



The role of fungus in the pathogenesis of chronic rhinosinusitis

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Purpose of review

The etiologic role of fungi in chronic rhinosinusitis remains controversial. The purpose of this review is to further our understanding of molecular immunologic pathways activated by fungi and clinical trials of antifungals in severe subtypes of asthma and allergic fungal rhinosinusitis.

Recent findings

Various fungal components such as protease and chitin are capable of eliciting a type 2 innate and adaptive immune response. However, definitive studies on the etiologic role of fungi in chronic rhinosinusitis (CRS) is dependent on the development of a fungi-induced murine model of CRS. Short of this model, extrapolations of observations and results from clinical trials in fungi-induced asthma subtypes support a key role of fungi in the pathophysiology of allergic fungal rhinosinusitis and possibly other CRS endotypes.

Summary

Fungi plays a key role in the pathophysiology of several subtypes of chronic inflammatory respiratory diseases. However, a fungi-induced murine model of CRS is needed to explicitly investigate the molecular pathways and potential therapeutic targets.

Keywords

allergic fungal rhinosinusitis, antifungals, chronic rhinosinusitis, fungi

INTRODUCTION

Several initiating agents have been proposed in the pathophysiology of chronic rhinosinusitis (CRS) including bacteria, viruses and fungi [1]. Recent appreciation of molecular pathways associated with the characteristic type 2 immune profile, typically chronic rhinosinusitis with nasal polyps (CRSwNP), have facilitated further investigation of potential triggers in the pathophysiology of CRS. Allergic fungal rhinosinusitis (AFRS) is a distinct subtype of CRSwNP that affects atopic, immunocompetent patients [2]. In this disease process, fungus is linked to an exaggerated type 2 immune response. The exact molecular mechanisms by which fungi contribute to AFRS and other CRS endotypes remain unclear.

FUNGI AND THE TYPE 2 IMMUNE RESPONSE

The sinonasal and airway mucosa serve as a physical barrier to the entry of pathogens into the airway. Sinonasal epithelial dysfunction leads to chronic and overactive stimulation of the adaptive immune

system. Fungi are ubiquitous organisms in nature and are an essential component of the sinonasal microbiome. Fungal wall components like chitin, beta glucans, galactomannans, and mannoproteins are well recognized allergens that disrupt the delicate balance in the sinonasal microbiome [3[¶]]. Pathogen recognition receptors like toll-like receptors (TLRs) and C-type lectin-like receptors (CLRs) recognize fungal elements and activate the epithelium to release innate inflammatory cytokines like interleukin (IL)-1b, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) [4,5[¶],6]. IL-33 induces progenitor

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Curr Opin Otolaryngol Head Neck Surg 2022, 30:58–62

DOI:10.1097/MOO.0000000000000775

KEY POINTS

- Allergic fungal rhinosinusitis highlights the pathogenic role fungi play in the type 2 immune response associated with chronic rhinosinusitis (CRS) with nasal polyps.
- Several fungal components can trigger a type 2 immune response including chitin, proteases and beta-glucans.
- Fungi-induced murine model for CRS is critically needed to clearly investigate the role of fungi in the pathophysiology of type 2 mediated CRS.

innate lymphoid cells to develop into group 2 innate lymphoid cells (ILC2s) that secrete type 2 inflammatory cytokines like IL-5 and IL-13 [4,5[■],6].

Proteases, another important component of fungi, degrade polymers and capture nutrients from plant and mammalian hosts. Proteases degrade airway epithelial tight junctions during fungal invasion thereby increasing and activating serum proteins like fibrinogen to activate macrophages through TLR4 [5[■],6]. This further enhances IL-13 production, especially in the lungs, and activates dendritic cells, which induce differentiation of naive T cells into T helper 2 (Th2) and Th17 effector cells [5[■],6]. The type 2 adaptive immune response is defined by the action of the Th2 cells. These cells drive eosinophil recruitment, goblet cell hyperplasia, mucus production, and antigen-specific IgE production via secretions of IL-4, IL-5, and IL-13 in response to fungal antigens [4,5[■],6–8]. Products of the type 2 response further disrupt the barrier function of the sinonasal mucosa, creating a positive feedback loop. Den Beste *et al.* [9] found decreased expression of intercellular proteins like occludin and junctional adhesion molecule-A (JAM-A) responsible for the epithelial barrier in AFRS patients compared to controls. Wise *et al.* [10] found intercellular protein disruption in the sinonasal mucosa of AFRS patients when exposed to IL-4 and IL-13 *in vitro*. On a genomic level, AFRS tissue demonstrates higher gene expression variations compared to that of CRSwNP. When using pathway analysis software, gene expressions in AFRS are strongly linked to type 2 immune responses [11].

Although various fungal components have all been shown to initiate and contribute to the type 2 immune response characteristic of AFRS, we currently lack an animal model that implicates fungi and fungal elements as a causative factor in the type 2 immune response in AFRS.

ANIMAL MODELS OF Chronic Rhinosinusitis AND ALLERGIC FUNGAL RHINOSINUSITIS

Animal models have made it easier to study the impact of various pathogens on the respiratory mucosa. Mice are commonly used for research as they are inexpensive, easy to handle, and have a modifiable genetic makeup [12–14,15[■],16–20]. Murine models for allergic rhinitis and allergic asthma are widely available, but no such model has been widely adopted for CRS, CRS with eosinophilia, or nasal polyposis [12–14,15[■],16–20].

Numerous limitations exist with the currently proposed murine models for CRS. First, murine sinonasal anatomy is not well pneumatized into the bony facial skeleton [21]. Additionally, the majority of a mouse's nasal epithelium is olfactory mucosa as opposed to respiratory mucosa [21]. Lastly, the genetic makeup of mice also impacts how they react to various airway pathogens. BALB/c and C57BL/6 mice are widely utilized strains due to their well characterized immunological responses, and mimics atopic human response to airway pathogens in CRS models [14,20]. However, the response to these pathogens is not identical between the two species. Furthermore, numerous murine models utilized ovalbumin intraperitoneally to sensitize the mice, which may limit translational utility to humans because it fails to recapitulate the contribution of the innate immune responses in CRS [12,13,15[■],16]. Genetically modified mice like C57BL/6 have been tested with intranasal inhalants and are more suited to demonstrate the relationship between the innate and adaptive immune responses in CRS [14,20].

Many of the concerns around these murine models center around the choice, duration and route of exposure of the trigger. The inducing agent, often Staphylococcal enterotoxin B (SEB) and *Aspergillus fumigatus*, is delivered via an intraperitoneal injection or in the presence of an injected adjuvant that does not reflect physiologic exposure. In some cases, a form of fungi that is not typically inhaled such as the protease component has been applied intranasally. Another significant barrier to validation of any given model for CRS is the currently limited ability to assess the immunologic profile of the sinonasal mucosa. Finally, the inability of mice to create nasal polyps is another limitation. When SEB, a superantigen capable of stimulating a type 2 immune response and is strongly associated with CRSwNP and AFRS, is co-administered intranasally with house dust mite, authors claimed that the resulting mouse modeled CRSwNP [3[■]]. However, a close evaluation of the sinonasal immunohistochemistry demonstrated

thickening of areas of sinonasal mucosa rather than actual polyps as found in human sinus cavities [14].

Despite these limitations, murine models may be useful for investigating fungi-induced CRS. Pathogens like *Aspergillus* and *Alternata* have been used to model CRS and have solidified our understanding of the role of fungi in the type 2 inflammatory response. By intranasally challenging sensitized mice with *Aspergillus*, Lindsay *et al.* [12] found increased eosinophilic submucosal infiltrate in nasal contents. Interestingly, fungus is the only known trigger that incites type 2 inflammation from intranasal exposure alone without presensitization. Shin *et al.* [15[■]] found increased IL-4 levels and total serum IgE levels in nasal lavage fluid of mice when treated intranasally with *Alternata* extracts. The pathogenicity of fungal proteases has also been studied in mice. Kim *et al.* [17] showed that mice intranasally instilled with *Aspergillus* protease and OVA albumin extracts develop significant eosinophilic inflammation and higher levels of IL-4 and IL-6 compared to OVA albumin alone. Even pathogens functionally similar to proteases, like papain, have been shown to induce the type 2 inflammatory response in mice. Thakaran *et al.* [20] demonstrated influx of eosinophils into the sinonasal mucosa and nasal lavage fluid with increased type 2 cytokine production, especially alarmin IL-33 and IL-13, after only 11 days of intranasal administration of papain. These proposed models further our understanding of the pathogenicity of fungi. However, there is a paucity of murine model that encompasses the chronicity and exposures that reflect the CRS process in humans. As such, a model of fungi-induced CRS is needed to identify molecular pathways, which can then be used to develop novel therapeutic options.

ROLE OF FUNGI IN ASTHMA

Similar to CRSwNP and AFRS, allergic asthma (AA) is characterized by a type 2 immune response involving Th2 helper cells, eosinophils, mast cells, and Th2-associated cytokine expression. Allergic inflammation affecting the upper airway, such as allergic rhinitis (AR), CRSwNP, and AFRS, share many epidemiologic and pathophysiologic features with AA. In fact, over 50% of CRSwNP patients have asthma, and more than 90% of asthmatic patients have correlative radiographic abnormalities consistent with nasal and/or paranasal sinus inflammation to the severity of their asthma [21,22]. Although the role of fungi in asthma remains controversial, as with CRSwNP, it is clear that fungi play a role. Porter *et al.* [23] found that CRS or AFRS patients with asthma were significantly more likely to have positive fungal cultures compared to those without

asthma. Furthermore, fungi-specific memory T cells were found in 88% of asthmatic patients compared to 20% of controls [23]. These similarities in AA and CRSwNP are supportive of a common pathologic process that involves fungi.

A strong correlation between fungal exposure and asthma severity also exists [24,25]. Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS) are two phenotypes of severe asthma where fungal colonization has been implicated as a causative factor [26]. SAFS is a newly recognized entity that presents with early-onset asthma, lower asthma control test scores, fungal sensitization, increased rates of intensive care unit admissions, and a greater need for mechanical ventilation [25,27]. It is a diagnosis of exclusion based on the following criteria: severe asthma, fungal sensitization, and exclusion of ABPA. The proposed pathogenesis of SAFS involves inhalation of ubiquitous fungal spores, such as *Aspergillus*. These fungi enter the respiratory tract resulting in fungal sensitization and an exaggerated type 2 immune response in genetically susceptible individuals.

Upon entry into the respiratory tract, a complex interaction between fungal proteases and mucosal epithelium triggers a robust type 2 inflammatory response. In the pathogenesis of AFRS, defective antimicrobial expression, including surfactant proteins, lactoferrin, and antifungal histatin peptides [11,28,29], may permit fungal colonization. Of note, fungal spores do not contain proteases, but are instead derived from fungi growing in the filamentous form, thereby suggesting the importance of fungal colonization in allergic airway inflammation. Kheradmand *et al.* [30] found that protease activity was essential in driving the type 2 immune response, and that catalytically inactivated proteases did not induce a response. Moreover, Porter *et al.* [31] found that the majority of active proteases found within dust sampled from the homes of asthmatic patients were extracted from fungi, particularly *Aspergillus* species. Although culture-independent techniques identified a relatively higher prevalence of *Aspergillus* within inflammatory tissues from the sinus cavities and lungs of patients with CRSwNP, AFRS, ABPA, and SAFS, the mycobiome in these individuals notably lack diversity. Together these findings support a combination of permissive fungal growth and protease activity leading to a type 2 immune response in allergic airway disease.

In a murine model of reactive airway disease, *Alternaria* extract provoked the development of a robust type 2 inflammatory response, precipitated by a rapid release of IL-33 [32]. In other mouse models, intranasally introduced *Alternaria* extract

and chitin induced an expansion of ILCs, eosinophils, Th2 helper cells, as well as production of Th2-associated cytokines IL-4, IL-5, IL-13, IL-25, IL-33, and TSLP [33,34]. Taken together, mucosal barrier dysfunction, fungal species, and fungal allergens promote a type 2 inflammatory response in the airway by stimulating epithelial-derived cytokines (i.e. IL-25, IL-33, TSLP) activating the innate and adaptive arms of the immune response and expression of additional type 2 inflammatory cytokines. While these specific molecular pathways remain an ongoing area of investigation, it is clear that fungi and their proteases play an important role in type 2 immune response in reactive airway disease.

ANTIFUNGALS IN ALLERGIC AIRWAY INFLAMMATION

The cornerstone of medical therapy for SAFS involves a stepwise treatment protocol that includes inhaled corticosteroids (ICS) and bronchodilators. In nonresponders with persistent exacerbations, omalizumab and itraconazole may be included. Approved for the treatment of moderate to severe asthma and nasal polyps by the US Food and Drug Administration (FDA), omalizumab is a recombinant, humanized, monoclonal antibody that targets free immunoglobulin E (IgE) molecules thereby inhibiting interactions with IgE receptors on inflammatory cells, such as basophils and mast cells, that propagate the type 2 immune response found in allergic airway disease. In a meta-analysis of 25 randomized controlled trials (RCT), omalizumab was found to significantly reduce asthma exacerbations and hospitalizations, and eliminate ICS use compared to placebo [35]. Omalizumab is also effective in the treatment of ABPA, and is beneficial as a biologic therapeutic for SAFS [36,37*].

Oral antifungal therapy is also proven to improve symptoms in SAFS. Ward *et al.* [38] found that patients with *Trichophyton*-sensitive severe asthma who were treated with fluconazole for a period of five months demonstrated decreased bronchial sensitivity to inhaled *Trichophyton* and oral steroid use, as well as improved asthma symptom scores and peak expiratory flow rates when compared to placebo. In another RCT, patients with SAFS treated with oral itraconazole were found to have improved asthma quality-of-life and rhinitis scores, increased expiratory peak flow rates, and decreased total serum IgE relative to placebo-treated controls [39]. Although more robust studies are needed to fully elucidate the role of oral antifungals in the treatment of SAFS, these findings suggest that fungal exposure plays an important part in this cohort of AA patients.

Due to the overlapping features of CRSwNP and AFRS, the treatment options are similar. However, treatment of AFRS typically starts with surgery to remove fungi-laden eosinophilic mucin followed by extended courses of oral and topical corticosteroids postoperatively to reduce inflammation. In CRSwNP, surgery is advocated only after failure of appropriate medical therapy. The role of immunotherapy, immunomodulators, and biologics in the treatment of CRSwNP and AFRS is a growing field of interest. The use of antifungal therapy in the treatment of CRSwNP and AFRS is also under study, but current clinical trials do not support their routine use. In a systematic review investigating topical and systemic antifungal therapy in CRSwNP, Head *et al.* [40] were unable to conclude whether antifungal therapy conferred a benefit to patients when compared to placebo or no treatment at all, but these studies were limited by low-quality evidence and few investigated subtypes of CRSwNP, like AFRS. Gan *et al.* [41] performed a systematic review comparing medical therapies in the management of AFRS and found that antifungals could be considered in the management of refractory AFRS cases, but further recommendations regarding antifungals could not be made due to insufficient evidence. Rains and Mineck examined their case series of AFRS patients treated with oral itraconazole therapy in addition to standard postoperative corticosteroid regimen and found a reoperation rate of 20.5%, a figure much lower than the 48% to 56% reported in the literature [42–44]. Lastly, Verma *et al.* [45] compared preoperative to postoperative administration of oral itraconazole in addition to a standard postoperative corticosteroid regimen in AFRS patients and found improvements in SNOT, Lund Mackay, and nasal endoscopy scores, although preoperative itraconazole was associated with a statistically significant improvement compared to the postoperative itraconazole group. Furthermore, the two groups combined were associated with a lower recurrence rate compared to the control group, although statistical significance was not achieved [45]. While the success of antifungal therapy in the management of AFRS is highly variable and remains unclear at this time, our understanding of the pathophysiology and success, albeit limited, in the treatment of AFRS warrants further attention and prospective, multiinstitutional, blinded RCT.

CONCLUSION

Fungi plays a clear role in certain subtypes of chronic upper and lower airway disease including AFRS, ABPA, and SAFS. Identification of fungi activated molecular pathways in these specific subtypes are improving our

understanding of the role of fungi in the pathophysiology of other types of CRS. These studies also highlight the need for murine models for fungi-induced CRS to delineate the pathways involved and conduct preclinical studies of treatment options extrapolated from fungi-induced asthma subtypes.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

A.U.L. serves as a consultant for Aerin Medical (Austin, TX, USA), Glaxo-SmithKline (Brentford, UK), Lyra Therapeutics (Watertown, MA, USA), Sanofi (Paris, France), and Stryker (Kalamazoo, MI, USA). She also serves on the advisory boards for ENTvantage and Third Wave Therapeutics. The remaining authors have no conflicts of interest.

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