REVIEW ARTICLE

Fungi: the neglected allergenic sources

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Abstract

Allergic diseases are considered the epidemics of the twentieth century estimated to affect more than 30% of the population in industrialized countries with a still increasing incidence. During the past two decades, the application of molecular biology allowed cloning, production and characterization of hundreds of recombinant allergens. In turn, knowledge about molecular, chemical and biologically relevant allergens contributed to increase our understanding of the mechanisms underlying IgE-mediated type I hypersensitivity reactions. It has been largely demonstrated that fungi are potent sources of allergenic molecules covering a vast variety of molecular structures including enzymes, toxins, cell wall components and phylogenetically highly conserved cross-reactive proteins. Despite the large knowledge accumulated and the compelling evidence for an involvement of fungal allergens in the pathophysiology of allergic diseases, fungi as a prominent source of allergens are still largely neglected in basic research as well as in clinical practice. This review aims to highlight the impact of fungal allergens with focus on asthma and atopic dermatitis.

Keywords

allergy; fungi; immunoglobulin E; moulds; recombinant allergens.

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Allergy is a disease with many faces that can affect different organs like upper and lower respiratory tract, eyes, intestinal tract and the skin. Depending on the affected organ, allergic symptoms manifest as allergic rhinitis (1), allergic asthma (2), IgE-associated atopic dermatitis (3), food allergy (4) or insect venom allergy (5), to mention only the most important ones. The common hallmark of allergic diseases is a switch to the production of allergen-specific IgE raised against normally innocuous environmental allergens (6) that, in special cases, might also cross-react with self-antigens (7, 8). At this asymptomatic stage, the individual is sensitized to a given allergenic source due to the presence of allergen-specific IgE in serum, a condition also called ‘atopy’. Detection of allergen-specific IgE is considered as a specific biomarker for the atopic state in clinical practice, which allows in most cases a linkage of a symptom to a particular allergen exposure (9). Measurement of allergen-specific IgE antibodies in serum is normally performed with fully automated devices (10) and used to confirm sensitization to a particular allergen in support of a history-based clinical diagnosis of allergy or a symptom-based suspicion. In sensitized (atopic) individuals, however, re-exposure to the offending allergen induces cross-linking of the high-affinity receptor FceRI-bound allergen-specific IgE on effector cells and, thus, immediate release of anaphylactogenic mediators (11). Although the mechanisms leading to allergic reactions (12, 13) and the sources of exposure are quite well known, our knowledge about the repertoire of molecular structures involved in the pathogenesis of allergic reactions is still rudimentary (14) even if it is well recognized that only a minor fraction of the myriad of proteins to which humans are exposed provokes allergic reactions. Bioinformatics analyses based on structural motifs (15) and BLAST similarity search methods (16) involving 101 602 and 135 850 protein entries deposited in the Swiss-Prot database predict 4093 (4%) and 4768 (3.5%) different potential allergenic structures, respectively. Therefore, one can assume that the size of the allergen repertoire involved in eliciting allergic symptoms is in the range of 5000 different structures (14). The modest number of 753 allergenic proteins approved by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Subcommittee (www.allergen.org) clearly shows our lack of knowledge in this field. Allergenic structures can be found in every species (Fig. 1), and the number of single allergens characterized is unevenly distributed among the species ranging from 1 for the phylum Cnidaria (sponges and jellyfish) to 252 for the Magnoliopsida trees (flowering plants). However, this is rather due to the number of laboratories working with the different allergenic sources than to the true presence of allergenic structures among these species. Interestingly, the most recent review dealing with nomenclature and structural biology of allergens (17) states ‘most major allergens from
Table 1: Prevalence of mould allergy induced by different fungal species in % of the respective populations investigated

<table>
<thead>
<tr>
<th>Genus</th>
<th>General population</th>
<th>Atopics*</th>
<th>Asthmatics</th>
<th>Mould-allergic individuals†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternaria</td>
<td>3.6–12.6 (20, 29)</td>
<td>3–14.6 (31, 139)</td>
<td>13.5–14.6 (140, 141)</td>
<td>66.1 (29)</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>2.4 (29)</td>
<td>15–27.6 (22, 140)</td>
<td>5–21.3 (140, 141)</td>
<td>12.6 (29)</td>
</tr>
<tr>
<td>Candida</td>
<td>8.5 (29)</td>
<td>28.9 (22)</td>
<td>23.1 (141)</td>
<td>44.3 (29)</td>
</tr>
<tr>
<td>Cladosporium</td>
<td>2.5–2.9 (20, 46)</td>
<td>3–18.2 (31, 139)</td>
<td>15.9 (141)</td>
<td>13.1 (29)</td>
</tr>
<tr>
<td>Penicillium</td>
<td>1.5 (29)</td>
<td>7.3–13.1 (22, 139)</td>
<td>33 (142)</td>
<td>33 (142)</td>
</tr>
<tr>
<td>Trichophyton</td>
<td>1.9 (29)</td>
<td>ND</td>
<td>NA (29)*</td>
<td>10.2 (29)</td>
</tr>
</tbody>
</table>

*Individuals suffering from allergen-specific IgE-mediated sensitization against any allergic source.
†Individuals sensitized to at least one mould. The prevalence of sensitization to single moulds in the subpopulation of subjects with multiple fungal sensitizations might reach prevalences surpassing 80% for Alternaria (92.2%), Aspergillus (83.1%), Candida (89.6%) and Cladosporium (84.4%) (29).
involved in their pathogenesis is reported in Table 2. As this review focuses on IgE-mediated type I allergic reactions, hypersensitivity reactions of types II, III and IV will not be further discussed in detail.

Fungal type I allergy is induced by a large number of fungal genera, the most important ones belonging to the ascomycota followed by basidiomycota and zygomycota (23). Clinically, the IgE-mediated sensitization to fungal allergens can manifest as allergic rhinitis and rhinosinusitis (35), allergic asthma (36) and atopic dermatitis (37).

**Allergic rhinitis and rhinosinusitis**

Allergic rhinitis affects up to 40% of the population and results in nasal itching, congestion, sneezing and clear rhinorrhea. Allergic rhinitis causes extranasal adverse effects including decreased quality of life, decreased sleep quality and obstructive sleep apnoea (38). However, epidemiologic studies have failed to demonstrate a direct relationship between fungal allergy and allergic rhinitis via either outdoor or indoor exposure. Fungal allergy is clearly linked to a subset of chronic rhinosinusitis (CRS) known as allergic fungal rhinosinusitis (AFRS) (39). In the patient’s mucus, fungal hyphae are detectable and patients show coetaneous hypersensitivity to specific fungal allergens along with specific IgE and IgG antibodies against the sensitizing fungus and an increased total serum IgE level (40). Immunologically, allergic fungal rhinosinusitis is a mixed type I, type III and type IV allergic reaction.

**Allergic asthma**

There is compelling evidence that fungal allergy is associated with severe asthma (41). Although the precise prevalence of fungal sensitivity is unclear, recent estimates indicate that 24.6 million people in the United States suffer from asthma (42). Depending on the definition, about 10–20% of these patients might be classified as subjects suffering from severe asthma, and in this group, 30–70% can be expected to be sensitized to at least one fungal species (Table 1). Extrapolating this figure to the industrialized countries, we have to assume that several millions of asthmatic patients are affected by fungal allergy (27). However, with exception of special cases such as workplace exposure or allergic bronchopulmonary aspergillosis (ABPA), which are well documented, the contribution of fungal sensitization to the severity of asthma remains to be investigated.

**Table 2 Classification of hypersensitivity reactions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Humoral response</th>
<th>Soluble mediators</th>
<th>Time course</th>
<th>Cellular response</th>
<th>Clinical examples</th>
<th>Fungal diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>IgE</td>
<td>Histamine, leukotrienes</td>
<td>Minutes</td>
<td>Smooth muscle constriction, eosinophil infiltration</td>
<td>Rhinitis, allergic asthma (143)</td>
<td>Allergic rhinitis (39) ABPA (133–137) ABPM (23)</td>
</tr>
<tr>
<td>Type II</td>
<td>IgG, IgM</td>
<td>Complement</td>
<td>1–24 h</td>
<td>Neutrophil activation and lysis of target cells</td>
<td>Autoimmunity(144)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Type III</td>
<td>IgG, IgM</td>
<td>Complement</td>
<td>1–24 h</td>
<td>Infiltration and activation of granulocytes</td>
<td>Rheumatoid arthritis (145)</td>
<td>Hypersensitivity pneumonitis† Aspergiloma (137) ABPA (133–137)</td>
</tr>
<tr>
<td>Type IV</td>
<td>T cells</td>
<td>Lymphokines</td>
<td>2–3 days</td>
<td>T-cell and macrophage activation</td>
<td>Tuberculosis, contact dermatitis (146, 147)</td>
<td>Hyper sensitivity pneumonitis (135, 136)</td>
</tr>
</tbody>
</table>

*Modified from references (33) and (34).
†Most of the IgE-associated fungal diseases are mixed forms involving combinations of types I, III and IV hypersensitivity reactions (23).
‡Also termed extrinsic allergic alveolitis (137).
all asthmatic patients (51). In this regard, recombinant allergens might contribute to a more reliable diagnosis of ABPA.

Other fungi, including Candida, Penicillium and Curvularia species, are occasionally responsible for a similar syndrome termed ‘allergic bronchopulmonary mycosis’ (ABPM) (52). The endotype classification of asthma syndromes proposed recently (53) also include ABPM. Like ABPA, the characteristics of ABPM include severe asthma, blood and pulmonary eosinophilia, marked increased levels of total and allergen-specific IgE, bronchiectasis and mould colonization of the airways. The term ‘severe asthma associated with fungal sensitivitY’ (SAFS) has been introduced to illustrate the high rate of fungal sensitivity in patients with severe asthma (54). Because of the ambiguity in diagnostic criteria, SAFS is currently more a diagnosis by exclusion than a diagnosis of a specific disease entity (55).

Atopic dermatitis

Atopic dermatitis (AD) is a chronic relapsing, highly pruritic inflammation of the skin with a worldwide prevalence of 10–20% in children and of 1–3% in adults (22, 56). The pathophysiology of AD, also called atopic eczema, is complex and not fully understood (57). Recently, Malassezia sympodialis, a lipophilic yeast colonizing the skin of both AD and healthy individuals, has been shown to induce IgE-mediated sensitization exclusively in patients suffering from AD (22). The main reason for this specific sensitization may be the disrupted skin barrier facilitating allergen uptake, which may contribute to the perpetuation of the disease (58). Of special interest in this regard are cross-reactivity reactions between M. sympodialis allergens sharing a high degree of sequence identity to human proteins (8, 28). It has been convincingly shown, both, in vitro and in vivo that Mala s 11, the M. sympodialis manganese-dependant superoxide dismutase, sharing 50% sequence homology with the human enzyme (59), can elicit strong humoral- and T-cell-mediated immune reactions in a subset of AD patients (60). These reactions have been traced back to structural similarities between the two proteins (59) and studied in detail at the T-cell level (61). However, the phenomenon of autoreactivity to human proteins in AD patients is not limited to Mala s 11 and human superoxide dismutase as recently shown in studies investigating Mala s 13 and human thioredoxin (62, 63) and can be extended to a whole array of human proteins (64), whether sensitization to other fungi, except Saccharomyces cerevisiae, which shows a significant correlation between a positive skin prick test and AD (65), is involved in the pathogenesis of the disease remains to be determined.

Fungal allergens

The list of fungal allergens officially approved by the Nomenclature Subcommittee of the International Union of Immunological Societies (IUIS; www.allergen.org) spans 105 iso-allergens and variants from 25 fungal species belonging to the Ascomycota and Basidiomycota phyla (20). However, the number of fungal proteins able to elicit type I hypersensitivity reactions described in the literature is much longer, even if many of these allergens are poorly characterized. A recent catalogue of the fungal allergens described (23) lists 174 allergens for the genus Ascomycota and 30 for the genus Basidiomycota. However, this list does not include many fungal allergens, which have been only partially characterized in terms of primary sequence. For example, it has been shown by high-throughput screening technology that A. fumigatus, perhaps the most important allergenic mould, is able to produce at least eighty-one different IgE-binding proteins (66). The same approach applied to phage surface display libraries of Cladosporium herbarum, Coprinus comatus and Malassezia furfur yielded at last 28, 37 and 27 different clones, respectively, displaying IgE-binding proteins (67). These few examples clearly show that the repertoire of fungal allergens is far from being completely elucidated. Besides species-specific allergens such as Asp f 1 and Alt a 1, which are limited to genera or species (68), databases of allergen sequences compiled and used to search fungal proteomes revealed that some highly homologous allergen orthologue classes and allergen epitopes are ubiquitous in all fungi (69). It seems likely that many of these protein orthologues are potential allergens or at last capable of cross-reacting as proteins showing a high degree of sequence homology are likely cross-reactive (70). Cross-reactivity between homologous fungal allergens has been demonstrated in many cases between phylogenetically close (71, 72) and even distant species such as Candida boidinii and A. fumigatus (73). Some examples of major and cross-reactive fungal allergens are given in Table 3. Although the clinical relevance of cross-reactivity between fungal allergens remains to be investigated in more detail (7), the phenomenon is well understood at a scientific level. The availability of high-resolution three-dimensional structures of eight fungal allergens (74–81) allowed researchers to understand in details the structural basis of cross-reactivity (70), to homology model unsolved structures of fungal allergens (59, 82–84) and to test the correctness of the hypotheses by site-directed mutagenesis and immunological investigations (59,85). Moreover, serologic studies involving recombinant A. fumigatus allergens contributed to corroborate a clinical diagnosis of ABPA by the discovery of disease-specific allergens (86, 87). In contrast to secreted allergens, which are recognized by serum IgE of A. fumigatus-sensitized individuals with or without ABPA, some nonsecreted allergens are predominantly recognized by serum IgE of ABPA patients (45, 86–89). This differential immunological response is probably due to the fact that ABPA patients have or had the fungus growing in the lung (90). Therefore, as a result of fungal damage due to cellular defence mechanisms, they become more strongly exposed to nonsecreted proteins than A. fumigatus-allergic individuals, which mainly recognize environmental fungal allergens (91).

The diagnosis of fungal allergy: an unsolved medical need

As already mentioned and confirmed in a recent study supported by the European community (GA2LEN (92)), the
incidence of fungal sensitization is high (Table 1) and clinically relevant. However, the problems related to the *in vitro* and *in vivo* diagnosis of fungal and other allergies are far from being solved (93). Of course any *in vivo* treatment for these diseases. Because fungi are ubiquitous in the environment, it is important to keep in mind that more than 20% of the population is sensitized to fungi. In contrast to other allergies such as seasonal pollen-derived allergies, most patients sensitized to fungi are not aware of the source of exposure and can only report that the symptoms are more or less perennial. Technological developments in allergen cloning and microarrays (107–110), together with the proved superior diagnostic performance of recombinant allergens compared with extracts (111–113), might contribute to a more specific and sensitive diagnostic test. However, the high number of different allergens makes it impossible to produce consistent extracts containing the so-called cross-reactive carbohydrate determinants to which about 20% or more of the sensitized patients generate specific IgE (104). Even though antibody-binding glycoproteins are widespread in many extracts and therefore detected by *in vitro* diagnostic tests, cross-reactive carbohydrate determinants do not appear to cause clinical symptoms in most, if not all, patients, and can thus be considered as clinically irrelevant allergens (104). In fact, comparisons of skin test and serology obtained with recombinant allergens produced in *E. coli*, and thus lacking post-translational modifications, correlate fairly well (105) in contrast to those obtained with fungal extracts (106). Moreover, the clinical history that represents one of the most important diagnostic criteria for an allergy is difficult to reconstruct for patients with a fungal allergy. In contrast to other allergies such as seasonal pollen-derived allergies, most patients sensitized to fungi are not aware of the source of exposure and can only report that the symptoms are more or less perennial. Technological developments in allergen cloning and microarrays (107–110), together with the proved superior diagnostic performance of recombinant allergens compared with extracts (111–113), might contribute to a more specific and sensitive component-resolved diagnosis of allergy (114–116) in the future. However, due to the high number of different allergens produced by fungi, it is unlikely that a solution for this urgent medical need will be reached in the near future, and the first recombinant fungal allergens (Alt a 1, Asp f 1, Asp f 2, Asp f 3 and Asp f 4) immobilized in ImmunoCAPs are now commercially available from Thermo scientific (www.phadia.com).

The treatment of fungal allergy

As for all other allergies, avoiding exposure is still the best treatment for these diseases. Because fungi are ubiquitous in the environment, it is important to keep in mind that more than 20% of the population is sensitized to fungi. In contrast to other allergies such as seasonal pollen-derived allergies, most patients sensitized to fungi are not aware of the source of exposure and can only report that the symptoms are more or less perennial. Technological developments in allergen cloning and microarrays (107–110), together with the proved superior diagnostic performance of recombinant allergens compared with extracts (111–113), might contribute to a more specific and sensitive component-resolved diagnosis of allergy (114–116) in the future. However, due to the high number of different allergens produced by fungi, it is unlikely that a solution for this urgent medical need will be reached in the near future, and the first recombinant fungal allergens (Alt a 1, Asp f 1, Asp f 2, Asp f 3 and Asp f 4) immobilized in ImmunoCAPs are now commercially available from Thermo scientific (www.phadia.com).

**Table 3** Major fungal allergens with or without cross-reactivity

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Genus</th>
<th>Accession Number</th>
<th>MW (kDa)</th>
<th>Biological Function</th>
<th>Cross-reactive with*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alt a 1</td>
<td>Alternaria alternata</td>
<td>U82633</td>
<td>30</td>
<td>Unknown</td>
<td>NF</td>
<td>(69)</td>
</tr>
<tr>
<td>Asp f 1</td>
<td>Aspergillus fumigatus</td>
<td>M85781</td>
<td>18</td>
<td>Ribotoxin</td>
<td>Candida boidii</td>
<td>(68, 69, 148)</td>
</tr>
<tr>
<td>Asp f 3</td>
<td>A. fumigatus</td>
<td>US8050</td>
<td>19</td>
<td>Peroxisomal protein</td>
<td>Asp f 27, Mala s 6, Cyclophilins of <em>Candida albicans</em>, <em>Saccharomyces cerevisiae</em>, <em>Homo sapiens</em></td>
<td>(73)</td>
</tr>
<tr>
<td>Asp f 11</td>
<td>A. fumigatus</td>
<td>AJ006689</td>
<td>24</td>
<td>Cyclophilin</td>
<td>NF</td>
<td>(75, 149)</td>
</tr>
<tr>
<td>Asp f 29</td>
<td>A. fumigatus</td>
<td>AJ937745</td>
<td>13</td>
<td>Thioredoxin</td>
<td>Asp f 28, Mala s 13, <em>H. sapiens</em> thioredoxin</td>
<td>(72, 76)</td>
</tr>
<tr>
<td>Asp f 34</td>
<td>A. fumigatus</td>
<td>AM496018</td>
<td>20</td>
<td>Phi A cell wall protein</td>
<td>NF</td>
<td>(150)</td>
</tr>
<tr>
<td>Cla h 8</td>
<td>Cladosporium herbarum</td>
<td>AJ181916</td>
<td>28</td>
<td>Mannitol dehydrogenase</td>
<td>Alt a 8</td>
<td>(151)</td>
</tr>
<tr>
<td>Pen o 18</td>
<td>Penicillium oxalicum</td>
<td>AF243425</td>
<td>34</td>
<td>Vacuolar serine protease</td>
<td>Cla h 18, Asp f 18</td>
<td>(152)</td>
</tr>
<tr>
<td>Mals s 6</td>
<td>Malassezia sympodialis</td>
<td>AJ011956</td>
<td>17</td>
<td>Cyclophilin</td>
<td>Asp f 11, Asp f 27, Asp f 28, <em>H. sapiens</em> cyclophilin</td>
<td>(75)</td>
</tr>
<tr>
<td>Mala s 11</td>
<td>M. sympodialis</td>
<td>AJ548421</td>
<td>23</td>
<td>MnSOD</td>
<td>Asp f 6, <em>H. sapiens</em> MnSOD</td>
<td>(60, 74, 85)</td>
</tr>
</tbody>
</table>

*NF: not found.

These allergens are considered species specific and unique (69). Many phylogenetically highly conserved allergens react also with their human counterpart.
our environment, a complete avoidance of exposure is not feasible. However, reduction in asthma morbidity following interventions for improving indoor air quality and remediation of moisture incursion have been demonstrated (117).

Of course, allergen-specific immunotherapy is currently the only treatment capable of curing allergic diseases (118) and has been used in clinical practice for more than hundred years (119). A limited number of controlled immunotherapy trials with Alternaria alternata and C. herbarum extracts have indicated some clinical benefit (120); however, large-scale, double-blind, placebo-controlled studies of fungal allergen-specific immunotherapy are lacking. In general, immunotherapy for fungal allergy is not recommended mainly because of the lack of standardized therapeutic reagents (121).

As the majority of the patients suffering from fungal sensitization are severe asthmatics, inhaled corticosteroids and frequent courses of oral corticosteroids are used to control the asthma (122, 123) and contribute to alleviate the allergic symptoms (124). Severe conditions such as ABPA, ABPM or SAFS exacerbations are best treated with oral steroids over 3–6 weeks (125) corroborated by inhaled corticosteroids. Although there are conflicting data concerning the clinical utility of inhaled corticosteroids in reducing exacerbation frequency, they are an important therapeutic intervention to control the worst symptoms of underlying asthma (125, 126), but with the well-known adverse side-effects (127). An alternative or adjunctive strategy in the treatment of these diseases is to reduce or clear the lung of fungal colonization by antifungal agents (128). Although some placebo-controlled randomized studies demonstrated the benefit of itraconazole therapy for ABPA (129, 130), the adjuvant role of antifungal treatment in severe forms of fungal allergy should be investigated in more detail with special attention to the effects on corticosteroid dose, frequency of exacerbations, quality of life, immunological changes and side-effects.

Other diseases associated with fungal exposure

Fungi play an important role also in other important diseases associated with fungal exposure, although not primarily IgE mediated. As this review is focused on fungal allergy, these diseases are only briefly mentioned here. The most dangerous diseases caused by fungi are invasive mycoses (131, 132). Most opportunistic mycoses occur in individuals with congenital or acquired immunodeficiency; morbidity and mortality rates are high, and prevention, diagnosis and treatment of these infections remain difficult (133). Less harmful but widespread in the population are fungal infections of the skin. Superficial mycoses are characterized by invasion restricted to the stratus corneum and therefore usually not associated with inflammatory or immune responses of the host (134). Other diseases caused by fungi partially are related to exposure at the workplace (135). Included in this disease group are hypersensitivity pneumonitis also called extrinsic allergic alveolitis (136), farmer’s lung, bagassosis and mushroom worker’s lung, which result from occupational exposure to thermophilic actinomycetes present in hay, bagasse and mushroom compost, respectively (137).

Conclusions

The impact of fungal allergy on human health, especially in patients suffering from asthma or cystic fibrosis, and an emerging role of Malassezia sensitization in the exacerbation of atopic dermatitis have been clearly demonstrated during the past years. There is no doubt that fungi are involved in many allergic disorders and, as best documented example, in ABPA.

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Conflicts of interest

The authors declare no conflicts of interest.

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