



Role of innate immunity in the pathogenesis of allergic rhinitis

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Purpose of review

The immunologic causes of allergic rhinitis underscore the important roles of both adaptive and innate immune systems. In recent years, appreciation of the role of nasal innate immunity has grown and evidence suggests that the pathogenesis of allergic rhinitis is partially mediated by the innate immune system. This review focuses on our current knowledge and recent discoveries in nasal innate immunity as they pertain to the cause and management of allergic rhinitis.

Recent findings

Previously thought to be nonspecific, innate immunity also possesses specific mechanisms as demonstrated by toll-like receptors. The interplay between the external environment and nasal mucosa contributes to innate-immune-mediated development of allergic rhinitis. Certain innate immune cells such as plasmacytoid dendritic cells and natural killer T cells may be important in the induction of Th2 cytokine production characterized in allergic airway disease.

Summary

The increasing knowledge of nasal innate immunity gained from recent research not only expands our understanding of the causes of allergic rhinitis, it also leads to new therapeutic approaches. Although current management of allergic rhinitis includes one or a combination of pharmacotherapy, immunotherapy, and/or surgery, novel treatments such as toll-like receptor agonists used as targets or adjuvants for immunotherapy are being tested and may hold promising roles in future allergic rhinitis treatment.

Keywords

allergic rhinitis, chitinase, innate immunity, mucus, pathogenesis, surfactant protein, therapy, toll-like

INTRODUCTION

The review examines the role of innate immunity in the pathogenesis of allergic rhinitis. The growing body of literature centered on this relationship identifies correlations and risk factors between alterations in innate immunity and those suffering from allergic rhinitis. Absolute causative evidence does not currently exist; however, the growing knowledge base linking innate immunity and allergic rhinitis is suggestive of causative pathways. Newer treatment strategies hinging on addressing innate immune dysfunction are being developed and potentially offer an alternative or complementary form of allergic rhinitis therapy.

ALLERGIC RHINITIS

Allergic rhinitis is an extremely common upper respiratory disease. Approximately 15–20% of the industrialized world suffers from this health problem, costing an estimated \$5 billion per year [1]. Even in the setting of increased prevalence of atopic

diseases, allergic rhinitis remains the most common allergic disease. The negative impact on quality of life is substantial and comparable to other chronic diseases such as asthma, angina, chronic pulmonary obstructive disease, and chronic back pain [2]. Allergic rhinitis patients frequently report reduced quality of sleep, daytime productivity and concentration levels [3,4].

Allergic rhinitis is IgE-mediated and thought to be caused by environmental factors in genetically predisposed individuals, partly due to alterations in their immune system. The adaptive immune system plays an important role in allergic rhinitis through

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KEY POINTS

- The sinonasal epithelium lies at the interface between the host and the environment and is the primary site of innate immune modulation in allergic rhinitis.
- There exists a complex interplay between genetic and environmental risk factors in the pathogenesis of allergic rhinitis which may have potential future diagnostic and therapeutic value.
- In addition to avoidance, pharmacotherapy, immunotherapy and surgery, novel therapies directed toward the innate immune system (such as TLRs) are in development for treatment of allergic rhinitis.

the development of sneezing, pruritis, nasal congestion, rhinorrhea, and late-phase reactions. As our understanding continues to expand, there is evidence that alterations in the innate immune system relate to the development and immunomodulation of allergic rhinitis.

Established management strategies of allergic rhinitis include avoidance, pharmacotherapy, immunotherapy, and occasionally surgery if anatomic obstructions exist. However, the future holds promising new therapies that are being developed on the basis of targeting nasal innate immunity.

INNATE IMMUNITY

Traditionally, the innate immune system was thought to be primitive with little overlap with the adaptive immune system. Whereas the adaptive immune system conferred memory and specificity, the innate immune system was thought to be non-specific and lacking memory. Therefore, the innate immune system, which operates in a more immediate fashion, allowed time for the adaptive immune system to generate antigen-specific memory in lymphocytes to carry out the function of major immune effectors.

We now understand that the innate immune system is substantially more complex than originally thought. Whereas the innate immune system was previously thought to be composed of only secreted proteins, work over the past decade has uncovered numerous pattern-recognition receptors that have been evolutionarily conserved from *Drosophila*. Recent studies now demonstrate that the innate immune system directs the adaptive immune system through providing early signals and cytokines to allow lymphocytes to develop and mount pathogen-specific or inflammatory immune responses [5,6].

Recent attention has focused on the altered homeostasis of the innate immune system in

chronic inflammatory diseases in the sinonasal cavity [7]. In the nose, the epithelium is a critical barrier mechanism providing mucus production and mucociliary function. In addition, the nasal epithelium is unique, unlike other epithelia, as it constantly engages in immunomodulation between the host and the environment. Evidence supports an important role of sinonasal epithelial cells as both mediators and regulators of innate immune responses and adaptive immune responses in the pathogenesis of allergic rhinitis [8].

NASAL EPITHELIUM

The nasal cavity is often the first location of interaction between environmental antigens and airway mucosa. It possesses both nonspecific and specific defense mechanisms. Recent advances have reported specific innate immune defense mechanisms associated with the pathogenesis of allergic rhinitis.

NONSPECIFIC NASAL INNATE IMMUNITY

Mucociliary clearance provides a continuously flowing blanket carrying a variety of antimicrobial products such as immunoglobulins, opsonins, defensins and enzymatic proteins. It also serves as a filter that captures particulate matter and clears it through beating cilia. Ciliary beat frequency, mucus quantity and viscoelastic properties directly affect mucociliary clearance. Impaired mucociliary clearance leads to chronic stasis and is more common in patients with severe allergic rhinitis [9], and may predispose patients with allergic rhinitis to go on to further develop other sinonasal inflammatory diseases such as chronic rhinosinusitis [10].

Secreted antimicrobials including defensins, lactoferrin, lysozyme, and acute-phase proteins serve as mediators for chemoattraction and effector cell activation. They can also immobilize and kill micro-organisms. Many of the secreted antimicrobials work directly on pathogens; however, they may also have a role in the management of inhaled allergens through differentiating between self and nonself. This is best observed in the surfactant proteins, SP-A and SP-D, which are able to bind and agglutinate nonself structures such as bacteria and fungi as well as allergens.

Recent studies have demonstrated that genetic polymorphisms such as those associated with collectins, surfactant proteins SP-A and SP-D, and elevated mannose-binding lectin [11,12] potentially lead to more severe allergic rhinitis and could have future diagnostic value in the work-up of atopic airway disease [13].

SPECIFIC NASAL INNATE IMMUNITY AND ALLERGIC RHINITIS

Pattern recognition receptors (PRRs) in the form of toll-like receptors (TLRs) have been immunolocalized within the sinonasal epithelium and in the stroma just deep into the epithelial cell layer [14]. The sinonasal epithelium therefore is a unique interface between pathogens via their pathogen-associated molecular patterns and the innate immune system via PRRs.

Messenger RNA of human TLRs and alternate complement pathway factors, another important aspect of the innate immune system, are measurably expressed in sinonasal mucosa [15].

Toll-like receptor 9, which is the receptor for unmethylated CpG oligodeoxynucleotide DNA found only in bacterial DNA, is widely expressed in the sinonasal mucosa [16]. Sinonasal epithelial cells from patients who suffer from both recurrent acute rhinosinusitis and allergic rhinitis have elevated TLR9 expression when compared with those of patients who have allergic rhinitis alone. This indicates an enhanced mucosal innate immunity in individuals who suffer from recurrent but resolving bouts of sinus infections, whereas those with chronic allergic rhinitis have reduced innate immunity, which correlates with their atopic disease burden [17]. In addition, TLR9 expression in sinonasal mucosal brushings is relatively reduced in patients with allergic rhinitis when compared with normal controls, which also suggests deficient innate immunity in the nasal cavities of those suffering from allergic rhinitis [18^{***}].

ENVIRONMENTALLY MEDIATED INNATE IMMUNITY IN ALLERGIC RHINITIS

There exists a complex interplay between genetic and environmental factors in allergic rhinitis. There are known genetic disparities among Eastern and Western subgroups from the same racial and geographic background who suffer from allergic rhinitis [19]. In addition, microbial exposure through farming environments has also been shown to affect innate immunity and subsequently lower the incidence of developing atopic disease [20]. Studies have demonstrated that the reduced incidence of atopic diseases in these farming populations is likely due to polymorphisms in the TLR2 gene in farmers and nonfarmers [21,22^{***}].

Another environmental factor influenced by sun exposure, which is significantly decreased in the era of sunscreen and in certain geographic locations, is vitamin D deficiency. Evidence supports that vitamin D has significant impact on innate and adaptive immune function, and perhaps

a causal relationship exists between lower levels of vitamin D and atopic diseases, including allergic rhinitis [23].

Tobacco smoke has long been recognized as an airway irritant. Airway disease is worse in those with allergic rhinitis and asthma who also smoke. Evidence supports the direct influence of smoke on innate immunity, predisposing to Th2-associated respiratory diseases and increasing the risk for IgE-mediated sensitization [24].

Although exact cause and effect have not been fully discerned, there are data identifying possible risk factors in the development of allergic rhinitis and supporting its link to innate immune markers. Early exposure to endotoxin can alter the risk of allergic rhinitis and asthma. Studies looking at TLR4, which binds to bacterial endotoxin, show correlation between allergic rhinitis and TLR4 polymorphisms [25].

CHITINASES IN ALLERGIC RHINITIS

Although parasite infections are rare in the developed world, antiparasitic immunity pathways remain preserved in humans, and the development of atopy and allergic rhinitis may be a reflection of dysregulated antiparasitic immunity. Chitinases produced by mammals target chitin, an abundant polymer found in parasites. Specifically, acidic mammalian chitinase (AMCase) is expressed by nasal epithelial cells and independently promotes eosinophilic inflammation [26]. Up-regulation of AMCase serves as an inflammatory mediator in Th2 diseases, specifically, allergic rhinitis [27]. Perhaps the lack of parasitic exposure early in life results in a predilection towards Th2 inflammation through alterations in antiparasitic innate immunity.

THE LINK BETWEEN INNATE AND ADAPTIVE IMMUNITY IN ALLERGIC RHINITIS

Many inflammatory cells, including phagocytes in the form of polymorphonuclear leukocytes, eosinophils, basophils, and mast cells, confer a level of specificity to pathogenic cells. In allergic rhinitis, mast cell activation and degranulation is often the starting point for a previously sensitized individual and leads to a vicious cycle of T-cell activation and cytokine and inflammatory substance release. However, other innate immune cells not previously understood as players in Th2 inflammation have recently been found to possess properties important in the pathogenesis of allergic rhinitis. Plasmacytoid dendritic cells, historically found in only bone

marrow, organized lymphoid tissue, and blood, exert innate mechanisms that can induce Th2 cytokine production and secretion from T cells. In patients with silent allergic rhinitis, local plasmacytoid dendritic cells were found to increase in number within nasal mucosal biopsies after provocation by specific nasal allergen. Plasmacytoid dendritic cells may be involved in the triggering of airway allergy and they travel to the allergic effector site via adhesion molecules associated with leukocyte extravasation in organized lymphoid tissue [28].

Although natural killer T cells are known to be involved in the pathogenesis of autoimmune and oncologic diseases, there is emerging evidence that supports their implication in innate immune pathways leading to allergic diseases [29]. Patients with allergic rhinitis have a higher percentage of natural killer cells compared with nonatopic patients. Natural killer cytotoxicity is also found to be higher in patients with allergic rhinitis when compared with healthy controls [30].

NOVEL ALLERGIC RHINITIS THERAPIES TARGETING THE INNATE IMMUNE SYSTEM

Corticosteroids are a mainstay for the treatment of allergic rhinitis, especially inhaled topical administrations delivered to the sinonasal epithelium, which allow minimal systemic absorption and therefore reduce adverse drug reactions [31]. Corticosteroids suppress systemic adaptive immune responses; however, they exert little or no inhibitory effect on epithelial innate immune system. The epithelium continues to express antimicrobial substances and, in some cases, may even elevate their production. Therefore, corticosteroids may enhance the expression of TLRs and surfactant proteins SP-A and SP-D [32]. Although frequently effective, intranasal and systemic steroids do not always provide relief in allergic rhinitis. One possibility for this ineffectiveness was demonstrated in a study examining leukotriene B(4) [LTB(4)], a potent lipid mediator that is rapidly generated from activated innate immune cells [33]. Elevated levels of LTB(4) have been measured in atopic diseases including allergic rhinitis. LTB(4) receptor-1 is found to be unaffected by corticosteroids and thus this pathway offers a rationale for corticosteroid-resistant allergic diseases including allergic rhinitis.

Through modulation of mucosal epithelial innate immunity such as TLR agonists [34] and antagonists, novel allergic rhinitis treatments are currently in development. A randomized, double-blinded, controlled clinical trial using a TLR9 agonist conjugated ragweed vaccine demonstrated

long-term efficacy in treatment of ragweed-mediated allergic rhinitis. Another study examined the use of TLR9 immunotherapy for allergic rhinitis and found an improved safety profile compared with conventional allergen desensitization [35]. Furthermore, short ragweed allergen itself has been shown to be a TLR4 agonist and can induce TLR4 signaling pathways in allergic disease. Immunotherapy targeting this receptor as an adjuvant in those who already express the atopic phenotype is promising [36^{***}]. Preliminary trials of intranasal TLR4 agonists have shown them to be well tolerated and feasible for the treatment of allergic rhinitis [37]. Future studies looking at efficacy will further determine dosing and therapeutic role.

Therapies aimed at shifting the Th2 phenotype to a Th1 phenotype through tolerance mechanisms such as sublingual immunotherapy are postulated to work through dendritic cells which possess protolerogenic properties [38]. This concept may further open doors to better understanding the innate immune role of dendritic cells in allergic rhinitis.

CONCLUSION

The sinonasal epithelium lies at the interface between the host and environment and is the primary site of innate immune interaction. Both nonspecific and specific innate immune defense mechanisms clearly play a major role in the pathogenesis of allergic rhinitis and are now targets for emerging therapies. Recent studies have already demonstrated that TLR modulation through adjuvant therapy or inhibition is well tolerated and effective. Novel therapies directed at these targets will continue to emerge as our understanding of the role of the innate immune system in the pathogenesis of allergic rhinitis improves.

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Conflicts of interest

There are no 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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 218–219).

1. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004; 22:345–361.
2. Anand VK. Epidemiology and economic impact of rhinosinusitis. *Ann Otol Rhinol Laryngol Suppl* 2004; 193:3–5.

3. Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. *Clin Ther* 2004; 26:1876–1889.
 4. Santos CB, Pratt EL, Hanks C, *et al.* Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. *Ann Allergy Asthma Immunol* 2006; 97:579–586; quiz 586–589, 671.
 5. Schenten D, Medzhitov R. The control of adaptive immune responses by the innate immune system. *Adv Immunol* 2011; 109:87–124.
 6. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. *Science* 2010; 327:291–295.
 7. Ramanathan M Jr, Lee WK, Dubin MG, *et al.* Sinonasal epithelial cell expression of toll-like receptor 9 is decreased in chronic rhinosinusitis with polyps. *Am J Rhinol* 2007; 21:110–116.
 8. Wang Y, Bai C, Li K, *et al.* Role of airway epithelial cells in development of asthma and allergic rhinitis. *Respir Med* 2008; 102:949–955.
 9. Kirtsreesakul V, Somjareonwattana P, Ruttanaphol S. The correlation between nasal symptom and mucociliary clearance in allergic rhinitis. *Laryngoscope* 2009; 119:1458–1462.
 10. Vlastos I, Athanasopoulos I, Mastronikolis NS, *et al.* Impaired mucociliary clearance in allergic rhinitis patients is related to a predisposition to rhinosinusitis. *Ear Nose Throat J* 2009; 88:E17–E19.
 11. Kaur S, Gupta VK, Shah A, *et al.* Elevated levels of mannan-binding lectin [corrected] (MBL) and eosinophilia in patients of bronchial asthma with allergic rhinitis and allergic bronchopulmonary aspergillosis associate with a novel intronic polymorphism in MBL. *Clin Exp Immunol* 2006; 143:414–419.
 12. Deng Y, Chen S, Chen J, *et al.* Relationship between surfactant protein A polymorphisms and allergic rhinitis in a Chinese Han population. *Mol Biol Rep* 2011; 38:1475–1482.
- Case-control study of Chinese patients – 216 with allergic rhinitis and 84 controls. Looked for polymorphisms of SP-A and found a gene polymorphism in the SFTPA2 gene associated with allergic rhinitis.
13. Madan T. Potential of lung surfactant proteins, SP-A and SP-D, and mannan binding lectin for therapy and genetic predisposition to allergic and invasive aspergillosis. *Recent Pat Inflamm Allergy Drug Discov* 2007; 1:183–187.
 14. Rampey AM, Lathers DM, Woodworth BA, Schlosser RJ. Immunolocalization of dendritic cells and pattern recognition receptors in chronic rhinosinusitis. *Am J Rhinol* 2007; 21:117–121.
 15. Vandermeer J, Sha Q, Lane AP, Schleimer RP. Innate immunity of the sinonasal cavity: expression of messenger RNA for complement cascade components and toll-like receptors. *Arch Otolaryngol Head Neck Surg* 2004; 130:1374–1380.
 16. Fransson M, Benson M, Erjefalt JS, *et al.* Expression of Toll-like receptor 9 in nose, peripheral blood and bone marrow during symptomatic allergic rhinitis. *Respir Res* 2007; 8:17.
 17. Melvin TA, Lane AP, Nguyen MT, Lin SY. Allergic rhinitis patients with recurrent acute sinusitis have increased sinonasal epithelial cell TLR9 expression. *Otolaryngol Head Neck Surg* 2010; 142:659–664.
 18. Melvin TA, Nguyen MT, Lane AP, Lin SY. Allergic rhinitis is associated with decreased expression of Toll-like receptor 9 by sinonasal epithelial cells. *Int Forum Allergy Rhinol* 2011; 1:153–156.
- This study grew sinonasal epithelial cells from nine allergic rhinitis and eight control patients and found that TLR9 expression assessed by flow cytometry was significantly reduced compared with normals. These findings are analogous to eosinophilic chronic rhinosinusitis.
19. Zhang G, Candelaria P, Makela JM, *et al.* Disparity of innate immunity-related gene effects on asthma and allergy on Karelia. *Pediatr Allergy Immunol* 2011; 22:621–630.
 20. von Mutius E, Radon K. Living on a farm: impact on asthma induction and clinical course. *Immunol Allergy Clin North Am* 2008; 28:631–647; ix–x.
 21. Eder W, Klimecki W, Yu L, *et al.* Toll-like receptor 2 as a major gene for asthma in children of European farmers. *J Allergy Clin Immunol* 2004; 113:482–488.
 22. Kang I, Oh YK, Lee SH, *et al.* Identification of polymorphisms in the Toll-like receptor gene and the association with allergic rhinitis. *Eur Arch Otorhinolaryngol* 2010; 267:385–389.
- This study compared single-nucleotide polymorphisms for TLR2 and TLR4 in allergic rhinitis patients versus controls. Two specific haplotypes for TLR2 were associated with allergic rhinitis. This is one of the first studies to associate TLR polymorphisms with allergic rhinitis.
23. Akbar NA, Zacharek MA. Vitamin D: immunomodulation of asthma, allergic rhinitis, and chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2011; 19:224–228.
 24. Baena-Cagnani CE, Gomez RM, Baena-Cagnani R, Canonica GW. Impact of environmental tobacco smoke and active tobacco smoking on the development and outcomes of asthma and rhinitis. *Curr Opin Allergy Clin Immunol* 2009; 9:136–140.
 25. Senthilselvan A, Rennie D, Chenard L, *et al.* Association of polymorphisms of toll-like receptor 4 with a reduced prevalence of hay fever and atopy. *Ann Allergy Asthma Immunol* 2008; 100:463–468.
 26. Lalaker A, Nkrumah L, Lee WK, *et al.* Chitin stimulates expression of acidic mammalian chitinase and eotaxin-3 by human sinonasal epithelial cells in vitro. *Am J Rhinol Allergy* 2009; 23:8–14.
 27. Cho WS, Kim TH, Lee HM, *et al.* Increased expression of acidic mammalian chitinase and chitotriosidase in the nasal mucosa of patients with allergic rhinitis. *Laryngoscope* 2010; 120:870–875.
 28. Jahnson FL, Lund-Johansen F, Dunne JF, *et al.* Experimentally induced recruitment of plasmacytoid (CD123high) dendritic cells in human nasal allergy. *J Immunol* 2000; 165:4062–4068.
 29. Okamoto Y, Horiguchi S, Yamamoto H, *et al.* Present situation of cedar pollinosis in Japan and its immune responses. *Allergol Int* 2009; 58:155–162.
 30. Mesdaghi M, Vodjani M, Salehi E, *et al.* Natural killer cells in allergic rhinitis patients and nonatopic controls. *Int Arch Allergy Immunol* 2010; 153:234–238.
 31. Blaiss MS. Safety considerations of intranasal corticosteroids for the treatment of allergic rhinitis. *Allergy Asthma Proc* 2007; 28:145–152.
 32. Schleimer RP. Glucocorticoids suppress inflammation but spare innate immune responses in airway epithelium. *Proc Am Thorac Soc* 2004; 1:222–230.
 33. Ohnishi H, Miyahara N, Gelfand EW. The role of leukotriene B(4) in allergic diseases. *Allergol Int* 2008; 57:291–298.
 34. Nguyen TH, Casale TB. Immune modulation for treatment of allergic disease. *Immunol Rev* 2011; 242:258–271.
 35. Hayashi T, Raz E. TLR9-based immunotherapy for allergic disease. *Am J Med* 2006; 119:897 e1–e6.
 36. Li DQ, Zhang L, Pflugfelder SC, *et al.* Short ragweed pollen triggers allergic inflammation through Toll-like receptor 4-dependent thymic stromal lymphopoietin/OX40 ligand/OX40 signaling pathways. *J Allergy Clin Immunol* 2011; 128:1318–1325.e2.
- This study explores the mechanism of short ragweed pollen induced thymic stromal lymphopoietin (TSLP) triggered allergic rhinitis through epithelial innate immunity. They report the novel finding that ragweed pollen acts as a functional TLR4 agonist and initiates TLR4-dependent TSLP signaling and Th2-dominant allergic inflammation.
37. Casale TB, Kessler J, Romero FA. Safety of the intranasal toll-like receptor 4 agonist CRX-675 in allergic rhinitis. *Ann Allergy Asthma Immunol* 2006; 97:454–456.
 38. Allam JP, Bieber T, Novak N. Dendritic cells as potential targets for mucosal immunotherapy. *Curr Opin Allergy Clin Immunol* 2009; 9:554–557.