]

Il-26 and the Barrier Epithelial Cells

The barrier of bronchial epithelial cells constitutes an important immunological interphase lining the airways, thus forming a physical obstacle as well as biochemical barrier against inhaled particles, pathogens, allergens or toxins. IL-26 has a unique combination of properties in that it is very abundant in the airways, mediates innate as well as adaptive immune responses, while at the same time displaying both direct and indirect antimicrobial effects.[23]IL-26 emerges as a “dualistic cytokine”, an interpretation that seems feasible given that IL-26 is a member of the anti-inflammatory IL-10 family and at the same time is produced by pro-inflammatory Th17 cells. In analogy, IL-26 may in effect be pro- or anti-bacterial and pro- or anti-viral, for mechanistic reasons that are yet to be understood. Taken together, current evidence forwards a solid rationale for improving the understanding of the conditions that determine what specific role IL-26 plays in specific pathology, including inflammatory disorders as well as infections.[23]

Alveolar macrophages represent a broad spectrum of the immune barrier in the airways. Enriched alveolar macrophages have been shown to secrete IL-26 in the BAL and in the induced sputum and that this release is increased in response to the bacterial compound endotoxin in vitro. [23] Several arguments have confirmed that macrophages ($CD68^+$) produce IL-26 in the joints of patients with rheumatoid arthritis, which reinforces the argument that these cells are an important source of IL-26 in the human.[24] Macrophages express IL-26R, IL10R2 and IL20R1, as well as the downstream signaling molecules STAT1 and STAT3 [23] Thus, the production of IL-26 in alveolar macrophages and the simultaneous increase in the expression of its receptors. argue for feedback mechanisms that may be essential in directing host defense and inflammation in cells. respiratory tracts. Reported data indicated that bronchial tissue removed during bronchoscopy displays elevated levels of intracellular IL-26 protein in the lining epithelium. [25] Moreover, primary bronchial epithelial cells isolated from healthy individuals constitutively produce IL-26 and stimulation with viral stimuli including TLR3 agonist, TLR7 agonist or TLR8 agonist increased the production and release of IL-26.[25] Stimulation of CD4+ T cells in culture with monocytes by recombinant IL-26 promoted the generation of $RORgt^+$ $Th17^+$ cells inducing the production of the inflammatory cytokines (IL-17A, IL-1β, IL-6 and TNF-α). IL-26 expressed in the sputum of asthmatics was biologically active and induced the secretion of IL-17 in the presence of the cytokines IL-1β and IL-6 [18]. The presence of IL-26 and T cells in the airways are also reported by Che et al.[26]The immunostaining of leukocytes harvested from healthy subjects during bronchoscopy revealed co-expression of IL-26 protein with the T cell surface marker CD3, $CD4^+$, $CD8^+$ as well as a subset positive for RORCvar2, the transcription factor for Th17 cells.[26] Human bronchial tissue specimen obtained from patients with obliterative bronchiolitis after allogeneic stem cell transplantation display enhanced infiltration of $CD4^+$cells, $CD26^+$cells and IL-26protein, compared to healthy participant. [27]Additional reports in other disorders showed the expression of IL-26 in serum, BAL and cerebrospinal fluid in patients with Behcet disease.[28-29]This confirms the evidence of the production of IL-26 by various subtypes of T lymphocytes directly involved in the defense and in the inflammatory process. The IL-10R2 subunit is ubiquitously expressed by T cells.[30]To the best of our knowledge there are no studies investigating the role of IL-26, in pulmonary fibrosis and in endothelial cells and the

role of IL-26 needs to be elucidated.

Neutrophils constitute key effector cells in the airways of asthmatic patients.[31] Currently, there are no complete studies showing that neutrophils in the airways produce IL-26 that have been published. However, data from our laboratories indicates that sputum neutrophils from asthmatics were significantly correlated with IL-26.[17-18; 31] Interestingly, the IL-26R sub-units IL-10R2 and IL-20R1 can be detected in human blood neutrophils but the respective gene expressionis not altered in response to the bacterial components endotoxin and NFormylmethionyl-leucyl-phenylalanine (fMLF), nor in response to rhIL8 or rhIL-26 protein [32]. In addition, gene expression of, and phosphorylation of STAT1 and 3 are detected in blood neutrophils.[32]The induced release of IL-26 protein from blood neutrophils in response to endotoxin is indicative that localized airway neutrophils may respond in a similar manner. [24]

The airway epithelium is the first line of defense for the lungs, detecting inhaled environmental threats through pattern recognition receptors expressed transmembrane or intracellularly. Activation of pattern recognition receptors triggers the release of alarmin cytokines IL-25, IL-33, and TSLP. These alarmins are important mediators of inflammation, with receptors widely expressed in structural cells as well as innate and adaptive immune cells.[33]With genome-wide association studies demonstrating associations between single-nucleotide polymorphisms of the TSLP and IL-33 gene and risk of asthma, it will be important to understand which subsets of asthma patients will benefit most from anti-alarmin therapy.[34-36]TSLP was structured similarly to IL-17 and has been found to induce Th2 inflammatory responses. Ithas been hypothesized that the production of TSLP in the keratinocytes of atopicdermatitis lesions may play a key role in the pathway that leads to asthma from AD.[16]Epithelial cells induced mediators potentiate proinflammatory effects, increase the number of Th2 cells, activate dendritic cells, increase the number of mast cells, and recruiteosinophils, basophils, neutrophils, T-cells, monocytes and dendritic cells. The interactions between T lymphocytes, macrophages and resident cell cells must be analyzed, thus making it possible to delimit the mediators likely to be converted into treatments. IL-26 constitutes a potential target for diagnostic purposes and therapeutic modulation of the innate immune response in the airways of patients with asthma. It is possible that more

Table 1. Defined Role of IL-26 in Asthma

References	Expert opinion:Conclusion	Key words
36	Potential target for diagnostic purposes and therapeutic modulation	Asthma; COPD; IL-26; Th17; neutrophils
20	Exhaled IL-26 might be a perspective biomarker in non-obese and obese asthmatics.	Asthma; IL-26; obesity; systemic inflammation.
21	IL-26 may provide new leads for delineating the pathogenesis of severe asthma in children and identifying new targets for its diagnosis, prediction, and personalized treatment.	children; immune signature; pathogenesis; precision medicine; severe asthma.
22	IL-26 emerges as essential for host defense and inflammation/ apotential biomarker of disease.	Host defense; IL-10 cytokine family; IL-26 in airways; Inflammation; Th17 cytokines biomarkers.
16	It is worthwhile to pursue research into biologics as a more successful treatment option for moderate-to-severe atopic dermatitis.	atopic dermatitis; cytokines; inflammation;
17	A significant association of IL-26 gene polymorphisms with asthma which can serve as biomarkers for asthma.	Asthma; Genetic association; Interleukin-26 gene; Interleukine-26 protein; Single nucleotide polymorphism.
18	IL-26 appears as a novel pro-inflammatory cytokine, produced locally in the airways that may constitute a promising target to treat asthma inflammatory process.	IL-17A; IL-1β; IL-26; IL-6; asthma; inducedsputum.
19	inhaled corticosteroids may account for the average decrease in extracellular IL-26 protein in all patients with asthma.	IL-26 protein; airway lumen and tissue; gene expression
22	IL-26 is a potential biomarker of disease severity in pediatric asthma	Asthma; Children; Eosinophil; FENO; IL-26; Neutrophil; Sputum.

conclusive evidence of the usefulness of IL26 in the clinic will arrive in the coming years. [37]

CONCLUSION

The pathogenesis of asthma is complex and underscores the need to individualize treatment(s) specifically for sufferers. Asthma patients suffer from pulmonary barrier dysfunction and are susceptible to environmental triggers and pathogens, resulting in poor quality of life. Inflammation is mainly mediated by Th1, Th2 and Th17. After many efforts by the scientific community, certain cytokines have been invested in the treatment of asthma. IL-26, given its secretion by a large number of lymphocyte subpopulations and resident cells, could be a pro- or anti-inflammatory mediator in severe asthma. Large studies still need to be conducted to prove the safety and effectiveness of IL-26 as an asthma treatment.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Sabrine Louhaichi and *Basma Hamdi* conceptualized the study, investigated the data.

Agnes Hamzaoui and *Kamel Hamzaoui* conceptualized the study, wrote the original draft, wrote, reviewed and edited the manuscript, designed the methodology and supervised the data.

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