Review Article

Potential contribution of fungal infection and colonization to the development of allergy

DAVID L. GOLDMAN* & GARY B. HUFFNAGLE†

*Department of Pediatrics, Childrens’ Hospital at Montefiore, Albert Einstein College of Medicine, and †Department of Microbiology and Immunology, University of Michigan Medical School, USA

Fungi have long been recognized as an important source of allergens in patients with atopic disease. In this review, we explore the hypothesis that fungal exposures resulting in colonization or infection directly influence the tendency of an individual to develop allergic disease. According to this hypothesis, fungal exposures especially those early in life may influence the manner in which the immune response handles subsequent responses to antigen exposures. Studies detailing this potential connection between fungi have already provided important insights into the immunology of fungal-human interactions and offer the potential to provide new approaches and targets for the therapy of allergic disease. The first half of this review summarizes the data concerning fungal infections and asthma, including possible connections between fungal infections and urban asthma. The second half explores the potential role of the fungal gastrointestinal microbiota in promoting allergic inflammation.

Keywords Fungi, allergy, asthma, Candida, infection

Introduction

Fungi are well recognized allergens for individuals with atopy, a genetic pre-disposition to develop allergic manifestations including asthma, dermatitis and rhinitis. In atopics, these manifestations reflect the effects of antigen-elicited TH2 inflammation and associated IgE production. Fungal sensitization for these individuals is generally thought to occur as a result of repeated, transient inhalational exposures to a variety of fungal antigens. Results from recent epidemiologic studies, however suggest that fungal exposures may also somehow exacerbate allergic diseases, including asthma (reviewed in [1]). In this regard, patients with evidence of fungal sensitization are more likely to experience life-threatening asthma and die from their asthma [2–5].

In this review, we explore the hypothesis that host-fungal interactions outside the traditional sensitization process contribute to the development of TH2 inflammation and associated allergic disease. We suggest that these fungal-host interactions directly promote the development of a TH2 pre-disposition and atopic disease. The first part of this review will explore evidence regarding the role fungal infections play in allergic diseases, while the second part examines the role of fungal microbiota.

Fungal infections and allergy

Allergic bronchopulmonary aspergillosis

A wide array of clinical and laboratory studies highlight the importance of viral and bacterial respiratory infections in the pathogenesis of allergic asthma [6–8]. The best documented example of asthma related to fungal infection is allergic bronchopulmonary...
Aspergillus fumigatus (ABPA), which was first recognized as a distinct entity by Hinson in 1952 [9]. In ABPA, airway infection with Aspergillus exacerbates asthma symptoms, primarily in patients with chronic asthma and cystic fibrosis (CF). ABPA has been reported to occur in 1–40% of chronic asthmatics [10–12] and 2–10% of patients with CF [13–15]. Aspergillus fumigatus is most commonly implicated, though several different species of Aspergillus have also been associated with ABPA [16–18]. A role for other fungi in ABPA, including Candida albicans has also been hypothesized [19,20].

The clinical features of ABPA include: asthma, eosinophilia, elevated total serum IgE and elevated serum IgE and IgG specific to Aspergillus. Affected patients have mucus plugging and may develop central bronchiectasis with pulmonary fibrosis. The importance of Aspergillus fumigatus as an immediate cause of ABPA (and not just an indicator of a severely diseased airway) is highlighted by recent studies that reveal improvements in pulmonary function and clinical symptoms in association with anti-fungal therapy [21,22].

The mechanisms by which persistent airway infection with Aspergillus spp. leads to ABPA appears to involve dysregulation of both innate and adaptive immunity (reviewed in [23,24]). In this regard, Aspergillus directly induces activation of macrophages, granulocytes and dendritic cells via Toll-like receptors 2 and 4 [25,26]. Inhibition of dendritic cell maturation following stimulation with Aspergillus protease has recently been demonstrated and hypothesized to contribute to the development of allergic (TH2) response to infection [27].

Both type I (IgE-mediated) and type III (IgG-mediated) hypersensitivity reactions contribute to the pathogenesis of ABPA [28]. The tendency of patients with ABPA to develop allergic (type I hypersensitivity, TH2) responses to Aspergillus is reflected in the isolation of antigen specific TH2 T cells from affected individuals [29–31]. Furthermore, antigen specific T cell clones isolated from patients with ABPA secrete a TH2 cytokine profile and proliferate in response to IL-4 [30]. Interestingly, the enhanced allergic responsiveness of patients with ABPA appears to be antigen specific and may not reflect an overall change in TH bias. In this regard, there was no increase in overall frequency of circulating TH2 cells in patients with ABPA compared to CF patients without ABPA. Though, there was a decreased frequency of circulating TH1 cells [24].

Infection-induced airway damage appears to be important in the pathogenesis of ABPA and TH2 skewing. This may occur as a result of the direct effects of infection and or toxin production [32–34]. Epithelial damage as manifested by cell shrinking and desquamation can be induced in vitro by exposure of epithelial cells to Aspergillus proteases [35]. Epithelial damage induced by Aspergillus has been hypothesized to promote hypersensitivity by allowing for increased antigen exposure [24]. In addition, epithelial damage induced by Aspergillus is associated with the release of IL-6 and IL-8, which promote inflammation [35,36]. Furthermore, inflammation-induced lung damage may perpetuate Aspergillus infection by hindering normal clearance mechanisms. Neutrophils are thought to play a prominent role in this process. In a murine model of ABPA, genetically enhanced of neutrophil influx was associated with worsening of allergic inflammation and increased airway responsiveness [37]. Likewise, increased neutrophil numbers in the sputum has been correlated with diminished respiratory function in patients with ABPA [38,39].

Both host and pathogen related factors leading to ABPA have been identified. Many Aspergillus-associated allergens have proteolytic activity that promote airway damage (i.e., epithelial cell detachment in vitro) and subsequent pro-inflammatory cytokine (IL-6) and chemokine (IL-8, MCP-1) production [36,40]. These antigens may also directly activate T and B cells [30] and play a role in promoting a Th2 bias. Antibodies to these proteases are present in patients with ABPA and in one study increased antibody levels correlated with disease exacerbations [41]. Specific host factors that have been implicated in the pathogenesis of ABPA include: HLA type, mutations in the cystic fibrosis transmembrane regulator gene (CFTR), IL-10, both IL-4R and surfactant polymorphisms (reviewed in [42]).

**Allergic fungal sinusitis**

An allergic response to non-invasive fungal infection of the respiratory sinuses has been hypothesized to produce a condition known as allergic fungal sinusitis (AFS). The diagnostic criteria for AFS were established by Bent and Kuhn and include the use of both major and minor criteria. Major criteria consist of the following: evidence of type I, IgE-mediated hypersensitivity, nasal polyposis, characteristic CT findings; eosinophilic mucus without fungal invasion into sinus tissue and positive fungal smear or culture [43]. The pathogenesis of allergic fungal sinusitis is thought to be similar to ABPA and to involve both type I and type III hyper-sensitivity responses (reviewed in [44]). The role of TH2 inflammation and type I hypersensitivity in the pathogenesis of AFS is supported by studies that document elevated fungal specific IgE in the serum of...
patients with suspected AFS [45,46]. In one study, fungal specific IgE was commonly found in the mucin of affected patients [47]. Staining for major basic protein and neutrophil elastase has revealed increased amounts of these proteins in the mucin of patients with AFS suggesting that neutrophil and eosinophil degranulation contribute to pathogenesis of AFS [48]. Nonetheless, the precise immunologic basis of this condition remains poorly understood and several controversies surround both diagnostic criteria and pathogenesis [49,50]. A variety of fungi have been implicated, including Curvularia, Bipolaris, Drechslera, Exserohilum and Aspergillus species [51–53]. Affected individuals are usually immunocompetent with a history of atopy and present with chronic nasal congestion, nasal obstruction and thick dark nasal secretions. Proptosis may be present. Nasal secretions contain large number of eosinophils and fungal stains are typically positive. Treatment generally involves a combination of surgical (endoscopic removal of sinus contents) and medical therapies (anti-inflammatory corticosteroids). The roles of de-sensitization and anti-fungal therapy require further study.

**Dermatomycotic infections**

Chronic fungal infections outside the respiratory tract may also exacerbate allergic symptoms. Fungal skin infections have been reported to worsen symptoms of both atopic dermatitis (AD) [54] and asthma [55] and also produce chronic urticaria [56,57]. A link between fungal infections of the skin, especially Malassezia spp., and AD especially in the head and neck area has been suggested by several groups [58,59]. Evidence to support a causal association between Malassezia infection and AD include the following: isolation of Malassezia from patients with AD [60], a correlation between a positive skin test to Malassezia and atopic dermatitis [59], and an association between high IgE titers to Malassezia and AD [61,62]. The basis by which skin infection with Malassezia could lead to AD is unknown. In vitro experiments indicate that Malassezia induces pro-inflammatory and TH2 cytokine production by keratinocytes [63,64]. Malassezia is ingested by dendritic cells and induces dendritic cell maturation without IL-12 production, which may in turn promote TH2 inflammation [65]. Studies to define the role of anti-fungal therapy in AD associated with Malassezia have yielded mixed results [66–68].

A role for dermatophytic infections in asthma pathogenesis has also been hypothesized on more limited data. This hypothesis is based on the following observations: (i) asthmatic patients with dermatophytic infections exhibit immediate hypersensitivity reactions and elevated serum IgE levels to Tricophyton spp. [69,70], and (ii) anti-fungal treatment of asthmatic patients with dermatophytic infections has been reported to improve asthma symptoms in affected patients [71–73]. The basis by which fungal infections of the skin can lead to an exacerbation of allergic symptoms in the respiratory tract or skin is unclear. It has been suggested that fungal infection of the skin leads to allergen exposure within the lung, either as a result of unrecognized, associated pulmonary exposure or the migration of fungal antigen loaded dendritic cells from the skin to the lung [74]. Alternatively, it is possible that skin fungal infection actively modifies the immune response to subsequent antigen exposures.

**Asthma, an urban fungal infection?**

The prevalence and severity of asthma in children from urban areas are disproportionately high when compared with the national average leading some to term the problem an epidemic [75,76]. In NYC asthma is the leading cause of visits to the Pediatric Emergency Department and hospitalization among children (New York City Department of Health: www.nyc.gov/html/doh). The basis for the high prevalence of asthma in urban areas is unknown, but likely to be multifactorial, involving both host and environmental elements, including: substandard healthcare [77], sedentary lifestyle leading to obesity [78] and air pollution [79]. Residential exposures (such as cockroaches [80]) have also been hypothesized to contribute significantly to the problem of urban asthma.

Given the high prevalence of asthma in urban areas and the potential for fungal infections to modify allergic inflammation, including asthma we have investigated a potential connection between fungal infections, especially those due to C. neoformans and asthma. C. neoformans is typically isolated from sites contaminated with avian excreta, especially pigeon excreta. Pigeons have adapted particularly well to living in metropolitan area. It is estimated that pigeon populations are roughly the size of 2% of the human population in large cities [81]. Pigeons are so ubiquitous in urban environments that exposure to pigeon antigens has been hypothesized to produce respiratory disease (hypersensitivity pneumonitis) in some urban residents [82]. Pigeon guano serves as an excellent environmental reservoir for C. neoformans. The acidic nature and high nitrogen content of pigeon excreta provides excellent growth conditions for C. neoformans and densities of greater than 10 million organisms per gram of excreta can be reached. Furthermore,
C. neoformans can survive in desiccated pigeon excreta for prolonged intervals (almost two years in one study) [83].

C. neoformans infection is acquired through the inhalation of infectious forms in the environment. While cryptococcal disease is recognized primarily in immunocompromised individuals, the vast majority of infections in immunocompetent individuals are likely asymptomatic or incorrectly diagnosed as viral illnesses. Furthermore, it is likely that infection persists for prolonged periods. This hypothesis is supported by a variety of clinical observations, including: (i) inadvertent detection of pulmonary cryptococcosis as a result of chest radiographs done for other reasons [84,85]; (ii) autopsy studies demonstrating a primary cryptococcal complex [86]; (iii) molecular typing studies showing discrepancies between clinical and environmental isolates [87]; (iv) serology studies showing the presence of antibodies to C. neoformans prior to clinical presentation of disease [88,89] and (v) transplant-associated infections in which the donor lung was the source of infection [90]. Using an immunoblot assay we found that a large proportion of children living in the Bronx, an area with an extraordinarily high rate of asthma, have serologic evidence of subclinical cryptococcal infection [91]. In contrast, we found a low prevalence of subclinical infection as inferred by serology in children living in a northern suburb of New York, where the prevalence of asthma is low [92].

A potential role for C. neoformans in the pathogenesis of allergic inflammation is further supported by animal experimentation which demonstrates the tendency of C. neoformans to elicit allergic inflammation. The tendency of C. neoformans to induce allergic inflammation in mice has led one of the authors of this review (GH) to label this experimental system as a model of allergic bronchopulmonary mycosis [93]. Using a rat model, we (DG et al.) demonstrated that pulmonary C. neoformans infection enhances allergic inflammation to aerosolized antigen as manifested by increased specific IgE and eosinophil infiltration [94]. Pulmonary infection was also associated with an increased number of airway goblet cells and non-specific airway hyper-reactivity, both features of asthma. Anti-fungal treatment in rats with pulmonary cryptococcosis partially ameliorated the enhancement of allergic inflammation induced by infection.

The mechanisms by which C. neoformans elicits allergic inflammation have not been fully defined. In mice, cryptococcal virulence is linked to the ability to promote Th2 polarization [95,96]. Infection-related IL-12 suppression and enhancement of IL-10 production have been observed [97,98]. Experimental cryptococcal infection also inhibits the production of interferon-gamma, TNF-alpha, and IL-18 [99]. Cryptococcal polysaccharide (CNPS), the main component of which is glucuronoxylomannan (GXM) promotes Th2 cytokine production. GXM is a potent down regulator of macrophage TNF-α release after LPS stimulation [100]. Apart from reducing secretion of the pro-inflammatory cytokines, soluble CNPS induces secretion of IL-10 [101]. CNPS also promotes proliferation of murine CD4+ T cells that produce high levels of IL-4 [102]. Other components of C. neoformans may contribute to enhanced Th2 inflammation. C. neoformans produces both prostaglandins and leukotrienes (see below).

Fungi, chitinase and asthma

An alternative mechanism by which fungal pulmonary infections including cryptococcosis may promote allergic inflammation relates to the presence of chitin and the induction of host chitinases. Chitin is a significant component of fungal cell walls, including C. neoformans. In a murine model, chitin has recently been shown to induce the accumulation of eosinophils and basophils via the production of leukotriene B4 [103]. Mammalian chitinases consist of a family of enzymes known as Glycoside Hydrolase 18. Some of these enzymes have chitinolytic activity, while others do not. The potential connection between chitinase and asthma was first suggested by the Elias group [104]. This group demonstrated that acidic mammalian chitinase (AMCase) acts as a down-stream modulator of IL-13 in a murine model of asthma. In this system, over-expression of IL-13 induced endogenous chitinase activity and resulted in airway hyperreactivity, while blockage of chitinase activity attenuated this response [104]. Subsequent studies have suggested an association between certain AMCase polymorphisms and asthma [105]. More recently, YKL-40, another member of the Glycoside Hydrolase family has been found to be elevated in the serum and lungs of asthmatics when compared to controls [106]. In these studies, YKL-40 levels were found to correlate with the asthma severity.

A potential connection between fungal infection and the induction of host chitinase was first observed in guinea pig model of Aspergillus infection. In these studies, serum levels of chitinase were found to be elevated in animals experimentally infected with Aspergillus [107]. Our studies indicate that pulmonary but not systemic infection with C. neoformans in the rat induces chitinase activity within the lung and that this correlates with increased AMCase expression within airway epithelial cells and alveolar macrophages [108]. These findings suggest a previously unrecognized
mechanism by which pulmonary fungal infections, including cryptococcosis can directly alter asthma pathogenesis.

**Fungal colonization and allergy**

*Candida albicans* colonization

*Candida albicans* is a normal part of the human microbiota and resides in low numbers in the mouth, vagina, and gastrointestinal tract of healthy individuals (reviewed in [109]). The factors affecting *C. albicans* numbers on mucosal surfaces is multi-faceted and includes the composition of the microbiota, hormones, stress, innate immunity and adaptive immunity. However, this fungus can also be pathogenic and cause life-threatening systemic infections. It is a frequent cause of morbidity and mortality in immunosuppressed critically ill patients and those with indwelling catheters. In addition treatment with antibiotics also increases the risk of complications due to *C. albicans* overgrowth. Thus, control of *C. albicans* by the normal microbiota is very important.

*Control of Candida colonization by the immune system*

One mechanism to control over-exuberant inflammatory responses on the mucosa is via regulatory T (Treg) cells. Through the production of various anti-inflammatory mediators, these cells can down-regulate effector mechanisms of both innate and adaptive immunity, protecting the host mucosa from damage and allowing colonization by non-pathogenic microbes, including *C. albicans* (and probably other far less numerous fungi in the microbiota). There are a number of subsets of Treg cells, with the major distinction being: (i) Tregs that are induced in the periphery following antigen encounter (inducible Tregs), and (ii) Tregs that arise from normal T-cell thymic development (naturally occurring Tregs) [110,111].

Nave CD4 T-cells can be induced to differentiate into inducible Treg cells both *in vivo* and *in vitro*. Inducible Tregs can be further divided into two subsets based on differential cytokine secretion and function: Th3 and Tr1. Culture of nave T-cells in the presence of TGFβ results in the generation of a Treg population termed Th3 cells (reviewed in [112]). Th3 cells secrete TGFβ and to a lesser extent IL-4 and IL-10 and induce IgA production from Peyer’s Patch B-cells. Deficiencies in TGFβ-producing Th3 cells have been implicated in human food allergies. For example, fewer TFGβ-secreting lymphocytes were isolated from the duodenum and lamina propria of children with food allergies [113]. Tr1 cells are generated when nave T-cells are antigenically stimulated under the influence of IL-10 and IFNγ. Tr1 cells proliferate poorly when stimulated; however they secrete high levels of IL-10 and TGFβ. Differentiation of Tr1 cells appears to be controlled by intestinal dendritic cells that secrete high levels of IL-10 and have been isolated from both PP and MLN cells following oral allergen exposure [114–117].

Naturally occurring Treg cells arise during normal thymic T-cell maturation and comprise 5-10% of the peripheral CD4 T-cell population. These cells are most commonly identified by their constitutive expression of CD25 and thus are referred to as CD4+/CD25+ Treg cells. These cells also can be identified by expression of CTLA-4, GITR, and FoxP3. Studies of oral feeding of ovalbumin have implicated CD4+CD25+ Tregs as key mediators of oral tolerance [118]. The clinical relevance of CD4+CD25+ Treg cells can be seen in patients with X-linked autoimmunity-allergic dysregulation syndrome [119]. These patients have a mutation in their FoxP3 gene resulting in heightened IgE production and food allergies [120]. Additionally, children who have outgrown milk allergies have higher frequencies of allergen-specific CD4+CD25+ T-cells in their peripheral blood [121]. In mouse models of *C. albicans* infection or colonization, CD4+CD25+ Treg cells prevent excessive inflammation and promote colonization/persistence in the gastrointestinal tract [122].

Romani and colleagues have also shown that fungal growth, inflammation, and tolerance are controlled by the coordinate activation of naturally occurring Treg cells and induced Treg cells [123]. Activation via the TRIF pathway is critical for migration of both types of Treg cells to sites of *C. albicans* colonization or infection and the upregulation of MyD88-mediated signaling pathways can dampen the suppressive activity of the naturally occurring Treg cells. Th1-mediated inflammation can be modulated by induced Treg cells through activation of the enzyme indoleamine 2,3-dioxygenase (IDO) in dendritic cells and antagonism of Th17 cell activity antagonism. A mediator of tryptophan catabolism, IDO is induced at sites of infection or colonization, including in dendritic cells and neutrophils, via IFN-γ. Treatment of mice with an IDO inhibitor can greatly exacerbate inflammatory pathology [124]. Blocking IDO accelerates hyphal formation and this is partially reversed by the addition of tryptophan, implicating the potential of host metabolic control of *C. albicans* morphogenesis. Thus, the regulatory response of the host can control both *Candida* morphology as well as the inflammatory and adaptive responses to this organism and promote the generation of adaptive Th1 immunity in secondary lymphoid organs.
Therefore, immunity to *C. albicans* can be characterized as an 'immune paradox'. Namely, hosts normally develop strong Th1 responses systemically (as measured by skin DTH responses to *Candida* extracts and serum IgG antibodies against *C. albicans*) but Treg responses in the mucosa. Thus, our immune response against *C. albicans* is normally set in a balance between inflammatory and anti-inflammatory reactions. Therefore, it is easy to imagine how environmental factors that affect either side of this balance might tip the reaction toward hypersensitivity reactions to *C. albicans*.

**Control of Candida colonization by the microbiota**

The major effects of antibiotic treatment on the microbiota are the direct killing of a large proportion of the microbiota and decreased colonization resistance within the GI-tract [125]. Colonization resistance results when obligate anaerobic microbiota inhibit the overgrowth of potentially harmful microbes. In humans, yeast infections (including *C. albicans*), at mucosal sites are one of the most common side effects of antibiotic therapy [126–128]. Interestingly, changes in the microbiota population can persist for months after completion of antibiotic treatment and can result in long-term decreases in beneficial anaerobic organisms (*Bifidobacterium, Lactobacillus, Bacteroides*) [129–131] and increases in potentially harmful microbes (gram negative aerobic enteric bacteria, anaerobic *Clostridium difficile*, and *C. albicans*) [128,132–134].

**Changes in the fungal and bacterial microbiota as a factor in allergic disease?**

The increase in the incidence of allergic diseases over the past 20-30 years, coupled with the dichotomy in the rate of allergic disease between industrialized and developing countries, suggests that environmental changes are a major factor in the development of allergies. These observations have led researchers to propose the 'hygiene hypothesis' for allergies and asthma, which states that a lack of early microbial stimulation results in aberrant immune responses to innocuous antigens later in life [135,136]. However, an alternative interpretation of the hygiene hypothesis is the 'microflora hypothesis', which proposes that perturbations in gastrointestinal microbiota composition due to antibiotic use and poor diet (low fiber, high sugar) in westernized areas have disrupted mechanisms involved in the development of immunological tolerance. Data supporting this interpretation include the correlation between asthma/allergies and antibiotic use in industrialized countries [137–140] and the correlation between altered fecal microflora and atopic disease [141–145]. In addition, germ-free animals display numerous defects in immune response generation [146–151], further supporting the hypothesis that antibiotic-induced changes in the gastrointestinal (GI) microbiota can be a predisposing factor for allergic disease.

Our laboratory has tested whether the disturbance of the bacterial microbiota, combined with colonization by *C. albicans*, can promote the development of allergic airway disease [152,153]. Using a brief treatment with the broad-spectrum antibiotic cefoperazone in conjunction with low-level *C. albicans* GI-tract colonization, we were able to eliminate the need for systemic allergen priming (for example, OVA plus alum) in the development of allergen-induced airway inflammation. In the absence of systemic priming with OVA, only mice with altered GI-tract microbiota developed airway allergic responses to intranasally administered OVA. These mice produced: (i) a significant increase in the number of eosinophils in the lungs, (ii) high serum IgE levels, (iii) elevated IL-5 and IL-13 production, and (iv) increased numbers of mast cells in the lungs. The most striking change following microbiota disruption was in the development of a widespread goblet cell metaplasia. Similar changes were seen if conidia from *A. fumigatus* were used as the allergen. In the absence of CD4+ T cells or IL-13, the response did not develop. Similar allergic responses could be induced in the airways of both inbred mouse strains tested, C57BL/6 and Balb/c. Finally, these responses were not seen in mice in which only antibiotics or only a gavage of *C. albicans* was given, implicating a need for a change in both the bacterial and fungal microbiota to promote the development of allergic disease.

Other studies by Yamaguchi and colleagues have investigated, using a mouse model, whether gastrointestinal colonization by *C. albicans* can increase antigen permeability across the mucosa, a factor that would promote the development of food allergies and manifest in a variety of allergic symptoms [154]. They first inoculated the GI tract of mice by intragastric delivery of *C. albicans* and then fed the mice a synthetic diet to maintain colonization. They had previously demonstrated that the composition of the diet was key to maintaining *C. albicans* GI colonization in mice in the absence of antibiotics [155]. Mice were then given OVA intragastrically every other day for nine weeks. Extraluminal 'leak' of OVA and OVA-specific IgG and IgE titers were higher in *C. albicans*-colonized mice than in *C. albicans*-free mice. Furthermore, sensitization depended on the presence of mast cells. Thus,
GI colonization by *C. albicans* can alter the GI environment which may promote allergic sensitization.

Our lab and others have reported that *C. albicans*, *C. neoformans*, *A. fumigatus* (and many other fungi) secrete prostaglandins and prostaglandin-like molecules de novo or via conversion of exogenous arachidonic acid [156–159]. PGE2 and PGE2-cross reactive compounds can be purified from *C. albicans* that are biologically active on mammalian cells with activity comparable to commercially available PGE2 [156]. Prostaglandins are potent immunomodulatory molecules that can inhibit Th1 type immune responses, chemokine production, phagocytosis, and lymphocyte proliferation and promote Th2 type responses and tissue eosinophilia [160]. PGD2 receptor [DP] knockout mice do not develop airway Th2 responses to OVA [161]. Evidence is now accumulating that prostaglandins (especially PGE2) play a role in overall immune regulation (positive and negative) [162]. Microbe-derived PGD2 can alter dendritic cell migration and biology [163,164]. Fungal cell wall glucans are also powerful inflammatory stimulants in tissues [165] and may also play a role in the immunomodulatory activity of yeast in the GI tract. Thus, increased levels of fungal microbiota, such as often occurs during antibiotic therapy, may diminish the ability to generate Treg/Th3 responses to swallowed antigens, possibly by interfering with tolerance-inducing antigen presentation via fungal oxylipins and glucans.

*Candida albicans* and hypersensitivity diseases

While *Candida albicans* is a normal part of the human microbiota, some otherwise healthy individuals develop hypersensitivity diseases to *C. albicans* (both Th1 and Th2 responses) and the mechanism underlying this is not clear. In addition, increased mucosal colonization by *C. albicans* has been implicated for decades in a number of other hypersensitivity diseases, although a definitive understanding (or some would argue, ‘proof’) has been lacking. For example, it has been hypothesized that *C. albicans* colonization of the gastrointestinal mucosa may exacerbate or promote some forms of atopic dermatitis [166–168]. Due to conserved sequences with α-gliadin and γ-gliadin T-cell epitopes, the hyphal wall protein Hwp1 has been suggested to be an immune target in patients with celiac disease, an allergic/autoimmune reaction to gluten, thereby contributing to the pathology [169,170]. Patients with Crohn’s disease, an inflammatory bowel disease, very often possess high levels of anti-*Saccharomyces cerevisiae* antibodies (ASCA), which have recently been shown to react with a cell wall epitope of *C. albicans* that is expressed *in vivo* but not in standard culture [171,172].

Perhaps more intriguing is the human condition that has been loosely defined as the following: ‘a number of symptoms which improve on a diet low in refined carbohydrates and mold-related foods with or without antifungal therapy. It does not cause death, but its chronicity makes the lives of sufferers a misery...’ [173]. As reviewed by Eaton, this collection of symptoms is diverse and complex and includes food sensitivities, allergic responses, digestive problems and psychoneurological manifestations (‘brain fog’) [173]. The symptoms can last for years and can improve radically in a short period of time. It has been reported in the popular media as ‘Yeast Syndrome’. Since there is increasing evidence that changes in the microbiota (dysbiosis) can alter host physiology and there is circumstantial evidence for a role of fungi or fungal products; Eaton and others have proposed the term 'fungal-type dysbiosis' to describe it [173]. However, more research is clearly needed to understand any cause-and-effect relationships ascribed to this perplexing collection of symptoms.

Does *Candida* play a role in these various hypersensitivity diseases? As mentioned above, the data is not definitive, but there is increasing evidence that in some physiologic host states, *C. albicans* may be more than a commensal but less than a pathogen. The immune response to this fungus may promote or exacerbate an already existing hypersensitivity response.

**Conclusion**

Historically, the focus has been on fungal spores as allergenic triggers or stimuli. Thus, the reason for tracking mold spore counts during high allergy seasons of the year. However, more recent evidence is beginning to accumulate that fungal infection and colonization may play a role in promoting a variety of hypersensitivity diseases, including allergy and asthma. Much work remains to be done but well-characterized animal models are providing new insights into how fungal infection/colonization can stimulate or exacerbate allergies and asthma. With this increased understanding, come opportunities for new therapeutic strategies that treat allergic airway disease by targeting fungal infection/colonization.

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