



The paradigm of cytokine networks in allergic airway inflammation

Ruby Pawankar, Miyuki Hayashi, Shingo Yamanishi, and Toru Igarashi

Purpose of review

Cytokines are immunomodulatory proteins important in cell signaling. Complex interactions of innate and adaptive immune cells, as well as structural cells and their cytokines, play crucial roles in regulating allergic airway inflammation. Here, we summarize current knowledge about the potential roles of known and newly identified helper T cells and epithelial cell-derived cytokines [interleukin (IL)-9, IL-17, IL-22, IL-25, and IL-33] in allergic rhinitis and asthma.

Recent findings

Although T-helper (Th)2 cells were considered to be the main orchestrators of allergic airway inflammation, recent studies have revealed the potential interaction of other helper T cells and their cytokines in this process. Th17 cells may have a role in allergic rhinitis and asthma, and chronic rhinosinusitis with nasal polyps. An IL-9-producing subset called Th9 cells, Th22 cells which primarily secrete IL-22, IL-13, tumor necrosis factor- α , Th25 cells via producing IL-25 and epithelial cell-derived thymic stromal lymphopoietin, IL-33, IL-31, and IL-25 are believed to be important for the initiation of allergic reactions and inducing airway inflammation.

Summary

A new paradigm of an interplay of cytokines is important in allergic rhinitis and asthma in orchestrating the allergic inflammatory response. Potential therapeutic applications emerging from the roles of these cytokines are promising, but need further research.

Keywords

allergic rhinitis, asthma, IL-31, IL-33, Th17, Th2 cytokines, thymic stromal lymphopoietin

INTRODUCTION

Allergic diseases like allergic rhinitis and asthma affect 20–30% of the world population and are public health issues with an increasing prevalence worldwide. Allergic rhinitis is an IgE-mediated disease of the upper airways that has a major impact on the quality of life of patients, and is a socio-economic burden. Allergic rhinitis is often associated with asthma and acts as a risk factor for asthma, increasing morbidity, costs, and worsening the quality of life of those with comorbid disease. Asthma pathology is associated with different release of pro-inflammatory substances. Whereas allergic rhinitis is an IgE-mediated chronic inflammatory disease of the upper airways characterized by symptoms of sneezing, rhinorrhea, nasal itching, and nasal obstruction, asthma is a chronic, inflammatory condition of the lower airways characterized by largely reversible airflow obstruction, airway hyperresponsiveness, and episodic respiratory symptoms, including wheezing, productive cough, and sensations of breathlessness and chest tightness [1].

Understanding the underlying triggers, risk factors, genetics, and immune mechanisms is central to developing better and more targeted therapies.

All cells within airways such as T cells, mast cells, eosinophils, basophils, fibroblasts, smooth muscle cells, and epithelial cells play key roles in orchestrating the chronic inflammation in allergic rhinitis and asthma by recruiting, activating, and promoting the survival of multiple inflammatory cells in the respiratory tract. These inflammatory processes are connected by a complex molecule as a cytokine network. Within the paradigm of this complex network have emerged new pathways such as local synthesis of IgE, the IgE–IgE receptor mast cell

Department of Pediatrics, Nippon Medical School, Tokyo, Japan

Correspondence to Professor Ruby Pawankar, MD, PhD, FRCP, FAACAP, Division of Allergy, Dept. of Pediatrics, Nippon Medical School, 1–1–5, Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. Tel: +81 3 5802 8177; e-mail: pawankar.ruby@gmail.com

Curr Opin Allergy Clin Immunol 2015, 15:41–48

DOI:10.1097/ACI.0000000000000129

KEY POINTS

- Allergic rhinitis is a Th2-mediated disease, with important regulatory cytokines like IL-4, IL-5, and IL-13.
- Newer Th2 cytokines have been identified in asthma and allergic rhinitis, as well as in CRS with nasal polyps, including IL-17 family cytokines.
- Epithelial cell-derived cytokines like TSLP, IL-33, IL-25, and innate lymphoid cells play a crucial role in the regulation of allergic airway inflammation.
- Modulating this network with biological therapy presents a new paradigm for treatment.

cascade, and the role of epithelial-derived cytokines [i.e. thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33].

Clinically, allergic rhinitis is a T-helper (Th)2-type inflammatory disease, whereas asthma may be allergic or nonallergic, distinguished by the presence or absence of IgE antibodies to common environmental allergens. About 80% of childhood and 50% of adult asthma is allergic (i.e. IgE-associated). In the latter, the triggers are not so well defined, but are probably microbes or microbial components, viruses, and so on. However, both forms of asthma are characterized by Th2-type inflammation, stimulation of inflammatory cells like mast cells, causing eosinophilia, leukocytosis, and enhanced B-cell IgE production, leading to airway hyperresponsiveness and tissue remodeling. The determinants for an individual to develop an asthmatic phenotype require both exposure to appropriate stimuli and a genetic predisposition [2,3]. About 10% of asthmatic patients are difficult to treat and have a disproportionate use of healthcare resources, and significant morbidity and mortality, and therefore represent an unmet clinical need.

Cytokine network in allergic airway inflammation

Cytokines are immunomodulatory proteins that are important in cell signaling (Fig. 1) [4]. They are produced and released by a wide variety of cell types, including immune cells like macrophages, B and T lymphocytes, and mast cells, as well as structural cells like endothelial cells, fibroblasts, and epithelial cells. Whereas cell to cell interaction is crucial in immunological mechanisms of disease, cytokines orchestrate several immune responses in allergic, inflammatory, and autoimmune diseases. The inflammatory process underlying allergic rhinitis and asthma is coordinated by a cytokine

network. Modulating this network with biological therapy presents a new paradigm for treatment.

Th2 type cytokines

T-helper 2-type cytokines like IL-4, IL-5, IL-6, and IL-13 are crucial in the regulation of allergic airway inflammation. Apart from their role in the induction of IgE synthesis, Th2-type cytokines up-regulate the production of cytokines/chemokines in epithelial cells and fibroblasts [5]. In turn, these chemokines and cytokines are implicated in the migration of other inflammatory cells, as in the case of normal T-lymphocyte expressed (RANTES) and transforming growth factor (TGF)- β regulated upon activation, which are implicated in the intraepithelial migration of mast cells [6,7]. IL-5, IL-4, IL-13, and IL-4 levels were increased from 2 to 3 h after grass pollen nasal allergen challenge and showed progressive increases to 5–6 h [8]. A strong correlation between clinical responses and local biomarkers was also found following nasal allergen challenge. A strong correlation between the levels of IL-13 and serum IgE has been demonstrated and IL-4 has been shown to up-regulate the Fc epsilon receptor 1 (Fc ϵ RI) on mast cells. An increase in Th2 chemokines has also been reported. Levels of thymus and activation-regulated chemokine (TARC), macrophage-derived chemokine (MDC), eotaxin RANTES, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein-1 alpha (MIP-1 α) have also been found to be increased in allergic rhinitis [9–12].

As compared with those with viral rhinitis, those with seasonal allergic rhinitis had elevated eosinophil cationic protein (ECP), tryptase, and IL-5, whereas those with viral rhinitis had increased levels of a range of inflammatory cytokines, including IL-1 β , IL-6, IL-7, IL-17, interferon (IFN) γ , IL-8, tumor necrosis factor (TNF) α , and granulocyte macrophage colony-stimulating factor (GM-CSF), and also IL-4 and IL-5 [13]. An increased level of IL-9 has been reported and in one study was shown to be associated with an increase in c-kit + mast cells [14,15]. The number of IL-10+ cells was smaller in the nasal mucosa of patients with seasonal allergic rhinitis after grass pollen challenge as compared with controls [16].

Modest associations between single-nucleotide polymorphisms (SNPs) in Th2 cytokine genes and risk of allergic rhinitis, with IL-4 and IL-13 SNPs, were reported in some studies [17,18], but not in others [19].

Apart from T cells, airway mast cells are an important source of Th2 cytokines, pro-inflammatory cytokines like TNF α (preformed in mast cells), and chemokines like TARC, as well as the IL-7-like cytokine TSLP [5,20–22]. Fc ϵ RI-mediated TSLP

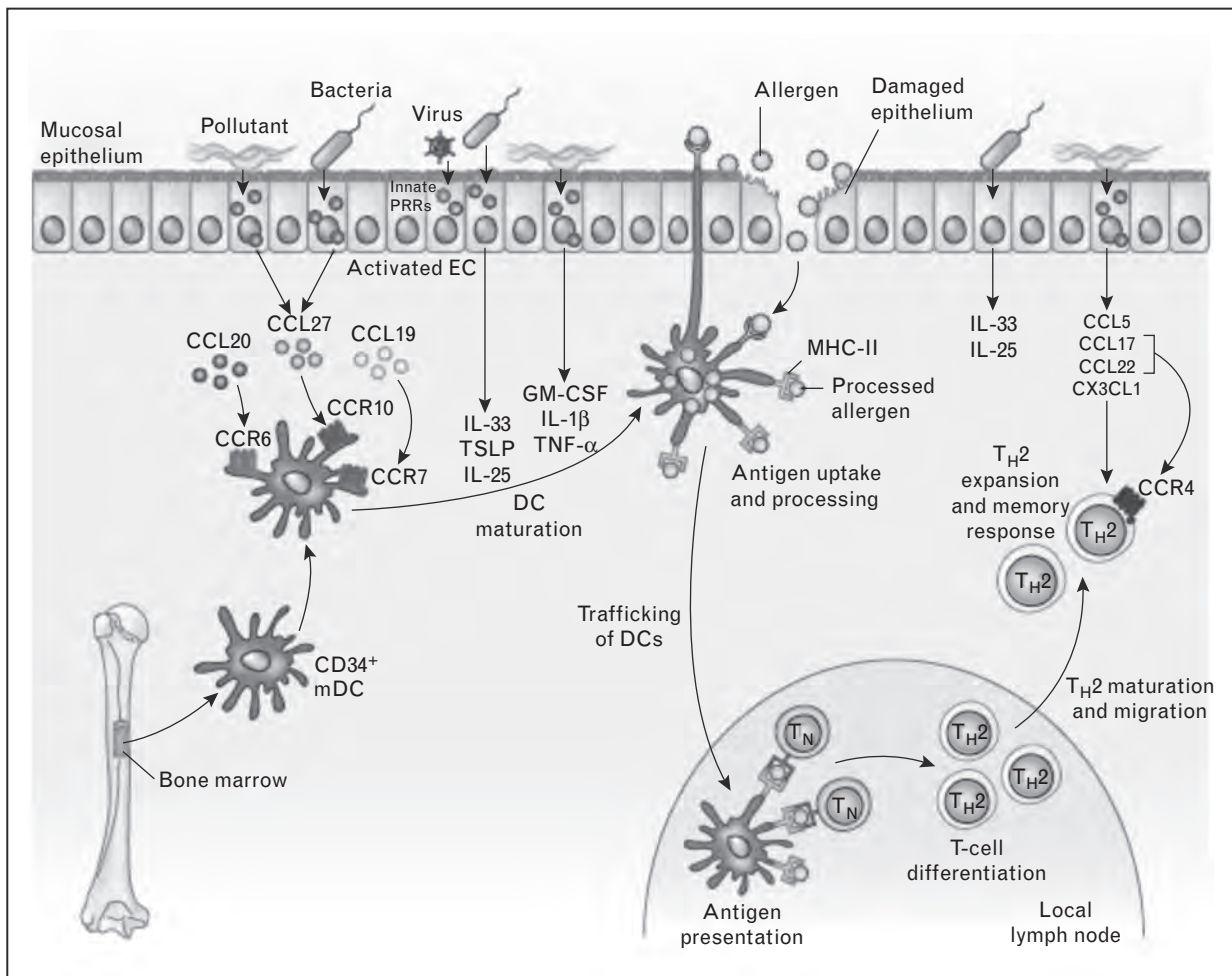


FIGURE 1. Cytokine network in allergic airway inflammation (reproduced with permission from [4]).

production from mast cells is further enhanced in an autocrine manner by IL-4 [23]. Moreover, mast cells can interact with structural cells like epithelial cells to enhance the production of cytokines and chemokines from epithelial cells. TNF α , in concert with IL-4 and IL-13, enhances the production of TARC, TSLP, and eotaxin from epithelial cells [6]. These result in increased infiltration of Th2 cells, eosinophils, and differentiation of dendritic cells. Moreover, tryptase and chymase from mast cells can up-regulate RANTES and GM-CSF production from epithelial cells [6]. TNF α also promotes antigen and Th17 cell-dependent neutrophilia after allergenic stimulation and induces dendritic cell migration [24,25]. Murine mast cells have been shown to induce CD4 $^{+}$ T-cell migration *in vitro*, but down-regulate Fc ϵ R1 expression in regulatory T (Treg) cells, whereas activated Treg cells suppress mast cell Fc ϵ R1 expression.

Interleukin-13 from mast cells plays a crucial role in mast cell-induced IgE synthesis in B cells, and local IgE synthesis has been demonstrated in

the nasal mucosa of patients with allergic rhinitis [26,27]. Both IL-4 and IgE can up-regulate FcεRI expression in mast cells, suggesting a crucial role for the mast cell–IgE-IgE receptor cascade in ongoing inflammation in allergic rhinitis and asthma [26]. Moreover, these cytokines play a crucial role in asthma as well as eosinophilic nasal polyps [28,29].

Th17 family cytokines

Although conventionally, both allergic rhinitis and allergic asthma have been considered to be due to a disruption in the normal Th1/Th2 balance, more recently, there is new evidence on the emerging roles of Th17 cells, which are a distinct subpopulation of CD4⁺ T cells that produce IL-17A, IL-17F, IL-22, TNF- α , and IL-21 [30]. Th17 cells were found in the nasal mucosa of allergic rhinitis patients [31] and in bronchial biopsies of asthmatic patients [32]. IL-17 induces the release of pro-inflammatory cytokines/chemokines from a variety of cell types [31], is linked to the development of airway neutrophilia, and its presence in the asthmatic airway correlates

with increased severity of disease. Treg cells play roles in the determination of self-tolerance and the regulation of immune responses. Th17 and Treg cells have opposing actions, and Treg cells secrete IL-10 and TGF β , and are increased in patients after immunotherapy.

In seasonal allergic rhinitis during natural seasonal exposure, IL-17A was rather undetectable, but 5 h after nasal allergen challenge, the levels of IL-17A in nasal secretions were increased [33²²]. In another study [34], nasal allergen challenge with grass pollen did not produce increases in nasal fluid IL-17, despite increases in several Th2 cytokines and chemokines. On the contrary, increased levels of IL-17A were reported in the serum of patients with grass pollen seasonal allergic rhinitis: during the season [35], and before and after house dust mite bronchial challenge in patients with house dust mite allergy [36], and increased numbers of IL-17A⁺ cells and IL-17A mRNA were demonstrated in the nasal mucosa of patients with perennial allergic rhinitis to dust mite [37]. Grass or birch pollen allergen-challenged peripheral blood mononuclear cells were found to have significantly up-regulated IL-17 receptor (IL-17RB) gene expression – more so than IL-5, GATA binding protein 3, or Fc ϵ R1I. Protein levels of IL-17RB were also increased on basophils after challenge [38]. Although polysensitized allergic rhinitis patients exhibited higher IL-17A-producing CD4⁺ T-cell levels and eosinophil counts, the precise role of the Th17 family of cytokines, particularly IL-17A in allergic rhinitis, is not well established, and these cytokines have been reported to have pro-inflammatory effects in asthma [39] and in chronic rhinosinusitis (CRS) with nasal polyps that is neutrophilic in nature [40].

The expression of IL-17F in the airways of asthmatic patients correlates with disease severity and induces several asthma-related molecules such as CCL20 that can attract Th17 cells into the airway, thus amplifying airway inflammation. A recent study [41²²] demonstrated that bronchial epithelial cells express IL-17F in response to IL-33 via ST2-ERK1/2-MSK1 signaling pathway. Moreover, IL-17F is involved in airway remodeling and steroid resistance. Hence, IL-17F may be a valuable therapeutic target for development of novel strategies.

Eosinophils are a major source of macrophage migration inhibitory factor [42] and nerve growth factor [43], express 5-lipoxygenase, FLAP, and leukotriene C4 synthase, and cysteinyl leukotrienes (CysLT)₁ and CysLT₂ receptors [44], are involved in the loss of epithelial integrity [45], and are also seen in the esophageal mucosa of symptomatic patients with respiratory allergy [46]. IL-5 has a key role modulating eosinophil differentiation

and survival. Targeting IL-5 as a therapeutic strategy for allergic asthma in selected patients with refractory, eosinophilic asthma, anti-IL-5 monoclonal antibody (mepolizumab) reduced both peripheral blood and sputum eosinophil levels, asthma exacerbations, and resulted in a reduction in oral corticosteroid dose [47,48]. Eosinophil chemoattractants include eotaxin, macrophage/MCP4, RANTES, and CysLTs, among others [49,50]. They act on distinct cell surface receptors [e.g. CC chemokine receptor 3 (CCR3) and cysLT₁] present on the eosinophil, but not exclusively so.

Airway epithelial cells are an important source of a variety of inflammatory mediators including multifunctional cytokines and chemokines like IL-1, IL-6, IL-8, TNF α , GM-CSF, RANTES, eotaxin, and TARC, leading to their crucial role in the migration and activation of immune cells like eosinophils, basophils, and Th2 cells. On allergen recognition, epithelial cells release cytokines, such as IL-1, IL-25, IL-33, TSLP, and GM-CSF, and endogenous danger signals, such as high-mobility group box 1, uric acid, and ATP, that activate the dendritic cell network and other innate immune cells, such as basophils and type 2 innate lymphoid cells. Different allergens stimulate different aspects of this general scheme, and common environmental risk factors for sensitization, such as cigarette smoke and diesel particle exposure, do so as well. All of this is influenced by genetic polymorphisms affecting epithelial pattern recognition, barrier function, and cytokine production. More recently, TSLP, IL-25, and IL-33 derived from epithelial cells is increased in the nasal mucosa of allergic rhinitis patients, nasal polyps, and in the asthmatic airway [51,52]. TSLP can activate dendritic cells, promote Th2 responses, and activate mast cells [23]. TSLP, IL-33, and IL-25 are released by tissue damage, pathogen recognition, or even by allergen exposure, and regulate Th2 cell function, either directly or via innate lymphoid cells, which, in turn, produces IL-5, IL-9, and IL-13 [53]. These novel cytokines and innate lymphoid cells appear to be relevant to both asthma [54,55] and CRS with nasal polyps [56²²,57]; their relevance in allergic rhinitis is also under investigation. TSLP production by human nasal epithelial cells *in vitro* was stimulated by a Toll-like receptor (TLR)2 ligand, as well as by IL-1 β and TNF α [58]. Of particular interest is that in a candidate gene association study [59], in which 11 SNPs in the TSLP gene in 368 allergic rhinitis and 325 control adult Han Chinese patients from Beijing were studied, no association could be found between specific SNPs in the TSLP gene and allergic rhinitis susceptibility in this ethnic population. However, the same SNPs in TSLP gene were found

to exert a sex and/or nasal polyposis-dependent risk for development of CRS in Chinese patients [60].

Elevated levels of IL-33 were detected in nasal secretions, but not in serum, in patients with Japanese cedar pollinosis at peak season, and in patients with perennial allergic rhinitis as compared with preseason and the normal controls [61]. Moreover, the levels of IL-33 in nasal secretions correlated significantly with the total nasal symptom score. Kamekura *et al.* [62] reported that the levels of IL-33 in the sera of patients with allergic rhinitis were significantly higher than that in the normal controls, and the expression of IL-33 and ST2 was significantly elevated in the epithelium of patients with allergic rhinitis. Moreover, IL-33 mRNA in cultured nasal epithelial cells *in vitro* was significantly induced by treatment with IFN γ and the TLR9 ligand ODN2006 [62]. On the contrary, in another study [63], the researchers observed an up-regulation of soluble ST2 and IL-16 after nasal allergen challenge and during peak pollination season, but not IL-33. Serum levels of IL-33 in patients with intermittent allergic rhinitis (IAR) were reported to be comparable with patients with bronchial asthma, and were significantly higher in patients with IAR and bronchial asthma than in the controls; this correlated with disease severity [64].

Periostin [65] and IL-31 [66–68] were increased in allergic rhinitis patients compared with controls, thus indicating possible pathological roles. IL-31RA was up-regulated in allergic rhinitis primarily localized in the submucosal glands, and IL-31 was detected in the submucosal tissue and increased in allergic inflammation [67]. In another study by Liu *et al.* [69^{***}], IL-31 mRNA and protein levels in both serum and nasal lavage were significantly enhanced in allergic rhinitis patients compared with normal controls, especially in children with asthma. The nasal IL-31 was associated with enhanced local Th2 cytokines and mucin 5AC (MUC5AC) expression. MUC5AC gene expression was induced by IL-31 stimulation in epithelial cells, and IL-31 and Th2 cytokines up-regulated MUC5AC gene expression.

In a study [70^{***}] in asthmatic patients, epithelial expression of IL-25, but not IL-33 or TSLP, was increased in a subset of asthmatic patients. The IL-25-high subset had greater airway hyperresponsiveness, more airway and blood eosinophils, higher serum IgE, more subepithelial thickening, and higher expression of Th2 signature genes. Inhaled corticosteroids (ICS) improved forced expiratory volume in 1 second and hyperresponsiveness in the IL-25-high but not the IL-25-low subset.

Plasma IL-25 levels correlated with epithelial IL-25 expression, airway eosinophilia, and beneficial responses to ICS treatment.

CONCLUSION

The development of allergic rhinitis and asthma requires an interaction between the environment, immune system, and genetic susceptibility. Whereas pollen-induced rhinitis is the most characteristic IgE-mediated allergic disease, in perennial allergic rhinitis, the allergic triggers are more continuous, and lead to an ongoing inflammation. Several cells and cytokines/chemokines orchestrate and maintain this inflammation. Thus, the intricate interaction amongst cytokines, chemokines, neuropeptides, adhesion molecules, and various cells in the form of a complex network leads to the development of specific symptoms and the nonspecific hyperreactivity of allergic rhinitis.

Asthma is characterized by variable degrees of chronic inflammation and structural alterations in the airways which include epithelial denudation, goblet cell metaplasia, subepithelial thickening, increased airway smooth muscle mass, bronchial gland enlargement, angiogenesis, and alterations in extracellular matrix components, involving large and small airways. Chronic inflammation is thought to initiate and perpetuate cycles of tissue injury and repair in asthma, although remodeling may also occur in parallel with inflammation. While allergic rhinitis and asthma share several similarities in the inflammatory cell and mediator profiles and responses, remodeling as seen in asthma is not characteristic of allergic rhinitis. In asthma, the relationships of airway inflammation, remodeling, and lung function are becoming better understood. A variety of inflammatory cells and structural cells, and the cytokine–chemokine network play a role in orchestrating the inflammation and structural changes in asthma. Increased airway responsiveness is a surrogate marker of inflammation and may reflect the development of structural changes in the airways. Such persistent increased bronchial responsiveness indicates remodeling partly resistant to therapy.

Moreover, with the increasing evidence on the links between allergic rhinitis and asthma from epidemiologic, immunologic, and clinical studies, early intervention and down-regulation of inflammation are keys to better control both allergic rhinitis and asthma. New modes of immunomodulatory therapies and biologics that target specific phenotypes like IgE, IL-5, IL-13, and the IL-4 receptor alpha chain have shown some efficacy in phenotyped patients. For those without evidence

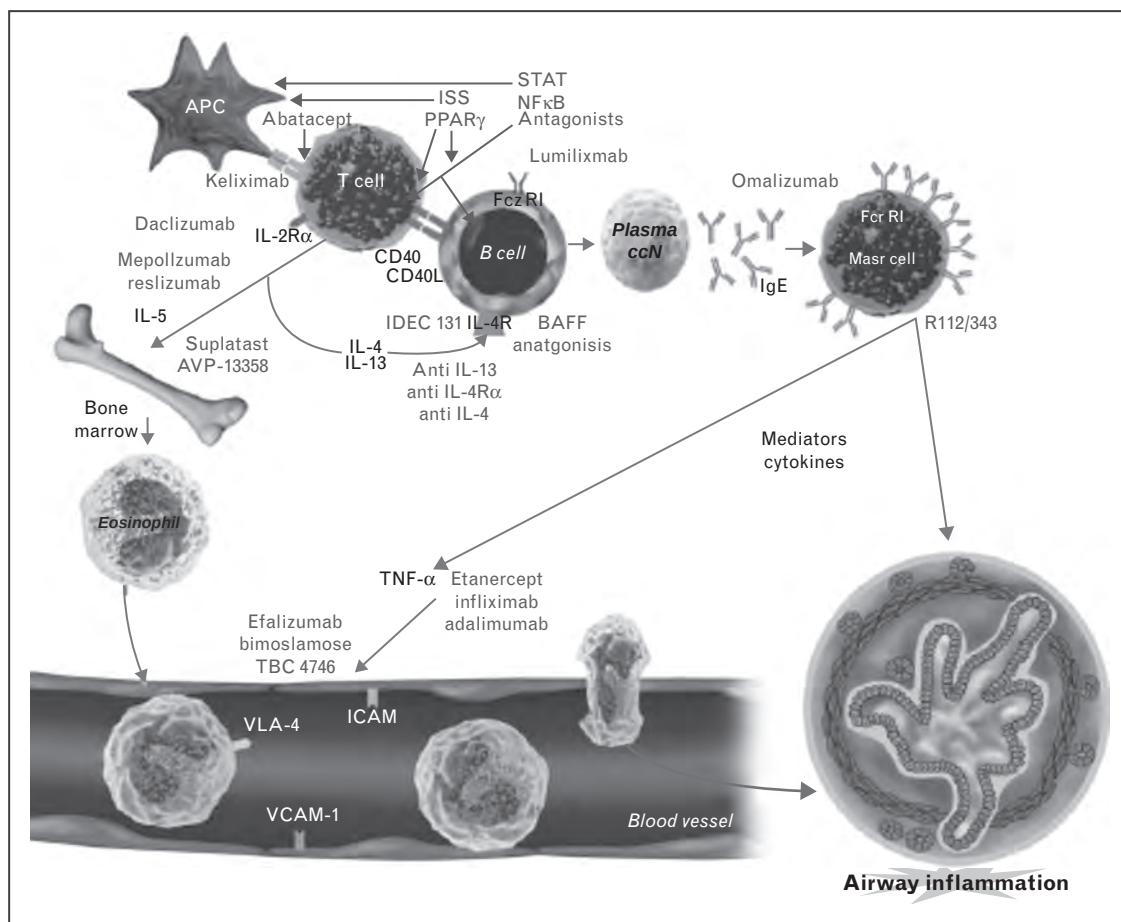


FIGURE 2. Potential therapeutic targets for asthma and rhinitis (reproduced with permission from [72]).

of Th2 inflammation, no specific therapies have been identified. Anti-IgE, and anti-IL-5, anti-IL-13, anti-IL-4R antagonists, and therapies that target TSLP, IL-33, and IL-17, as well as those that induce tolerance, hold more promising outcomes, but their effect on halting airway remodeling in severe asthma is not known. Clinical cluster analysis from the Severe Asthma Research Program (SARP) identified five asthma subphenotypes that represent the severity spectrum of early-onset allergic asthma, late-onset severe asthma, and severe asthma with chronic obstructive pulmonary disease characteristics. Analysis of induced sputum from a subset of SARP patients showed four sputum inflammatory cellular patterns. Patients with concurrent increases in eosinophil ($\geq 2\%$) and neutrophil ($\geq 40\%$) percentages had characteristics of very severe asthma [71]. This multivariate approach identified four asthma subphenotypes, representing the severity spectrum from mild-to-moderate allergic asthma with minimal or eosinophil-predominant sputum inflammation, to moderate-to-severe asthma with neutrophil-predominant or mixed granulocytic inflammation [70²²].

Given the immunological similarities that exist between the patterns of inflammation in asthma and allergic rhinitis, as well as CRS and asthma, and the impact of allergic rhinitis on asthma, treatment should have a global approach to treat both the upper and the lower airways for better outcomes. New knowledge about the pathogenesis of allergic and immunologic diseases has led to a variety of novel targeted therapeutic approaches. Many such immunomodulators and biologics targeting targets and specific cytokines/biomarkers are currently under development for the therapy of asthma and allergic diseases (Fig. 2) [72]. Such therapeutic strategies, when proven to be effective, place the patient at the center of healthcare and represent a form of personalized medicine.

Acknowledgements

None.

Financial support and sponsorship

None of the authors has received any sponsorship or financial support towards writing this review.

Conflicts of interest

None of the authors has any conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

- Bousquet J, Jeffery PK, Busse WW, *et al.* Asthma: from bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000; 161:1720–1745.
- Kabesch M, Schedel M, Carr D, *et al.* IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol* 2006; 117:269–274.
- Loza MJ, Chang BL. Association between Q551R IL4R genetic variants and atopic asthma risk demonstrated by meta-analysis. *J Allergy Clin Immunol* 2007; 120:578–585.
- Holgate ST. Innate and adaptive immune responses in asthma. *Nat Med* 2012; 18:673–683.
- Wilson AM, Duong M, Crawford L, Denburg J. An evaluation of peripheral blood eosinophil/basophil progenitors following nasal allergen challenge in patients with allergic rhinitis. *Clin Exp Allergy* 2005; 35:39–44.
- Pawankar R. Mast cells in allergic airway disease and chronic rhinosinusitis. *Chem Immunol Allergy* 2005; 87:111–129.
- Powe DG, Hiskisson RS, Carney AS, *et al.* Idiopathic and allergic rhinitis show a similar inflammatory response. *Clin Otolaryngol Allied Sci* 2000; 25:570–576.
- Scadding GW, Calderon MA, Bellido V, *et al.* Optimisation of grass pollen nasal allergen challenge for assessment of clinical and immunological outcomes. *J Immunol Methods* 2012; 384 (1–2):25–32.
- Erin EM, Zacharasiewicz AS, Nicholson GC, *et al.* Topical corticosteroid inhibits interleukin-4, -5 and -13 in nasal secretions following allergen challenge. *Clin Exp Allergy* 2005; 35:1608–1614.
- Erin EM, Leaker BR, Zacharasiewicz AS, *et al.* Single dose topical corticosteroid inhibits IL-5 and IL-13 in nasal lavage following grass pollen challenge. *Allergy* 2005; 60:1524–1529.
- Sim TC, Reece LM, Hilsmeier KA, *et al.* Secretion of chemokines and other cytokines in allergen-induced nasal responses: inhibition by topical steroid treatment. *Am J Respir Crit Care Med* 1995; 152:927–933.
- Terada N, Hamano N, Kim WJ, *et al.* The kinetics of allergen-induced eotaxin level in nasal lavage fluid: its key role in eosinophil recruitment in nasal mucosa. *Am J Respir Crit Care Med* 2001; 164:575–579.
- Klemens C, Rasp G, Jund F, *et al.* Kramer MF Mediators and cytokines in allergic and viral-triggered rhinitis. *Allergy Asthma Proc* 2007; 28:434–441.
- Ciprandi G. Serum interleukin 9 in allergic rhinitis. *Ann Allergy Asthma Immunol* 2010; 104:180–181.
- Nouri-Aria KT, Pilette C, Jacobson MR, *et al.* IL-9 and c-Kit+ mast cells in allergic rhinitis during seasonal allergen exposure: effect of immunotherapy. *J Allergy Clin Immunol* 2005; 116:73–79.
- Pilette C, Jacobson MR, Ratajczak C, *et al.* Aberrant dendritic cell function conditions Th2-cell polarization in allergic rhinitis. *Allergy* 2013; 68:312–321.
- Ying XJ, Zhao SW, Wang GL, *et al.* Association of interleukin-13 SNP rs20541 with allergic rhinitis risk: a meta-analysis. *Gene* 2013; 521:222–226.
- Movahedi M, Amirzargar AA, Nasiri R, *et al.* Gene polymorphisms of Interleukin-4 in allergic rhinitis and its association with clinical phenotypes. *Am J Otolaryngol* 2013; 34:676–681.
- Ying X, Zhang R, Yu S, *et al.* Association of interleukin-13 SNP rs1800925 with allergic rhinitis risk: a meta-analysis based on 1411 cases and 3169 controls. *Gene* 2012; 506:179–183.
- Pawankar R, Yamagishi S, Yagi T. Revisiting the roles of mast cells in allergic rhinitis and its relation to local IgE synthesis. *Am J Rhinol* 2000; 14:309–317.
- Bradding P, Holgate ST. The mast cell as a source of cytokines in asthma. *Ann N Y Acad Sci* 1996; 796:272–281.
- Pawankar R, Okuda M, Hasegawa S, *et al.* Interleukin-13 expression in the nasal mucosa of perennial allergic rhinitis. *Am J Respir Crit Care Med* 1995; 152 (6 Pt 1):2059–2067.
- Okayama Y, Okumura S, Sagara H, *et al.* FcεpsilonRI-mediated thymic stromal lymphopoietin production by interleukin-4-primed human mast cells. *Eur Respir J* 2009; 34:425–435.
- Nakae S, Suto H, Berry GJ, Galli SJ. Mast cell-derived TNF can promote Th17 cell-dependent neutrophil recruitment in ovalbumin-challenged OTII mice. *Blood* 2007; 109:3640–3648.
- Suto H, Nakae S, Kakurai M, *et al.* Mast cell-associated TNF promotes dendritic cell migration. *J Immunol* 2006; 176:4102–4112.
- Pawankar R, Okuda M, Yssel H, *et al.* Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc epsilonRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997; 99:1492–1499.
- Smurthwaite L, Durham SR. Local IgE synthesis in allergic rhinitis and asthma. *Curr Allergy Asthma Rep* 2002; 2:231–238.
- Otto BA, Wenzel SE. The role of cytokines in chronic rhinosinusitis with nasal polyps. *Curr Opin Otolaryngol Head Neck Surg* 2008; 16:270–274.
- Van Zele T, Holtappels G, Gevaert P, Bachert C. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy* 2014; 28:192–198.
- An important study comparing nonrecurrent and recurrent CRSwNPs having different types of inflammatory patterns. Nonrecurrent CRSwNPs exhibit a mixed pattern of T-helper cytokines with significant higher levels of IFN-gamma and lower concentrations of IgE, ECP, and IL-5, as compared with recurrent CRSwNPs that had a predominant Th2 type of inflammation.
- Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med* 2009; 361:888–898.
- Han D, Wang C, Lou W, *et al.* Allergen-specific IL-10-secreting type 1 T regulatory cells, but not CD4(+)CD25(+)Foxp3(+) T cells, are decreased in peripheral blood of patients with persistent allergic rhinitis. *Clin Immunol* 2010; 136:292–301.
- Pène J, Chevalier S, Preisser L, *et al.* Chronically inflamed human tissues are infiltrated by highly differentiated Th17 lymphocytes. *J Immunol* 2008; 180:7423–7430.
- Baumann R, Rabaszowski M, Stenin I, *et al.* Comparison of the nasal release of IL-4, IL-10, IL-17, CCL13/MCP-4, and CCL26/eotaxin-3 in allergic rhinitis during season and after allergen challenge. *Am J Rhinol Allergy* 2013; 27:266–272.
- Nasal IL-17, MCP-4, and, possibly, eotaxin-3 may aggravate and IL-10 may alleviate nasal mucosal allergy.
- Scadding GW, Eifan A, Penagos M, *et al.* Grass pollen nasal challenge is associated with increases in Th2 cytokines, eotaxin, MDC and IL-6 in nasal fluid: Th1 and Th17-associated cytokines are low and do not increase following challenge (Abstract). *EAACI SERIN meeting*, Leuven, March 2013.
- Ciprandi G, Fenoglio D, De Amici M, *et al.* Serum IL-17 levels in patients with allergic rhinitis. *J Allergy Clin Immunol* 2008; 122:650–651.
- Bajoriuniene I, Malakauskas K, Lavinskiene S, *et al.* Response of peripheral blood Th17 cells to inhaled dermatophagoides pteronyssinus in patients with allergic rhinitis and asthma. *Lung* 2012; 190:487–495.
- Liu Y, Yu HJ, Wang N, *et al.* Clara cell 10-kDa protein inhibits T(H)17 responses through modulating dendritic cells in the setting of allergic rhinitis. *J Allergy Clin Immunol* 2013; 131:387–394.
- Wang H, Mobini R, Fang Y, *et al.* Allergen challenge of peripheral blood mononuclear cells from patients with seasonal allergic rhinitis increases IL-17RB, which regulates basophil apoptosis and degranulation. *Clin Exp Allergy* 2010; 40:1194–1202.
- Molet S, Hamid Q, Davoine F, *et al.* IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. *J Allergy Clin Immunol* 2001; 108:430–438.
- Zhang N, Van Zele T, Perez-Novo C, *et al.* Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. *J Allergy Clin Immunol* 2008; 122:961–968.
- Ota K, Kawaguchi M, Matsukura S, *et al.* Potential involvement of IL-17F in asthma. *J Immunol Res* 2014; 2014:602846.
- Again, even with adequate ICS treatment, there are still patients who exhibit Th2/eosinophilic inflammation and develop airflow limitation, a functional consequence of airway remodeling.
- Nakamaru Y, Oridate N, Nishihira J, *et al.* Macrophage migration inhibitory factor in allergic rhinitis: its identification in eosinophils at the site of inflammation. *Ann Otol Rhinol Laryngol* 2004; 113 (3 Pt 1):205–209.
- Kobayashi H, Gleich GJ, Butterfield JH, Kita H. Human eosinophils produce neurotrophins and secrete nerve growth factor on immunologic stimuli. *Blood* 2002; 99:2214–2220.
- Figueroa DJ, Borish L, Baramki D, *et al.* Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin Exp Allergy* 2003; 33:1380–1388.
- Amin K, Rinne J, Haatela T, *et al.* Inflammatory cell and epithelial characteristics of perennial allergic and nonallergic rhinitis with a symptom history of 1 to 3 years' duration. *J Allergy Clin Immunol* 2001; 107:249–257.
- Onbasi K, Sin AZ, Doganavsargil B, *et al.* Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. *Clin Exp Allergy* 2005; 35:1423–1431.
- Haldar P, Brightling CE, Hargadon B, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360:973–984.
- Nair P, Pizzichini MM, Kjarsgaard M, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360:985–993.
- Pawankar R. Inflammatory mechanisms in allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2007; 7:1–4.
- Nonaka M, Pawankar R, Fukumoto A, *et al.* Induction of eotaxin production by interleukin-4, interleukin-13 and lipopolysaccharide by nasal fibroblasts. *Clin Exp Allergy* 2004; 34:804–811.
- Ying S, O'Connor B, Ratoff J, *et al.* Expression and cellular provenance of thymic stromal lymphopoietin and chemokines in patients with severe asthma and chronic obstructive pulmonary disease. *J Immunol* 2008; 181:2790–2798.

52. Kimura S, Pawankar R, Mori S, *et al.* Increased expression and role of thymic stromal lymphopoietin in nasal polyposis. *Allergy Asthma Immunol Res* 2011; 3:186–193.
53. Licona-Limón P, Kim LK, Palm NW, Flavell RA. TH2, allergy and group 2 innate lymphoid cells. *Nat Immunol* 2013; 14:536–542.
54. Saglani S, Lui S, Ullmann N, *et al.* IL-33 promotes airway remodeling in pediatric patients with severe steroid-resistant asthma. *J Allergy Clin Immunol* 2013; 132:676–685.
55. Shikotra A, Choy DF, Ohri CM, *et al.* Increased expression of immunoreactive thymic stromal lymphopoietin in patients with severe asthma. *J Allergy Clin Immunol* 2012; 129:104–111.
56. Shaw JL, Fakhri S, Citardi MJ, *et al.* IL-33-responsive innate lymphoid cells are an important source of IL-13 in chronic rhinosinusitis with nasal polyps. *Am J Respir Crit Care Med* 2013; 188:432–439.
- Elevated levels of ST2+ innate lymphoid cells in ethmoid sinus mucosa in patients with chronic rhinosinusitis with nasal polyps compared with patients with chronic rhinosinusitis without nasal polyps or healthy controls.
57. Mjösberg JM, Trifari S, Crellin NK, *et al.* Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CCR4 and CD161. *Nat Immunol* 2011; 12:1055–1062.
58. Kamekura R, Kojima T, Koizumi J, *et al.* Thymic stromal lymphopoietin enhances tight-junction barrier function of human nasal epithelial cells. *Cell Tissue Res* 2009; 338:283–293.
59. Zhang Y, Song X, Zhao Y, *et al.* Single nucleotide polymorphisms in thymic stromal lymphopoietin gene are not associated with allergic rhinitis susceptibility in Chinese subjects. *BMC Med Genet* 2012; 13:79.
60. Zhang Y, Wang X, Zhang W, *et al.* Polymorphisms in thymic stromal lymphopoietin gene demonstrate a gender and nasal polyposis-dependent association with chronic rhinosinusitis. *Hum Immunol* 2013; 74:241–248.
61. Asaka D, Yoshikawa M, Nakayama T, *et al.* Elevated levels of interleukin-33 in the nasal secretions of patients with allergic rhinitis. *Int Arch Allergy Immunol* 2012; 158 (Suppl 1):47–50.
62. Kamekura R, Kojima T, Takano K, *et al.* The role of IL-33 and its receptor ST2 in human nasal epithelium with allergic rhinitis. *Clin Exp Allergy* 2012; 42:218–228.
63. Baumann R, Rabaszowski M, Stenin I, *et al.* Nasal levels of soluble IL-33R ST2 and IL-16 in allergic rhinitis: inverse correlation trends with disease severity. *Clin Exp Allergy* 2013; 43:1134–1143.
64. Glöck J, Rymarczyk B, Rogala B. Serum IL-33 but not ST2 level is elevated in intermittent allergic rhinitis and is a marker of the disease severity. *Inflamm Res* 2012; 61:547–550.
65. Ishida A, Ohta N, Suzuki Y, *et al.* Expression of pendrin and periostin in allergic rhinitis and chronic rhinosinusitis. *Allergol Int* 2012; 61:589–595.
66. Baumann R, Rabaszowski M, Stenin I, *et al.* The release of IL-31 and IL-13 after nasal allergen challenge and their relation to nasal symptoms. *Clin Transl Allergy* 2012; 2 (1):13.
67. Shah SA, Ishinaga H, Hou B, *et al.* Effects of interleukin-31 on MUC5AC gene expression in nasal allergic inflammation. *Pharmacology* 2013; 91: 158–164.
68. Okano M, Fujiwara T, Higaki T, *et al.* Characterization of pollen antigen-induced IL-31 production by PBMCs in patients with allergic rhinitis. *J Allergy Clin Immunol* 2011; 127:277–279.
69. Liu W, Luo R, Chen Y, *et al.* Interleukin-31 promotes helper T cell type-2 inflammation in children with allergic rhinitis. *Pediatr Res* 2014.
- IL-31 expression in allergic rhinitis can aggravate and amplified Th2 inflammation as well as mucin production, and provide a possible explanation for IL-31s regulatory role in the pathogenesis of allergic rhinitis.
70. Cheng D, Xue Z, Yi L, *et al.* Epithelial interleukin-25 is a key mediator in th2-high, corticosteroid-responsive asthma. *Am J Respir Crit Care Med* 2014.
- IL-25 measurements identify two subsets of patients with distinct asthma phenotypes and different responses to ICS. Bronchial epithelial IL-25 expression is likely a key determinant of type 2 response activation in asthma. Plasma IL-25 level reflects airway IL-25/type 2 response activation and may be useful for predicting responses to asthma therapy.
71. Moore WC, Hastie AT, Li X, *et al.* National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol* 2014; 6:1557–1563.
72. Casale TB, Stokes JR. Immunomodulators for allergic respiratory disorders. *J Allergy Clin Immunol* 2008; 121 (2):288–296.