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The Etiologic Role of Fungi in Chronic Rhinosinusitis

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The etiologic role of fungi in chronic rhino sinusitis 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 rhino sinusitis.

Various fungal components like protease and chitin are capable of eliciting a kind 2 innate and adaptive immune reaction. However, definitive studies on the etiologic role of fungi in chronic rhino sinusitis (CRS) are 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 rhino sinusitis and possibly other CRS endotypes [1].

Recent findings

Several initiating agents have been proposed in the pathophysiology of chronic rhinosinusitis (CRS) including bacteria, viruses and fungi. Recent appreciation of molecular pathways associated with the characteristic type 2 immune profile, typically chronic rhinosinusitis with nasal polyposis (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. 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.

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 micro biome. Fungal wall components like chitin, beta glucans, galactomannans, and Nano proteins are well recognized allergens that disrupt the delicate balance in the sinonasal micro biome. 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). IL-33 induces progenitor innate lymphoid cells to develop into group 2 innate lymphoid cells (ILC2s) that secrete type 2 inflammatory cytokines like IL-5 and IL-13 [2].

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. 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. 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. Products of the type 2 response further disrupt the barrier function of the sinonasal mucosa, creating a positive feedback loop. Found decreased expression of intercellular proteins like occluding and junctional adhesion molecule-A (JAM-A) responsible for the epithelial barrier in AFRS patients compared to controls. 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.

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 [3].

The cornerstone of medical therapy for SAFS involves a stepwise treatment protocol that includes inhaled corticosteroids (ICS) and bronchodilators. In no responders 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 calls, 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. Omalizumab is also effective in the treatment of ABPA, and is beneficial as a biologic therapeutic for SAFS [4].

Oral antifungal therapy is also proven to improve symptoms in SAFS. 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. Although more robust studies are needed to

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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.

Fungi play 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 is 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 [5].

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Conflict of interest

None

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