Role of Th17 Cytokines in Airway Remodeling in Asthma and Therapy Perspectives

Victor Margelidon-Cozzolino 1*, Anne Tsicopoulos 1, Cécile Chenivesse 1,2 and Patricia de Nadai 1

1 Univ. Lille, CNRS, INSERM, CHU de Lille, Institut Pasteur de Lille, Unité INSERM U1019-UMR9017-CIIIL-Centre d’Infection et d’Immunité de Lille, Lille, France, 2 CRISALIS (Clinical Research Initiative in Severe Asthma: a Lever for Innovation & Science), F-CRIN Network, INSERM US015, Toulouse, France

Airway remodeling is a frequent pathological feature of severe asthma leading to permanent airway obstruction in up to 50% of cases and to respiratory disability. Although structural changes related to airway remodeling are well-characterized, immunological processes triggering and maintaining this phenomenon are still poorly understood. As a consequence, no biotherapy targeting cytokines are currently efficient to treat airway remodeling and only bronchial thermoplasty may have an effect on bronchial nerves and smooth muscles with uncertain clinical relevance. Th17 cytokines, including interleukin (IL)-17 and IL-22, play a role in neutrophilic inflammation in severe asthma and may be involved in airway remodeling. Indeed, IL-17 is increased in sputum from severe asthmatic patients, induces the expression of “profibrotic” cytokines by epithelial, endothelial cells and fibroblasts, and provokes human airway smooth muscle cell migration in in vitro studies. IL-22 is also increased in asthmatic samples, promotes myofibroblast differentiation, epithelial-mesenchymal transition and proliferation and migration of smooth muscle cells in vitro. Accordingly, we also found high levels of IL-17 and IL-22 in a mouse model of dog-allergen induced asthma characterized by a strong airway remodeling. Clinical trials found no effect of therapy targeting IL-17 in an unselected population of asthmatic patients but showed a potential benefit in a sub-population of patients exhibiting a high level of airway reversibility, suggesting a potential role on airway remodeling. Anti-IL-22 therapies have not been evaluated in asthma yet but were demonstrated efficient in severe atopic dermatitis including an effect on skin remodeling. In this review, we will address the role of Th17 cytokines in airway remodeling through data from in vitro, in vivo and translational studies, and examine the potential place of Th17-targeting therapies in the treatment of asthma with airway remodeling.

Keywords: asthma, airway remodeling, Th17 inflammation, interleukine-17, interleukine-22
INTRODUCTION

Asthma is a chronic respiratory disease characterized by lower airway inflammation, leading to airway hyperresponsiveness (AHR) and airway obstruction, resulting in recurrent symptoms (chest wheezing, cough, dyspnea), exacerbations (flare-up) and altered quality of life. As one of the most frequent chronic respiratory disease, asthma is estimated to affect around 5–10% of adults (up to 20% in high-income countries) and from 5 to 20% of children. As a consequence, asthma is a major public health issue (1–4). The cornerstone of the treatment of asthma is inhaled steroids (ICS). Severe asthma is defined as asthma requiring at least high doses of ICS in association with another controller (generally long-acting beta-agonist bronchodilators) and/or oral steroids more than half a year to be controlled, or that remains uncontrolled despite these therapies (5–7). The burden of asthma is particularly heavy in patients with severe asthma who experience a severely impaired quality of life, respiratory disability, frequent and severe exacerbations, poorer control of symptoms, and hospitalisations. Severe asthma is also associated with lower respiratory function with persistent airway obstruction, representing about 50% of severe asthmatic patients, and sometimes loss of reversibility of airway obstruction (6–8). These patients account for the major part of asthma-related healthcare cost (6, 7).

From a pathophysiological point of view, persistent airway obstruction and loss of reversibility are the clinical hallmark of airway remodeling. Airway remodeling is a complex biological process, found in most chronic inflammatory airway diseases, which contributes to airway obstruction (9). In asthma, airway remodeling is characterized by several elementary structural changes in bronchial mucosa: loss of epithelial integrity, epithelial-mesenchymal transition (EMT), goblet cell hyperplasia, mucus hypersecretion, subepithelial fibrosis with thickening of epithelial basement membrane, smooth muscle cell proliferation, and hypertrophy. Inflammatory cell infiltration in bronchial mucosa can also be associated with airway remodeling and contribute to this process (10–12). These changes lead to increased lower airway resistances and reduced bronchial lumen, thus contributing to persistent airway obstruction. Although airway remodeling is present in asthma in all degrees of severity, airway remodeling intensity correlates with asthma severity (11, 13–17).

Asthma has long been considered as an allergic Th2-driven inflammatory disease, involving the “canonical” Th2 cytokines [ interleukines (IL)-4, IL-5, IL-13], eosinophilic inflammation, and mediators of allergic inflammation (mainly immunoglobulins E and mast cells) (18). Over the last 20 years, major advances have been made in the understanding of asthma immunobiology and heterogeneity. Cluster analyses of large cohorts of patients allowed to identify several homogeneous subpopulations of asthmatic patients according to clinical characteristics (phenotypes), and their correlates in inflammatory and immunobiological processes (endotypes) (18–20). Hence, asthmatic patients are currently categorized according to the dominant inflammatory pathway driving bronchial inflammation, and particularly the degree of involvement of T2 inflammation: T2high asthma (typically allergic and non-allergic eosinophilic asthma) vs. T2low asthma (21). T2low asthma refers to a heterogeneous group of patients with distinct endotypes, currently poorly characterized, like neutrophilic or paucigranulocytic inflammation.

Both patients with T2high or T2low asthma can present severe asthma. However, the neutrophilic endotype, characterized by a predominance of neutrophils in airway inflammation, has been particularly associated with severe asthma and resistance to ICS and oral steroids (22–25). In contrast, T2high asthma is more commonly associated with response to steroids. Additionally, patients with T2high severe asthma have now access to effective biotherapies that have emerged over the last decade, based on monoclonal antibodies targeting Th2 cytokines and immunoglobulins E (26). Although involvement of non-T2 pathways in asthma remains not fully understood, recent works have highlighted the role of Th17-driven inflammation in T2low asthma (27–29). Th17 CD4+ cells produce IL-17 and IL-22, two key cytokines involved in neutrophilic inflammation in the context of antimicrobial host defense, and in the regulation of epithelial function and repair. These cytokines are both also implicated in inflammatory disease pathology such as rheumatoid arthritis or psoriasis (30). As neutrophilic inflammation has been associated with T2low asthma and severe asthma (22, 23), a role for Th17-type cytokines in asthma and airway remodeling has been rapidly postulated and gradually investigated over the past few years.

In this review, after going over the molecular and cellular mechanisms of the Th17 pathway, we will further scrutinize the existing evidences of the involvement of the Th17-type cytokines in asthma and airway remodeling. We will also comprehensively focus on the biological clues involving IL-17 and IL-22 in each of the elementary pathological component of airway remodeling. Eventually, an updated overview of the perspectives of Th-17 targeted therapies in asthma will be provided.

TH17-CYTOKINE PRODUCING CELLS AND TH17 DIFFERENTIATION

In the 2000’s, a subpopulation of CD4+ T cells, distinct from Th1 et Th2 cells, and characterized by the production of IL-17A (also named IL-17), IL-17F and IL-22 was identified and named accordingly to these cytokines “Th17 cells” (31–35). Their role in general inflammatory pathophysiology and more specifically in respiratory diseases and asthma has rapidly been investigated and led to the concept of a “Th17 pathway” and Th17-type cytokines (IL-17, IL-17F, and IL-22). Alongside Th17 cells, other cell types were subsequently found to be sources of Th17-type cytokines. Moreover, a subtype of CD4+ T cells producing only IL-22 but not IL-17 (Th22 cells), was later discovered (36, 37). More recently, a specific subset of innate lymphoid cells (ILC), named ILC3, has emerged as another important local cellular source of IL-17 and IL-22, especially in asthma (38, 39). Eosinophils were also found to produce IL-17 in asthma (40). Other cell types have been shown to produce Th17-type cytokines but their contribution to asthma pathophysiology is not fully
FIGURE 1 | Th17 pathway. (Left) acquisition of Th17 differentiation. 1-IL-6 and TGFβ, and IL-1β promote RORγt expression and Th17 differentiation. 2-IL-6 and TGFβ induce IL-23R expression which allows IL-23 to stabilize Th17 differentiation. 3-Th17 differentiation also includes secretion of IL-21 which in turn enhances Th17 differentiation, acting as a positive feedback loop. 4- IL-21 secretion by Th17 cell. (Right) action of IL-17 and IL-22 on their respective receptors and activation of corresponding downstream pathways in an epithelial cell. 5- IL-22 binding protein (IL-22BP) regulates action of IL-22. 6-IL-22R activation induce Janus Kinase 1 (JAK) and Tyk2 associated kinases which lead to activation of transcription factor STAT3 by phosphorylation. 7 -IL-17R binding by IL-17 activates SEFIR intracellular domain which activates ERK, MAPK, C-Jun N-terminal pathways, and transcription factor NF-κB.

elucidated: γΔ T cells, CD8⁺ T cells, B cells, Natural Killer T cells (41–46). Of note, mixed cytokine phenotypes have been identified in asthmatic patients such as Th2/Th17 (co-expressing IL-4 and IL-17) and Th1/Th22 [co-expressing Interferon (IFN) and IL-22] profiles (47, 48). This might be of interest as *in vitro* data seem to indicate that IL-4 and IFN-γ play a role in Th1/Th2 polarization of human bronchial epithelial cells and may contribute to airway remodeling particularly through IL-4-induced expression of RUNX2 in epithelial cells which stimulates TGFβ production (49).

Th17 differentiation is dependent on the high expression of the master transcription factor Retinoic acid receptor-related Orphan Receptor-γt (RORγt) (and to a lesser extent RORα), leading to Th17-type cytokine production (50, 51). Th17 differentiation is initially promoted either synergistically by IL-6 and TGF-β, or by IL-1β, respectively through STAT3, SMADs, and AKT/mTOR and p38 pathway activations (52–61) (Figure 1). Aryl hydrocarbon receptor transcription factor ligands can also promote Th17 differentiation by binding their cytosolic receptor (62, 63). Amplifying auto-feedback loops involving IL-21 and IL-23 ensure stabilization of Th17 differentiation and proliferation of Th17 cells (44, 52). Of note, type 1 and 2 interferons, IL-27, and IL-4 cytokines have the ability to inhibit Th17 differentiation (64–67). Triggers of Th17 differentiation are multiple, including microbial environment (of which microbiome composition), sodium homeostasis, allergy, complement activation and inorganic particle exposure (61). Interestingly, in mice, the exposure to microbiota promotes the expansion of Th17 cells, ILC3, and regulatory T cells exhibiting characteristics of Th17 differentiation (expression of RORγt), which negatively regulates Th2 response, in intestinal mucosa (68). Th17 regular function is currently thought to promote tissue inflammation in order to ensure early clearance of extracellular pathogens for which Th1 and Th2 responses are insufficient (61, 69, 70). Th22 differentiation requires IL-6 and TNFa co-stimulation (Figure 1). IL-22 can also be co-secreted by Th1 and Th2 cells. Aryl hydrocarbon receptor has been suggested as the master transcriptional factor of Th22 cells but is not the only Th22 differentiation determinant (71).

**TH17 CYTOKINES AND PATHWAYS**

IL-17A, initially known as CTLA-8, belongs to a family of cytokines including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. Among them, IL-17A (also known as IL-17) and IL-17F have been the most comprehensively studied members, and have been shown to play a physiological and pathophysiological role in humans (61). IL-17A mainly exists under a homodimeric form (72). IL-17A promotes inflammation through stimulation of granulopoiesis, induction of neutrophil-attractant and neutrophil-activating cytokines and chemokines (CXCL1, CXCL2, CXCL5, CXCL8, CXCL9,
IL-22R, contributes to IL-22 pathway regulation (78–80). IL-17 effects are transduced by the SEFIR intracellular domain of IL-17R. Downstream IL-17R signaling noticeably activates NFkB, ERK, and MAPK and c-Jun N-terminal kinase pathways (61) (Figure 1).

IL-22 belongs to the IL-10 cytokine family. It plays an important role in host defense in barrier tissues, and in epithelial protection and regeneration after injury (42, 46, 81–85). It enhances proliferation and migration of cells expressing IL-22R, while it inhibits their apoptosis and differentiation (86–89). The antimicrobial activity of IL-22 includes the stimulation of S100 protein and defensin productions (90). Interestingly, IL-22 production is dependent of the Aryl hydrocarbon receptor transcription factor (62, 91). IL-22 binds a heterodimeric receptor made up of the IL-22R1 and IL-10R2 subunits. Interestingly, IL-22R is only expressed on structural cells (epithelial and endothelial cells, fibroblasts, and smooth muscle cells) and not in hematopoietic cells. This repartition of IL-22R is highly relevant regarding the potential role of IL-22 in airway remodeling as these cell types are involved in airway remodeling processes. IL-22R mainly activates downstream STAT3 through transduction signals involving the receptor associated Janus kinases Jak1 and ‘Tyk2 (92–94) (Figure 1). A soluble receptor for IL-22 [IL-22 binding protein (IL-22BP)], sharing high homology with IL-22R, contributes to IL-22 pathway regulation (95). IL-22 also plays a role in the tissue recruitment of neutrophils by inducing the production of neutrophil attracting chemokines, notably that of CXCL1 and CXCL5 by bronchial epithelial cells (96).

Interactions between IL-17 and IL-22 remain mostly not well-understood. Initially thought to be exclusively part of the same immunological response because of their common cellular source (Th17 cells, ILC3), each of these cytokines is also produced independently by many other cells (Th1 cells, Th22 cells, mixed Th1/Th22 cells for IL-22; Th2/Th17 for IL-17) (42, 48). Several studies suggest a mutual ability of IL-17 and IL-22 to inhibit each other production and respective Th17 and Th22 differentiation (97–99).

Beyond the homeostatic functions of IL-17 and IL-22, Th17 response is known to be involved in several chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, and atopic dermatitis (100–103). Among these diseases, some are particularly characterized by neutrophilic inflammation and tissue remodeling, such as psoriasis and atopic dermatitis. As a consequence, the role of IL-17 and IL-22 in asthma, has been questioned over the last two decades.

### INVOLVEMENT OF IL-17 AND IL-22 IN ASTHMA

The contribution of IL-17 in asthma was first suspected from the identification of asthmatic patients with neutrophilic inflammation in sputum as a distinct cluster of non-eosinophilic severe asthma (104, 105). Knowing the central role of IL-17 in neutrophil migration, recruitment and activation, multiple studies investigated the association between IL-17 levels in serum, sputum, bronchial biopsies and asthma. Most studies found not only increased IL-17 levels in asthmatic patients (28, 40, 106–108), but also positive correlation between IL-17 levels and asthma severity and association with airway neutrophilia (106, 109, 110). The presence of cells expressing IL-17 (ILC3 cells, Th17 cells) was also positively correlated with asthma severity (22, 39). Interestingly, specific Th2/Th17 CD4+ T cells, producing both Th2 and Th17 cytokines were identified in bronchoalveolar lavage (BAL) of asthmatic patients. Severe asthma was associated with increased Th2/Th17 cells predominantly polarized toward IL-17 production (Th2/Th17high) in BAL (111). The involvement of IL-17 in asthma pathogenesis was further confirmed in murine models, which globally found that ovalbumin sensitization (inhaled, intraperitoneal, or epicutaneous route) followed by inhaled challenge was associated with Th17 response, up-regulation of IL-17 in airways, and that up-regulation of IL-17 enhanced airway neutrophilia and steroid-resistant AHR (112–115). IL-17 production is also increased in obesity-associated murine models of asthma and asthmatic pediatric patients (38, 39, 116). Data from murine models are summarized in Table 1.

Similarly, IL-22 and IL-22R upregulation was suggested in several studies in serum and in bronchial biopsies from asthmatic adults and children (predominantly in severe asthmatic patients) and in murine models of asthma, as well as in patients with other allergic respiratory diseases such as atopic rhinitis (99, 121–124). IL-22 producing cells, particularly lymphocytes, are also increased in bronchial biopsies from asthmatic children (123).

However, the role of IL-22 as a protective or a pathogenic actor in asthma remains less clear than that of IL-17, as pathogenic effect failed to be constantly reproduced in murine models. Indeed, conflicting evidences have shown that IL-22 could have deleterious but also beneficial effects on airway epithelium in asthma (42, 95, 125, 126) (Table 2). Hence, a protective action of IL-22 on airway allergic inflammation, in particular on airway eosinophilic inflammation and Th2 cytokine production, on AHR and even on some pathological feature of airway remodeling (goblet cell hyperplasia) has been described in several studies (127–129, 131). On the other hand, as underlined by Hirowe et al. in an extensive review about dual effects of IL-22 on airway epithelium, atopic dermatitis models and some murine models of asthma found pro-inflammatory effects of IL-22, with enhanced AHR and airway remodeling (mucus hyperproduction and goblet cell hyperplasia, and smooth muscle cell hyperplasia) (95, 99, 133, 134). These contrasting results have been discussed in a previous review (125) (Table 2). One of the main differences between these studies is the route of
| Study | Murine Model | Allergen | Route of sensitization | Method to study IL-17 effects | Phase of allergic inflammation investigated | Global effect of IL-17 on Th2 cytokines | Effect of IL-17 on IL-22 | Effect on eosinophilic inflammation | Effect on neutrophilic inflammation | Effect on AHR | Effect on airway remodeling |
|-------|-------------|---------|------------------------|-----------------------------|---------------------------------------------|---------------------------------------|-----------------------|----------------------------------|---------------------------------|-------------|---------------------------|
| Hellings et al. (117) | Balb/c | OVA | Ip | Anti-IL-17 Ab | Se+Chal | ↓ | NS | ↑ | ↑ |
| He et al. (113) | Balb/c | OVA | • Ip • Ec | Anti-IL-17 Ab | Se+Chal | Pro-inflammatory | NS | NS | ↑ | ↑ |
| McKinley et al. (115) | Severe combined immunodeficient Balb/c | OVA | N/A | • IL-17RA KO • Infection with IL-17 overexpressing Adenovirus | Chal | Pro-inflammatory | NS | ↑ | ↑ |
| Wilson et al. (112) | C57BL/6 | OVA | • Ip • It | IL-17RA KO | Se+Chal | Pro-inflammatory | NST | ↓ | ↑ | ↑ | NS (mucus) |
| Wang et al. (118) | C57BL/6 | OVA | Ip | Anti-IL-17 Ab | Se+Chal | Pro-inflammatory | ↑ | ↑ | ↑ | ↑ (mucus, s.e. fibrosis, SM hypertrophy) |
| Ano et al. (114) | Transgenic C57BL/6 (RORγt overexpression) | OVA | Sc | Anti-IL-17 Ab | Se+Chal | Pro-inflammatory | NS | ↑ | ↑ |
| Zhao et al. (119) | C57BL/6 | OVA | • Ip • It | Stimulation with IL-17 | Se+Chal | Pro-inflammatory | ↑ | NS | ↑ (alteration of epithelial integrity) |
| Kim et al. (39) | C57BL/6 + High Fat Diet | N/A | N/A | IL-17 KO | N/A | Pro-inflammatory | ↑ | | |
| Camargo et al. (120) | Balb/c | OVA | Ip | Anti-IL-17 Ab | Se+Chal | Pro-inflammatory | ↑ | ↑ | ↑ | ↑ (s.e. fibrosis, MMP-9 production) |
| Lamb et al. (108) | Balb/c | N/A | N/A | Stimulation with IL-17 • Anti-IL-17 Ab | N/A | Pro-inflammatory | NS | NS | NS | NS |

OVA, ovalbumin; Ip, intraperitoneal; Sc, subcutaneous; Ec, epicutaneous; It, intratracheal; Ab, antibody; KO, knock out gene; Se, allergen sensitization; Chal, allergen challenge; NST, effect of IL-17 non-specifically tested; NS, non-significant effect; AHR, airway hyperresponsiveness; s.e, subepithelial; SM, smooth muscle; MMP-9, matrix metallopeptidase 9; N/A, non-applicable.
TABLE 2 | Summary of studies showing conflicting evidence about the role of IL-22 in asthma murine models.

| Study | Murine Model | Allergen Route of sensitization | Method to study IL-22 effects | Phase of allergic inflammation investigated | Global effect of IL-22 | Effect of IL-22 on Th2 cytokines | Effect of IL-22 on IL-17 | Effect on eosinophilic inflammation | Effect on neutrophilic inflammation | Effect on AHR | Effect on airway remodeling |
|-------|--------------|-------------------------------|-------------------------------|------------------------------------------|------------------------|---------------------------------|---------------------------|---------------------------------|-------------------------------|----------------|-----------------------------|
| Takahashi et al. (127) | Balb/c OVA | IP | Anti-IL22 Ab | Se + Chal | Protective | ↓ | ↓ | ↓ | ↓ | ↓ |
| Taube et al. (128) | C57BL/6 OVA | IP | IL-22 KO | Se + Chal | Protective during Se | ↓ only during Se | ↓ | ↓ | ↓ | ↓ |
| Nakagome et al. (129) | Balb/c OVA | IP | • IL-22BP | Se | Protective during Se | ↓ | ↓ | ↓ | ↓ | ↓ |
| Besnard et al. (99) | C57BL/6 OVA | Sc | • Anti-IL22 Ab | Se | Protective during Se | ↓ | ↓ | ↓ | ↓ | ↓ |
| Fang et al. (130) | C57BL/6 OVA | IP | • Lung-inducible IL-22 expression | Se + Chal | Protective | ↓ | ↓ | ↓ | ↓ | ↓ |
| Ito et al. (131) | C57BL/6 HDM | Intratracheal | IL-22 KO | Se + Chal | Protective | ↓ | ↓ | ↓ | ↓ | ↓ |
| Leyva-Castillo et al. (132) | Balb/c OVA | • Ec | Anti-IL22 Ab | Se + Chal | Pro-inflammatory with IL-17 | ↑ only during Ec | ↑ | ↑ | ↑ | ↑ |

OVA, ovalbumin; HDM, house dust mite; IP, intraperitoneal; Sc, subcutaneous; Ec, epicutaneous; Ab, antibody; KO, knock out gene; IL-22BP, IL-22 Binding Protein; Se, allergen sensitization; Chal, allergen challenge; wo, without; AHR, airway hyperresponsiveness.

Airway inflammation contributes to the airway remodeling process (10). In asthma, airway inflammation is usually characterized by Th2 inflammation with eosinophilic cell infiltration. In atopic dermatitis, a well-known Th22-driven inflammatory disease, this inflammatory signature is positively correlated with asthma severity (133). Similarly, Lamb et al. (134) found an upregulated Th17 transcriptomic signature in severe asthma with airway remodeling. Overall, the movement of IL-22 in asthma seems very likely, its exact role is still to be clarified.

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infiltration of airways. Nevertheless, airway neutrophilia is classically associated with severe asthma (23). Neutrophilic asthma is also associated with steroid resistance, poorer lung function (FEV1) and lower reversibility of airway obstruction, which can be accounted by airway remodeling (22, 25, 140–142).

IL-17 and IL-22 are involved in neutrophilic inflammation in asthma. As demonstrated on bronchial biopsies from a large cohort of asthmatic patients, airway neutrophilia is associated with both increased IL-17 and IL-22-producing cells (22, 108). More recently, Badi et al. showed in a cohort of asthmatic patients that the degree of enrichment in atopic dermatitis–similar transcriptomic signature, including overexpression of Th17 and Th22-related genes, was strongly associated with severe neutrophilic asthma (138).

Indeed, IL-17 is a key cytokine in the recruitment and activation of neutrophils (69, 76). Neutrophilia is correlated with IL-17 expression in airway epithelium (108). In murine models of asthma, IL-17 stimulates and orchestrates airway neutrophilic infiltration by inducing the expression of neutrophil-attractant chemokines like CXCL1, CXCL2, IL-6, and IL-8 in humans (75, 108, 112–115, 117, 143).

Though its place still needs to be clarified in airway neutrophilia, IL-22 seems also to be an important factor in neutrophil recruitment (144, 145). It is to also enhance production of neutrophil recruitment associated chemokines like CXCL8 (in humans), CXCL1, CXCL2, CXCL3, CXCL5, and IL-1b, particularly in mold allergen-induced asthma murine models (132, 137, 143, 144, 146). Interestingly, several data suggest a pro-inflammatory effect of IL-22 synergistically with IL-17 on airway neutrophilia by inducing the expression of chemokines by epithelial cells but also by airway smooth muscle cells (98, 108, 143, 147).

Overall, the association between both of these cytokines and neutrophilic inflammation is highly relevant, knowing that neutrophils are thought to be an effector cell of airway remodeling, particularly through the release of proteolytic enzymes like elastases and metalloproteases (notably MMP-9), thus participating in structural change of the extracellular matrix of bronchial epithelium (148, 149).

INVolVEMENT OF IL-17 AND IL-22 IN AIRWAY REMODELING

Experimental data provides substantial arguments for an involvement of IL-17 and IL-22 in airway remodeling through their contribution to the diverse pathobiological processes that lead to airway remodeling: subepithelial fibrosis, mucus hyperproduction, airway inflammation and smooth muscle cell hyperplasia and hypertrophy.

Out of the field of asthma, IL-17 and IL-22 enhance airway remodeling in murine models of lung injury by pollutants (airway neutrophilic infiltration, epithelial desquamation, subepithelial fibrosis) (150). They are also involved in tissue remodeling in other inflammatory diseases (bone remodeling in psoriatic arthritis, skin remodeling in atopic dermatitis) as well as in other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) (76, 100, 151–158).

The enhancement of airway remodeling by IL-17 has been confirmed in murine models of asthma in which its blockade by anti-IL-17 antibodies or genetic deficiency reduced mucus hypersecretion, goblet cell hyperplasia, subepithelial collagen deposition and airway smooth muscle layer thickening together with airway neutrophilia (118, 119). Interestingly, IL-17 seemed to increase epithelium permeability to allergen, indicating a loss of epithelial integrity, also observed in airway remodeling (119). IL-17-induced airway remodeling seemed to be dependent on IL-6 (119), and to be partially mediated through heparin-binding epidermal growth factor (HB-EGF) (118).

Regarding the specific topic of airway remodeling, the understanding of the role of IL-22 suffers from conflicting evidences. Fang et al. found a modulatory effect of IL-22 with decreased eosinophilic inflammation and Th2 cytokine secretion, decreased AHR but also reduced mucus production and goblet cell hyperplasia in lung-specific IL-22 transgenic model of ovalbumin-induced asthma (130). Paradoxically, in another murine model of dog allergen-induced asthma, which reproduces the characteristics of airway remodeling, Aryl hydrocarbon receptor antagonism decreased IL-22 levels (but not IL-17) in lungs together with decreased airway remodeling. The reduction of subepithelial fibrosis, mucus hyperproduction and smooth muscle thickness after treatment with Aryl hydrocarbon receptor antagonist suggests an association between airway remodeling and IL-22 (137). Interestingly, as previously underlined, IL-22R is not expressed on hematopoietic cells but only on structural cells (epithelial, endothelial cells, fibroblasts, smooth muscle cells) which are major contributors of airway remodeling (42).

Interestingly, B cells, particularly regulatory B cells, seem to have a beneficial regulatory effect on AHR and airway remodeling in a murine model of asthma (159). Although there is no specific data on the role of Th17 cytokines in this regulatory process, several works have showed that Th17 cells, IL-17 and IL-22 (though this is an indirect effect as B cells do not express IL-22R) may exert an important role of recruitment, stimulation and maturation of B cells and a regulatory role of B cell response in mucosal barriers (160–166). Subsequently, Th17 cytokines might also contribute to airway remodeling by an indirect effect of regulation of B cell response.

Respiratory tract infections, and in particular viral infections, may also contribute to the pathophysiology of asthma and the development of airway remodeling as a bronchial chronic inflammation trigger, especially in T2\textsuperscript{low} asthma (167–169). In this setting, knowing the role of IL-17 and IL-22 in antimicrobial host defenses in mucosal barriers (170–172), infections may play an important role of trigger of Th17-induced airway remodeling in patients with recurrent infection phenotype, by inducing chronically high levels of Th17 cytokines in lungs.

Overall, IL-17 involvement in airway remodeling seems well-established while it is less clear for IL-22. However, in vitro data provide numerous clues in favor of the involvement of both of these cytokines in several biological processes contributing to airway remodeling (Figure 2).
**FIGURE 2** | IL-17 and IL-22 cooperate to induce features of airway remodeling in asthma. ECM: extracellular matrix. Pro-inflammatory effect: release of IL-17 and IL-22 by Th17 cells and ILC-3 induce expression of neutrophil-attractant chemokines by endothelial cells and enhance neutrophil recruitment and diapedesis. IL-17 and IL-22 also induce expression of neutrophil-attractant and neutrophil-activating chemokines by epithelial cells and smooth muscle cells which lead to local neutrophilic inflammation with release of proteolytic enzymes (elastase, metalloproteases). Epithelial alterations: IL-17 and IL-22 also increase production of mucus by goblet cells and promotes goblet cell hyperplasia. They also alter epithelial integrity by enhancing E/N-cadherin switch which leads to epithelial-mesenchymal transition. Smooth muscle alterations: IL-17 and IL-22 promote smooth muscle cell proliferation, migration, and contractility (only IL-17). Subepithelial fibrosis: IL-17 and IL-22 stimulate fibroblast proliferation and switch to pro-fibrotic phenotype and promote collagen production and deposition in ECM resulting in thickening of basement membrane. IL-22 also promotes migration of myofibroblast in smooth muscle cell bundles which contributes to local fibrosis and smooth muscle contractility.

**Subepithelial Fibrosis**

Subepithelial fibrosis is a major feature of airway remodeling in asthma. It is mainly characterized by increased collagen deposition in the extracellular matrix (ECM), resulting in thickening of basement epithelial membrane of bronchial mucosa and reduced airway compliance. This phenomenon contributes to airway obstruction. Mainly fibroblasts, but also smooth muscle cells are the cellular effectors of subepithelial fibrosis in asthma. TGF-β and IL-11 are the main profibrotic cytokines which stimulate collagen secretion by fibroblasts (9–12).

In chronic inflammatory bowel diseases, the effect of Th17-type cytokines on subepithelial fibrosis through their action on myofibroblasts is well-described (173). If Th2-type cytokines IL-4 and IL-13 involvement in subepithelial fibrosis in asthma is acknowledged (174, 175), pro-fibrotic effects of IL-17 are also well-documented. Indeed, IL-17 induces the production of pro-fibrotic cytokines IL-6 and IL-11 by fibroblasts obtained from bronchial biopsies of asthmatic patients (40). Additionally, Bellini et al. showed that circulating fibrocytes isolated from exacerbating asthmatic patients had increased expression of IL-17RA as compared to fibrocytes from control healthy subjects (175). Both IL-17A and IL-17F (but not Th2 cytokines) have demonstrated the ability to induce release of pro-neutrophilic chemokines (CXCL1, CXCL8, and TNFa) by fibrocytes, and to enhance fibrocytes switching toward a pro-fibrotic phenotype (increased production of α-smooth muscle actin (SMA) mediated by CXCL8, of collagen, and of proangiogenic factors like VEGF and angiogenin) and fibrocyte proliferation (175, 176). This proliferative effect could be mediated by IL-6 and the Leukemia inhibitory factor (LIF), which were both found increased after IL-17 stimulation in this model (175). Al-Muhsen et al.
suggested that eosinophils could also contribute to the IL-17-driven subepithelial fibrosis process. *In vitro*, the stimulation of eosinophils from asthmatic patients by IL-17 (but not by Th1 nor Th2 cytokines) induces the expression of the pro-fibrotic cytokines IL-11 and TGF-β1. However, this effect requires a co-stimulation with both IL-17A and IL-17F and can be synergistically enhanced by co-stimulation with IL-23, a known inducer and upregulator of IL-17R. This effect is driven by the p38 MAPK signaling pathway (177). More recently, an original work highlighted that IL-17 induces autophagy and mitochondrial dysfunction in human fibroblasts from asthmatic patients, associated with impaired apoptosis and increased pro-fibrotic response (178).

Similar data suggests an involvement of IL-22 in subepithelial fibrosis in asthma. Liu et al. showed that blood from asthmatic children containing high levels of IL-22 and IL-22-producing lymphocytes had the ability to stimulate embryonic fibroblast proliferation and production by fibroblasts of collagen (α-1 and α-2 chains of collagen 1), thus suggesting a contribution of IL-22 to subepithelial fibrosis in asthma through its action on fibroblasts. This effect is linked to the activation of JAK/STAT3 signaling pathway by IL-22R1 (123).

Moreover, fibroblasts from bronchial biopsies of asthmatic patients have also been shown to promote Th17 differentiation of naïve CD4+ lymphocytes and secretion of IL-17 and IL-22, which in turn stimulates the production of pro-fibrotic cytokines (IL-6, TGFβ) by fibroblasts but also cytokines favoring Th17 differentiation (IL-23, IL-6, and IL-1b). This suggests that the microenvironment can also promote a Th17 response in asthmatic patients, through the existence of amplifying loops in the fibroblastic processes (179).

Subepithelial fibrosis also requires ECM remodeling involving proteolytic activity. In this setting, several studies interestingly showed, in murine models of asthma exacerbation, that IL-17 enhanced the production of metalloproteases MMP-9 and MMP-12, neutrophil elastase, and the myeloperoxidase activity, as well as ECM collagen deposition (120, 180).

Finally, biopsies from moderate to severe asthmatic patients showed increased expression of IL-17 in epithelial and specifically in subepithelial compartments, the latter being the location of subepithelial fibrosis, thus arguing in favor of a likely involvement of IL-17 in subepithelial fibrosis in humans. However, downregulation of IL-17 by a 2 week-course of oral steroids did not affect collagen deposition (181).

Taken together, these data suggest that IL-17 and IL-22 can promote subepithelial fibrosis in asthma by a direct action on fibrocytes and fibroblasts, activating collagen production and deposition in ECM, promoting metalloprotease activity, angiogenesis and cell proliferation, enhancing Th17 response and *in situ* neutrophil recruitment, and inhibiting fibroblasts apoptosis.

### Mucus Hyperproduction and Goblet Cell Hyperplasia

Another critical aspect of airway remodeling is represented by changes in mucus secretion function. From a pathological point of view, in asthma, airway remodeling is associated with goblet cell hyperplasia/metaplasia and mucus hypersecretion. From a biochemical point of view, changes in mucus rheology and composition are also observed (9–12).

Normal mucus composition is dominated by mucin glycoproteins, of which MUC5AC and MUC5B are the most abundant. It has been demonstrated *in vitro* that IL-17 (but not Th2 cytokines) was able to increase MUC5AC and MUC5B expression by bronchial epithelial cells (182–184). Stimulation of MUC5AC production is dependent on NfκB transcription factor (183). IL-17 also induces IL-6 production through activation of the JAK2 pathway, which in turn activates the ERK pathway, responsible for enhancement of MUC5B production (182).

At the tissue-scale, IL-17 stimulation increases the number of goblet cells which are the cellular source of mucus in airways (185, 186). Moreover, a recent work seems to implicate IL-17 in goblet cell metaplasia (187).

In addition, a chronic exposition to Aspergillus-induced model of allergic asthma in mice showed features of airway remodeling, noticeably airway inflammation and goblet cell hyperplasia with mucus hyperproduction, associated with lung function alteration. Dectin-1 is a C-type lectin receptor (CLR) that is primarily responsible for β-glucan recognition and control of fungal infection. Interestingly, the features of asthma in this model of chronic exposure to aspergillus were reduced by Dectin-1 deficiency which also downregulated IL-17 and IL-22 production. Of note, neutralization of IL-22 improved lung function in this model. These data suggests that IL-22 could be also involved in alteration of mucus secretion in asthma (146).

### Epithelial-Mesenchymal Transition (EMT) and Epithelial Alterations

Epithelial structure alteration is a key component of airway remodeling. In this process, most structural changes lead to altered epithelium integrity, epithelial cell damage and apoptosis, as well as increased epithelial permeability. Among these changes, a phenotypic switch to mesenchymal cell characteristics is observed in epithelial cells, thus achieving the epithelial-mesenchymal transition (EMT). One of the most critical changes concerns junction proteins, with loss of intercellular tight junction, especially downregulation of the expression of E-cadherin, leading to increase in epithelial permeability (9–12). Additionally, acquisition of a mesenchymal phenotype is likely to contribute to airway fibrosis (188).

In this setting, a potential role for IL-22 is very likely regarding its role in protection, restauration and maintenance of epithelial barrier homeostasis (125, 156). *In vitro*, TGF-β1-induced EMT in primary epithelial bronchial cells of severe asthmatic patients is enhanced by addition of IL-22. IL-22-enhanced EMT is characterized by acquisition of morphologic characteristics of mesenchymal cells (“spindle cells”), further decrease in E-cadherin expression and further increase in N-cadherin expression. This effect seems to be driven by Zeb1 transcription factor (121).

IL-17 has been involved in EMT in various respiratory diseases, like idiopathic pulmonary fibrosis, lung cancer, or...
COPD (189–192). In a translational work on obliterans bronchiolitis, Vittal et al. found that IL-17 could induce EMT, partially through TGF-β production, resulting in decreased expression of E-cadherin (193). In in vitro models, IL-17 induces, synergistically with IL-4 and TGF-β, reentering in cell cycle (proliferation) of epithelial cells, fibroblast morphotype switch, downregulation of E-cadherin, and upregulation of α-SMA (157, 194). A synergistic effect of cigarette smoke together with IL-17 on EMT was also reported by Ma et al. (191).

Interestingly, neutrophils from asthmatic patients were recently shown to have the ability to induce EMT (195). Given the preponderant role of IL-17 and IL-22 in neutrophil recruitment, this supports the involvement of both of these cytokines in EMT in asthma.

**Increase of Airway Smooth Muscle Mass**

Increase of airway smooth muscle mass participates to airway obstruction in asthma and is one of the hallmark of airway remodeling (9–12). It results from several mechanisms including increased smooth muscle cell proliferation (hyperplasia), smooth muscle cell hypertrophy, abnormal migration properties leading to increased number of cells in smooth muscle bundles, especially myofibroblasts which also contributes to local fibrosis (12).

In in vitro models, IL-17A and IL-17F, as well as IL-22 promote airway smooth muscle cell (ASMC) proliferation, induce ASMC migration through activation of their respective cognate receptors and downstream activation of MAPKinas and NFκB pathways, and inhibit ASMC apoptosis (196, 197). IL-17-induced ASMC migration is also mediated by Growth-Related Oncogens (GRO), GROα being CXCL1, also involved in neutrophil migration (198). Neutrophils contribute to smooth muscle cell hyperplasia, which is critical given that IL-17 and IL-22 play an important role in neutrophil recruitment, particularly in airway smooth muscle bundles (199).

Additionally, translational data from two studies indicate that IL-17 but not IL-22 can enhance smooth muscle cell contraction via NF-κB/RhoA/ROCK2 signaling cascades, which are involved in regulation of phosphorylation of myosin light chain and thus ASMC contractility (200–202).

Overall, IL-17 and IL-22 stimulates ASMC proliferation and contractility, smooth muscle cell infiltration by neutrophils, migration of myofibroblasts into the smooth muscle layer, inhibit ASMC apoptosis, leading to thickening of airway smooth muscle mass.

**THERAPEUTIC DIRECTIONS**

As they are tightly linked to asthma immunobiology, and especially to severe asthma, IL-17 and IL-22 appear as promising targets in the treatment of severe asthma. In regard to the overview of the very likely role of IL-17 and IL-22 in airway remodeling in asthma that we provide in this review, this therapeutic perspective is particularly interesting as there is currently no specific pharmacological treatment targeting airway remodeling in asthma, whereas several biotherapies are available for patients with severe T2-high asthma. To date, mainly bronchial thermoplasty, an interventional endoscopic procedure, offers a treatment option for these patients (203). Recently, tezepelumab, a human monoclonal antibody blocking thymic stromal lymphopoietin (TSLP), an epithelial-cell–derived cytokine which, as an alarmin, plays an early role in the inflammatory cascade in asthma, showed significant reduction of exacerbation rate in non-selected patients with severe asthma, including patients with non-T2 asthma. The effect was consistent in the subgroup of patients with low T2 biomarkers (low blood eosinophil count and low FeNO), suggesting that the effectiveness of this biotherapy is maintained in patients with non-T2 asthma (204). Of note a recent phase 2 clinical trial did not show any improvement on airway remodeling (epithelial integrity and basement membrane thickness) (205). Nevertheless, tezepelumab may offer a therapeutic option for patients with severe non-T2 asthma and could prevent the development of non-already established airway remodeling by early reduction of bronchial inflammation.

In the setting of Th17-targeting treatment of severe asthma, IL-17 blockade strategy has been the most studied so far (Table 3). According to the results obtained in the previously mentioned murine models of asthma, the effect of brodalumab, a humanized anti-IL17 monoclonal antibody already approved in the treatment of psoriasis, was investigated in a randomized controlled trial (RCT) in non-selected patients with moderate-to-severe asthma (206). No significant difference was found on the primary outcome criteria, which was the control of asthma based on the Asthma Control Questionnaire (ACQ). Nevertheless, the results of this study have been extensively discussed on two points. First, there was no selection of patients according to phenotype or endotype, and, as a consequence, many patients with T2-high asthma may have been included, a category of patients for whom a beneficial effect of anti-IL-17 treatment would be less expected than for patients with neutrophilic asthma. Second, the primary outcome criteria was improvement of asthma control, a criteria which has not been found improved by any other already-registered biotherapies in severe asthma, and which also may not reflect improvement in airway remodeling. Interestingly, a subgroup of patients with high FEV1 reversibility at inclusion demonstrated a significant difference in asthma control, suggesting that patients with not-yet-established permanent obstruction and airway remodeling might benefit from IL-17 blockade strategy in the early phase of airway remodeling (206, 209, 210). Recently, a phase I trial studying the effect of a bispecific anti-IL-13 and anti-IL-17A antibody in asthma was early terminated due to high frequency of treatment immunization (207). Additionally, experimental data suggest that blockade of IL-17 may restore sensitivity to steroids, including airway remodeling features (211). Lastly, a phase 2a RCT found that risankizumab, an anti-IL-23 monoclonal antibody, induced downregulation of Th17 associated transcription factors, and showed deleterious effects of outcomes (time to first worsening, annual rate of asthma worsening) in an unselected population of severe asthmatic patients (208). This result may put in perspective the protective aspects of Th17 response in asthma (anti-microbial defense in particular, although the proportion of infectious exacerbations was not specifically reported in this study) (209). Therefore,
TABLE 3 | Summary of results from pre-clinical and clinical studies on Th17-related therapies.

| Drug            | Biochemical nature and target | Type of study | Population of study | Primary endpoint | Effect on primary endpoint | Effect on asthma control | Effect on exacerbations | Effect on FEV1 | Adverse events | Remark                                                                 |
|-----------------|-------------------------------|---------------|---------------------|------------------|---------------------------|--------------------------|-------------------------|----------------|----------------|----------------------------------------------------------------------|
| Brodalumab      | Human anti-IL-17RA IgG2 monoclonal Ab | Multicentric RCT, db, Ph3 | 18–65 y.o. moderate-to-severe asthmatics on stable ICS, no biomarker required (305 patients) | Asthma control (ACQ) | NS | NS | NS | Injection site reaction | Possible positive effect on asthma control in the high FEV1 reversibility subgroup |
| BITS7201A       | Humanized bispecific anti-IL-13 and -IL-17 IgG4 Ab | Monocentric RCT, ob, Ph1 | Healthy volunteers (41 patients) | Pharmacokinetic parameters | | | Frequent development of anti-drug antibodies | | |
| Risankizumab    | Humanized anti-IL-23 IgG1 monoclonal Ab | Multicentric RCT, db, Ph2 | 18–75 y.o. asthmatics on moderate ICS dose at least + 1 other controller, FEV1 40–85%, at least 2 severe exacerbations in the 12 last months (214 patients) | Time to first worsening: Worsening (shorter time to first worsening with treatment) | NS | Worsening | NS | Downregulation of Th17-associated transcriptome |
| BIX119          | Small molecule, specific RORγt inhibitor | Pre-clinical (murine model) | B6C3F1 mice | Reduction of neutrophilic inflammation and AHR in mice | | | | |
| Tezepelumab     | Human anti-TSLP IgG2 monoclonal antibody | Multicentric RCT, db, Ph3 | 12–80 y.o. asthmatics on high ICS dose + 1 other controller, no biomarker (1,061 patients) | Annualized exacerbation rate | Improvement | Improvement | Improvement | Improvement | Headaches, Upper respiratory tract infections |

RCT, randomized controlled trial; db, double blind; Ph, phase; y.o., year-old; NS, non-significant effect; AHR, airway hyperresponsiveness; ob, observer-blinded.
more data are needed on IL-17 blockade strategy. Trials selecting patients based on an “IL-17 phenotype” using biomarkers like sputum neutrophilia, IL-17 levels in blood or sputum, or airway remodeling biomarkers are expected to make progresses in this field.

Additionally, beyond the non-T2 asthma field, specific allergen immunotherapy in allergic rhinitis is associated with decreased serum levels of IL-17 mRNA and IL-17 as compared to non-treated controls (212, 213). Furthermore, the ratio between B regulatory cells (Breg) and Th17 cells (Breg/Th17 ratio) obtained from blood samples taken in the early phase of immunotherapy, positively correlates with a symptom score of response to this treatment at 3 years (214). This effect of immunotherapy on Th17 response might be driven through transdifferentiation of Th17 cells toward Treg cells, contributing to immunotolerance to allergens (215, 216). Interestingly, a recent work suggested that specific allergen immunotherapy-induced immunotolerance was associated with a decrease in “exhausted-like” Th2 cells in a murine model of chronic exposure to ovalbumin allergen and in patients with allergic rhinitis, a specific phenotype of Th2 cells characterized by the expression of CTLA-4 and PD-1 (217), which has paradoxically been proposed to contribute to the enhancement of Th2 response (218, 219).

Of note, in their murine model, immunotherapy was associated with decreased neutrophil count and levels of IL-17 in BAL but increased expression of IL-17 and IL-22 in lung homogenates (217). Similarly, modulation of ILC2 exhausted phenotype might be a relevant target, particularly knowing their involvement in regulation of chronic allergic inflammation and that a subset of these cells can produce IL-17 (220, 221). Improvement in the understanding of the regulatory role of exhausted phenotype of T2 inflammation-associated cells in allergic inflammation and of their interaction with Th17 pathway may contribute to the development of therapies indirectly targeting Th17 pathway which may also impact Th17-associated airway remodeling.

Although there are no currently clinical studies of IL-22 targeting therapies in asthma, some data suggest a potential role for such therapies. First, the efficacy of the anti-IL-22 antibody fezakinumab was demonstrated in a randomized controlled trial in atopic dermatitis, a disease which shares many pathophysiological features with asthma and especially neutrophilic asthma (tissue remodeling, neutrophilic inflammation) (222). As previously mentioned, data on IL-22 blockade strategy from murine models provide conflicting evidence of the benefit of this strategy. Interestingly, Badi et al. found a predictive transcriptomic signature of response to fezakinumab in atopic dermatitis which was enriched in blood of patients with severe asthma from U-BIOPRED cohort. This enrichment was especially associated with neutrophilic asthma. The response to fezakinumab signature was correlated with Th22 related gene expression in blood and sputum (especially IL-22, CCR10, Aryl hydrocarbon receptor). IL-22 expression in sputum correlated with the enrichment of the response signature (138). Given the established role of IL-22 in epithelial physiology and in tissue remodeling (157), it might be an interesting target for the treatment of airway remodeling in asthma.

Finally, a new and potent RORγt inhibitor, administered in a mouse model of house dust mite-induced asthma which exhibited a transcriptomic signature overlapping with that of a cluster of patients with severe neutrophilic asthma from the U-BIOPRED cohort, showed a decrease in IL-22, IL-17, and CXCL1 levels in BAL fluid, in BAL neutrophilia and more interestingly an improvement in airway resistances in a dose dependent manner (108). This effect was not achieved by an anti-IL-17 antibody alone. This result may confirm the synergistic action of IL-17 and IL-22 that has been suggested in several studies (98, 108, 143, 147). An anti-inflammatory effect targeting the Th17 response might require an abolition of both IL-17 and IL-22 actions. Considering this result and this hypothesis, the inhibition of RORγt, the master driver of Th17 differentiation may be a promising track in asthma.

Overall, substantial progresses are still to be done in the field of treatment targeting the Th17 response in asthma and airway remodeling. Clinical trials relying on relevant outcome criteria and with endotype-based selection of patients are needed. Moreover, timing of administration of biotherapies targeting airway remodeling might be a critical parameter affecting results of clinical trials. Have such therapies to be administered preventively before establishment of severe and fixed (maybe irreversible) airway remodeling and obstruction? Or should we expect to reverse already-established airway remodeling? Further responses are awaited on this burning topic.

CONCLUSION

Many evidences are accumulating to indicate a leading role of Th17 cytokines in patients with severe T2-high asthma, particularly in patients with neutrophilic asthma and airway remodeling. However, the exact role of Th17 cytokines, especially IL-22, still needs to be clarified in vivo, though an important number of experimental in vitro data show their involvement in elementary biological processes that contribute to airway remodeling (airway inflammation, subepithelial fibrosis, mucus hyperproduction, thickening of airway smooth muscle, epithelial-mesenchymal transition and alteration of epithelial integrity). Therefore, IL-17 and IL-22 are attractive therapeutic targets for new biotherapies in severe asthma while there is currently no pharmacological treatment targeting airway remodeling. Future clinical trials involving molecules targeting Th17 cytokines using appropriate outcomes and selected populations will be required to progress in this direction.

AUTHOR CONTRIBUTIONS

VM-C wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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