



Innate and adaptive immunity in allergic airway disease

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Purpose of review

This article explores recent findings on the involvement of innate immunity in allergic airways disease, concentrating on allergic rhinitis.

Recent findings

We speculate on the ways in which environmental influences act to initiate inflammation and on how these may have altered in recent decades. Improved understanding of the mechanisms involved may reveal future possibilities for therapy.

Summary

The complex nature of immunity – both innate and acquired – in airways disease has implications for prevention and for therapy and requires further elucidation.

Keywords

acquired immunity, airways disease, anti-thymic stromal lymphopoietin, innate immunity, microRNAs

INTRODUCTION

In our previous study [1^{*}], we explored recent knowledge on the involvement of the innate immune system in airways diseases such as allergic rhinitis, chronic rhinosinusitis (CRS) and asthma, and discussed possible therapeutic implications. We postulated on the relative importance of both innate and adaptive systems – essentially, type 2 innate lymphoid cells (ILC2s) versus type 2 T-helper cells (Th2s) – in these different conditions (specifically the classic type 2 phenotypes of these conditions) and what these implications might be for use of current and emerging monoclonal antibody therapies. This current study explores the area further, with reference predominantly to allergic rhinitis. It examines evidence for changes in innate disease-promoting influences over time and the possibility of future therapies with new biologicals and novel small molecule drugs, such as micro-RNAs.

TH2 INFLAMMATION

For several decades, allergic rhinitis was recognized as an immunological disorder involving the adaptive immune system with IgE as the major player and eosinophilic inflammation arising as the result of allergen exposure [2^{**}]. Such so-called Th2 responses (i.e. involving CD4⁺ helper T cells releasing interleukins 4, 5 and 13) are also implicated in

other allergic diseases, such as allergic asthma and atopic dermatitis, but, on an evolutionary basis, probably have their prime function in defence against parasitic infections [3].

The process of sensitization to an inhalant allergen begins in the epithelium, presumably the nasal mucosa in allergic rhinitis. Usually, substances arriving in the nose are dealt with by the first line of innate immunity: trapped in mucus, transported by cilia to the back of the throat and swallowed. However, if this process is malfunctioning secondary to infection or pollution, or the epithelium is damaged/incomplete due to a genetic abnormality [4], or disrupted by intrinsic proteolytic activity of allergens, or abraded by accompanying molecules such as PM 2.5 [5^{*}], the normal process of mucociliary clearance fails to remove them. Allergens may then succeed in penetrating the epithelium and meet further with the immune system, being taken up by dendritic cells, which determine the direction of

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KEY POINTS

- Innate immune mechanisms are involved in Type 2 airways disease.
- Aetiological factors may have altered in recent decades.
- Therapeutic options may eventually include small molecules such as micro-RNAs.

the subsequent response, based on their milieu. Dendritic cells carry allergens to local lymphoid tissue wherein antigen presentation in the form of peptides in association with MHC class II to naive helper T (Th0) cells occurs [2[■]].

In individuals who become allergic the immune response is directed towards Th2 via various epithelial secreted factors, including thymic stromal lymphopoietin (TSLP) [6]. This promotes Th2-skewing dendritic cells, which secrete chemokines to attract and amplify Th2-destined T lymphocytes and enhance memory B-cell survival as well as enabling eosinophil recruitment and mast cell and basophil activation [2[■]]. Various other factors are necessary for Th2 differentiation: co-stimulation of CD28 on T cells with CD80 and CD86 on antigen-presenting cells (APCs) [7] and the cytokine interleukin (IL)-4. This cytokine binds STAT-6 on the Th0 cell, activating the transcription factor GATA-3, a master switch that directs the cell toward a Th2 phenotype, resulting in production of factors including IL-4, IL-5 and IL-13 production. Of these, IL-4 and IL-13 promote B-cell class switching to IgE and the development of mature IgE-secreting plasma cells, alongside the capacity to produce long-lasting, IgE-switched, memory B-cells. IL-5 stimulates eosinophil differentiation, maturation and recruitment into the airway mucosa [2[■]]. IgE antibodies are rapidly and avidly taken up by their Fc tails by high-affinity receptors (FcεRI) borne by mast cells and basophils, leaving their allergen-binding sites exposed and rendering such coated cells sensitized to further allergen contact. When this occurs, crosslinking of the FcεRI receptor-bound IgE causes degranulation of mast cells and basophils with rapid release of their inflammatory mediators such as histamine, prostaglandins, PAF and leukotrienes, and consequent symptoms of sneezing, itching, running and nasal blocking [2[■]]. Free IgE is in plasma short-lived, but once receptor-bound, it remains attached to cells for weeks or months. The phenomenon of local allergic rhinitis (LAR) or entopy is now known to occur, whereby individuals with allergic rhinitis have local nasal IgE, no detectable plasma IgE, but respond to

nasal allergen challenge and can be treated with allergen-specific immunotherapy (AIT). LAR may remain localized, transmute into allergic rhinitis and, like allergic rhinitis, LAR is also a risk factor for asthma [8,9,10[■]].

INNATE IMMUNITY

Recently, it has become apparent that immunological processes other than the Th2-led adaptive response are present and important in allergic diseases [11[■]]. Innate immune mechanisms are initiated by the epithelium wherein inhaled aeroallergens and pollutants are initially encountered. Innate (natural) immunity is present from birth and is the first line of defence against pathogens. Incapable of fine distinction, it uses pattern recognition receptors specific for common structures on different microorganisms (bacteria, viruses, fungi, parasites). Binding to these can initiate basic disposal mechanisms, such as phagocytosis. Tissue damage also activates innate immunity, leading to inflammation, followed by resolution. Airway epithelial cells bear pattern recognition receptors called toll-like receptors (TLRs). Exposure of the airway epithelium to molecules such as viruses and allergens allows TLR recognition. Stimulation of these receptors can also cause production of alarmins: IL-25, IL-33 and TSLP, which in turn activate type 2 innate lymphocytes (ILC2s) [12]. Innate lymphoid cells (ILCs) are orchestrating cells important for protection against infiltrating pathogens and restoration of tissue integrity. They can also be involved in the pathogenesis of eosinophilic diseases such as allergic rhinitis, CRSwNP and asthma [1[■], 11[■], 12, 13]. ILCs lack cell surface lineage markers. Their subtypes correspond to those of T cells: as NK cells relate to CD8⁺ T cells, ILC1s, ILC2s and ILC3s relate to Th1, Th2, Th17 cells, respectively. The equivalent ILC and T-helper cell subgroups have similar functions and are subject to similar regulatory pathways [14]. ILC2s, the mirror of Th2 cells, are involved in inflammation and tissue repair in allergic diseases and in diabetes, as well as in the immune response to parasite infestation. ILC2s are predominantly situated, albeit in low numbers, in mucosal tissues such as airway epithelia, gut, skin and adipose tissue wherein they rapidly enhance type 2 inflammation by immediate production of cytokines, mainly IL-5, and IL-13. [15].

ILC2 regulation occurs in stages: stimulation is by alarmins: IL-25, IL-33 and TSLP, secreted mainly by epithelial cells; survival factors such as IL-2, IL-4, IL-7, IL-9, TL1A and GITRL maintain their functionality, and they respond also to other mediators, including PGD₂, LTD₄, neuropeptides [neuromedin

U (NMU), vasoactive intestinal peptide (VIP)], hormones (β -adrenaline) and the ILC2 inhibitory factor cluster (IL-10, TGF- β) [11[¶]]. Although innate immunity is usually characterized as lacking in specificity and memory, this is untrue of ILC2s, which, in mice stimulated with TSLP or IL-33, showed raised numbers for nearly 4 months and reacted faster to repeat antigen stimulation [16]. House dust mite (HDM), to which most allergic asthmatic patients are sensitized, acts on airway epithelial cells in a TLR-4 dependent manner, inducing IL-25, IL-33, TSLP and GM-CSF release. Interestingly, in murine experiments, lung ILC2s were a necessity for priming the adaptive type 2 immune response to inhaled HDM, but not to systemically applied ovalbumin [17]. Nasal allergen challenge in allergic rhinitis individuals increases peripheral blood ILC2s [18], which are therefore potential targets for therapeutics aimed at blocking the initiation of Th2 adaptive immunity. Nasal secretion IL-33 levels correlate with total nasal symptom scores [19] and have been used as a new treatment biomarker [20]. IL-33 antagonists may also be therapeutic [21].

Other subsets of innate cells are ILC1, which are functionally similar to Th1 cells may be involved in CRS [22] and ILC3, which mimic Th17 cells. Nasal epithelial cells also secrete other cytokines, including TNF- α , IL-1, IL-6, IL-8, which act on eosinophils, basophils and Th2 cells. In turn, these cells and mast cells elaborate their own cytokines, leading to an expanding cascade response with eosinophilic inflammation (Fig. 1).

It is likely that the original purpose of eosinophil recruitment was to use their potent toxins to kill and dispose of large parasitic invaders, such as protozoan worms [2^{¶¶}]. Why this reaction has come to be more commonly misapplied to harmless allergens is unclear and a matter of conjecture. What is clear, however, is the rise in prevalence of allergic rhinitis from a rare disorder of the upper classes as noted by John Bostock in 1829, to one affecting around a quarter of the UK population today and billions worldwide. From the mid-20th century onwards, the increase was marked and associated with Westernization of lifestyles [23]. Environmental influences such as detergents, pollutants and microplastics,

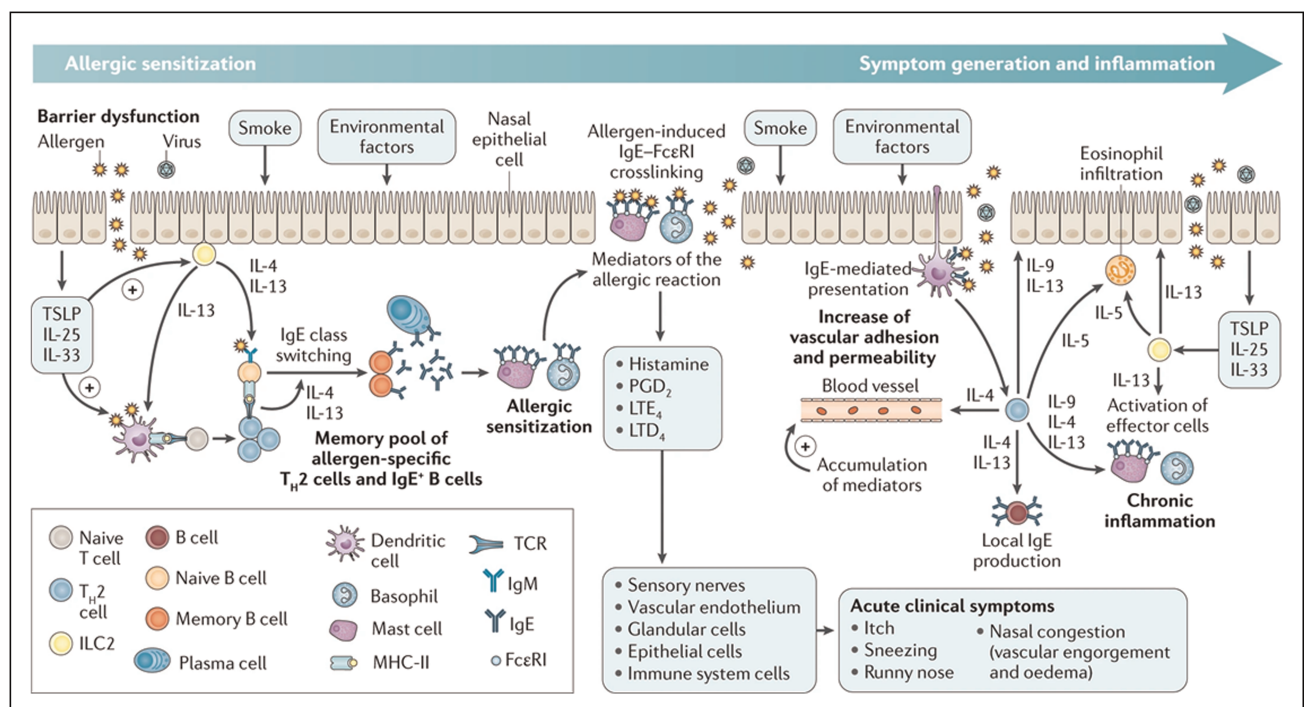


FIGURE 1. The pathophysiology of allergic rhinitis. Multiple influences on the respiratory epithelium can initiate inflammation via both innate and adaptive immune systems. Alarmins such as TSLP, IL-25 and IL-33 are capable of activating ILC2s, which rapidly release pro-inflammatory cytokines, IL-5, 9 and 13. These in turn activate further local cells, including mast cells and basophils. Meanwhile, dendritic cells bear allergen from the mucosa to local lymph nodes wherein T cell recognition occurs with subsequent IgE production. This arms mast cells for mediator release on subsequent allergen contact and enables B cell antigen presentation for further elaboration of the response. Eosinophil infiltration occurs in response to cytokines such as IL-5 and eotaxin. The original purpose of this complex reaction is likely to have been elimination of large parasites, which are not susceptible to phagocytosis, but which can be killed by eosinophil contents such as eosinophil peroxidase (EPO) and eosinophil-derived neurotoxin (EDN). Reproduced in black and white from [2].

particularly those acting on respiratory epithelia, may be relevant [2[¶]]. Properties of allergens themselves, such as protease activity, may also be relevant, as may the concurrence of viral exposure with allergen.

Abrogation of the Th2 inflammatory cascade can occur if the initiating dendritic cell is persuaded by an IL-12 and/or IL-10 rich milieu (as might occur in the presence of a pathogenic or healthy commensal bacterial environment) to favour the induction of a Th1 and/or T regulatory cell response instead. High allergen dose and tolerogenic signals such as vitamin D3, short chain fatty acids and adenosine can lead to induction of tolerance, featuring both T and B regulatory cells. The lower prevalence of allergic diseases in large families suggested that early microbial contact might be a protective factor, as highlighted by Strachan [24]. The inverse association between the number of older siblings and prevalence of hay fever was strongest in more affluent countries [25]. The gut microbiome is a putative relevant source for these microorganisms with lower bacterial diversity associated with increased allergic sensitization and allergic rhinitis ($P < 0.007$) [26]. Increased allergic sensitization by 2 years, odds ratio (OR) 1.54 (1.09–2.31), was noted if *Clostridium difficile* was present at 1 month [27] and raised IgE by age 1.5 years if Gram-negative bacteria were predominant at 1 year [28], whereas colonization with *Lactobacilli* and *Bifidobacterium bifidum* appeared protective [29]. Unfortunately, there is no convincing evidence that probiotics can reduce the incidence of allergic rhinitis [2[¶]].

MIXED IMMUNITY

There is evidence for both innate and acquired immune pathomechanisms in airway diseases such as allergic rhinitis, asthma and CRSwNPs [1[¶]]. Allergens, such as HDMs, with protease activity or those accompanied by viruses, endotoxins or inorganic particles, can evoke mixed immunity, including Type 2 (innate and acquired), IL-17 associated or Type 1 [30]. Th1 mechanisms are also found in atopic dermatitis and asthma, possibly initiated by the presence of micro-organisms, such as *Staphylococci* or rhinovirus concomitantly with allergen [31[¶]]. The balance between these mechanisms may vary between individuals, not only based possibly on their genetic makeup, as a family history of allergic rhinitis is a risk factor for allergic rhinitis development, but also on the timing, concomitant factors and the nature of the allergen to which they have been exposed. The clinical relevance of early inhalant allergen exposure to allergic rhinitis development remains uncertain, although food allergy at

2 years of age may be a risk factor, as for asthma [32]. The immunological nature of allergic rhinitis initiation may itself have changed. Observational studies reveal interesting temporal differences. Allergic rhinitis was consistently associated with high socioeconomic status (SES) in early studies in both the UK and Sweden [33–36]. However, this association weakened during the lifetime of the German MAS study [37] and has now reversed such that for children born in the West pre1970 high SES was a risk factor, whereas for those born after 1990, low SES was a risk factor [38].

The reduction in outdoor air pollution due to the lockdowns imposed in light of the Covid-19 pandemic may have a beneficial effect on future numbers of children with asthma. Almost half the childhood asthma in Barcelona – 48% of the total – could be attributable to air pollution each year [39[¶]]. The results suggested that if the WHO guidelines on annual exposure levels were met, 478 childhood asthma cases attributable to PM 2.5 (19% of all cases) and 454 cases attributable to NO₂ (18%) could be prevented in Barcelona annually [39[¶]]. A similar study [40] used census population data from 18 European countries. The analysis revealed that 66 600 childhood asthma cases (11% of the total incident cases) could be prevented per year if the 18 countries under study complied with the WHO air quality guideline for PM 2.5. Compliance with the NO₂ guideline was estimated to prevent 2400 childhood asthma cases per year (only 0.4% of the total incident cases).

Recent data on rhinitis and long-term pollution [41[¶]] reveals that particulate matter increases rhinitis severity in allergic and nonallergic rhinitis. Previous work suggested worsening of seasonal allergic rhinitis by PM 2.5 and NO₂ [42], but that data did not reach significance when adjusted for pollen levels. Several possible mechanisms exist for the interaction between particles and pollen [43].

TREATMENT IMPLICATIONS

The array of inflammatory mediators and pathways has many implications, including those related to treatment [1[¶]]. In brief, therapies directed against the Th2 arm, such as anti-IgE, anti-IL4 or AIT may be less efficacious where an ILC2 response is predominant. AIT for an allergen with rich protease activity, such as HDM, could be less effective than for one without, such as grass pollen. Blocking upstream factors, such as with an anti-TSLP monoclonal, might be the most effective therapies yet devised, given roles in initiation of both innate and adaptive arms of the response. However, the expense involved in production of monoclonal antibody

drugs limits their use to more severe cases in more developed healthcare systems, limiting the opportunity for widespread use. Other therapies, apart from monoclonals anti-TSLP, anti IL33 and 35, directed against the innate immune system are in development. These include micro-RNAs.

MicroRNAs (miRNAs) are small endogenous noncoding RNA molecules, which regulate post-transcriptional gene expression by silencing target mRNAs. They appear to play a role in regulating immune function and inflammation in several diseases, including those involving the airways [44[■]]. Low levels of miR-21 may be a useful cord blood biomarker for predicting allergic rhinitis [45]. Elevated levels of miR-155, miR-205, miR-498 and low levels of let-7e were found in individuals with current allergic rhinitis symptoms [46]. Micro-RNA-155 is an ancient immune system regulator [47], which is raised in allergic rhinitis, proportionately to the raised number of ILC2s, which in turn relate numerically to the amounts of IL-25 and IL-33 present in both mice and humans. Allergic rhinitis pathological changes and signs in mice were worsened after miR-155 agonist and ameliorated after miR-155 antagonist administration [48]. This regulation appears to occur via changes in c-Maf, a transcription factor that regulates T cell IL-4 expression and secretion, the differentiation of naive T cells into Th2 cells and the differentiation and development of T follicle helper cells and regulatory T cells [49]. Similar changes occurred with another microRNAs [50[■]].

CONCLUSION

Innate as well as acquired immunity is involved in allergic airways disease and is probably the means of its initiation. The possibility of employing small molecules to influence the direction of immune responses is exciting but will require considerable work in humans before reaching clinical use. During trials, we may learn more about the multiple drivers and amplifiers of allergic-type immunity in man.

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Chair of Data Monitoring Board for Paediatric AR trials of tablet SLIT

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- of special interest
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