

REVIEW ARTICLE

## Fungi: the neglected allergenic sources

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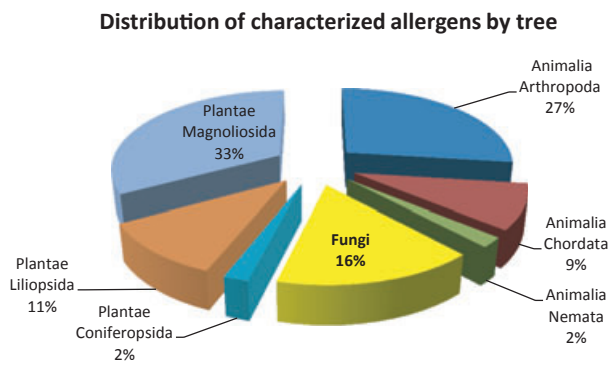
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### Abstract

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.

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 FcεRI-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 allergen 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](http://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



**Figure 1** Taxonomic distribution of the 753 allergens officially recognized by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Subcommittee (www.allergen.org). The WHO/IUIS allergen nomenclature database has been recently updated (138).

mites, animal dander, pollens, insects, and foods have been cloned, and more than 40 three-dimensional allergen structures are in the Protein Database' with fungal allergens conspicuously absent from this list. Fungal allergens are largely neglected in the field of molecular allergology and also in some reviews dealing with inhalant allergens and their role in allergic airways disease (18) despite the predominant role played by fungi in allergic asthma (19, 20).

### Allergenic fungi and exposure to fungal allergens

Indoor and outdoor exposure to fungal components, including spores, is a recognized triggering factor for respiratory allergy and asthma (21), as well as for atopic dermatitis (22). As highlighted in a pivotal review (23), among the over 100'000 fungal species reported (24), only a few hundred have been described as opportunistic pathogens (25) causing human illness through three specific mechanisms: direct infection of the host, elicitation of deregulated immune responses and toxic effects due to secondary metabolites (26). Among these, about 80 mould genera have been shown to induce type I allergies in atopic individuals (23). The most important

allergenic fungi belong to the genera *Alternaria*, *Aspergillus* and *Cladosporium* (27), whereas members of the genera *Candida*, *Penicillium*, *Clavularia* and others seem to be, with the exception of the genus *Malassezia* in patients suffering from atopic dermatitis (22, 28), less important as allergenic sources (29).

The exact prevalence of fungal sensitization among the general population is still unknown (27). This is not astonishing as no reference standards for fungal extracts are available to date even if dozens of commercial products are available (30). However, it is well known that the use of commercial extracts from different manufacturers can generate huge differences in the outcome of *in vitro* or *in vivo* prevalence studies (31) due to the extreme variability of both content and relative amounts of allergens in commercially available fungal extracts (32). In conclusion, the marked differences in source materials and manufacturing procedures used, the lack of generally accepted potency assays and the great number of potentially allergenic fungal species have hampered any significant progress in fungal extract standardization. The best estimates of fungal sensitization among allergic individuals come from a large skin prick test (SPT) survey on a cohort of subjects with respiratory diseases conducted with extracts from *Alternaria*, *Aspergillus*, *Candida*, *Cladosporium*, *Penicillium*, *Saccharomyces* and *Trichophyton* and indicate a prevalence of sensitization around 19% (29). The ranges of prevalence of fungal sensitization for the general population, atopic and asthmatic subjects, and mould-sensitized patients, not claimed to be exhaustive, are reported in Table 1.

### Clinical manifestations of fungal hypersensitivity

The clinical spectrum of hypersensitivity reactions elicited by fungi is very broad and includes, besides IgE-mediated type I allergy, reactions of types II, III and IV according to the old definition of Coombs and Gell (33, 34). Although the classification into types I to VI is widely used in clinical practice, it should be mentioned that the reality is more complex because frequently several mechanisms operate together in the pathogenesis of hypersensitivity reactions, and this is especially true for reactions to fungi. A brief classification of the different types of hypersensitivity reactions with the mechanisms

**Table 1** Prevalence of mould allergy induced by different fungal species in % of the respective populations investigated

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

\*Individuals suffering from allergen-specific IgE-mediated sensitization against any allergenic 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.

### Allergic bronchopulmonary aspergillosis and related conditions

ABPA is commonly caused by *Aspergillus fumigatus*, a ubiquitous mould frequently found indoors and outdoors. The syndrome is characterized by exacerbations of asthma, recurrent transient chest radiographic infiltrates, peripheral and pulmonary eosinophilia, and development of bronchiectasis (43). Although originally considered a rarity (44), ABPA is currently recognized as a serious disease affecting approximately 3% of asthmatic patients (41) and up to 10% of patients with cystic fibrosis (45). However, in asthmatic and CF patients sensitized to *A. fumigatus*, the incidence of ABPA might be much higher ranging from 15 to 35% (46, 47). Immunologically, ABPA is a mixed type I, type III and type IV hypersensitivity lung disease induced by bronchial colonization with *A. fumigatus* causing symptoms ranging from asthma exacerbation to fatal destruction of the lung (48). ABPA as a syndrome suspected from clinical signs is not trivial to be diagnosed, and several criteria that are, however, not specific for the disease have been suggested (45, 49, 50). Therefore, serological findings showing sensitization to *A. fumigatus* are essential diagnostic tools to confirm or exclude the disease. ABPA is a disease with a high risk of the development of irreversible end-stage fibrosis, and therefore, it is recommended to rule out sensitization to *A. fumigatus* in

**Table 2** Classification of hypersensitivity reactions\*

Category†	Humoral response	Soluble mediators	Time course	Cellular response	Clinical examples	Fungal diseases
Type I	IgE	Histamine, leukotrienes	Minutes	Smooth muscle constriction, eosinophil infiltration	Rhinitis, allergic asthma (143)	Allergic rhinitis (39) Allergic asthma (42, 48) ABPA (133–137) ABPM (23)
Type II	IgG, IgM	Complement	1–24 h	Neutrophil activation and lysis of target cells	Autoimmunity(144)	Unknown
Type III	IgG, IgM	Complement	1–24 h	Infiltration and activation of granulocytes	Rheumatoid arthritis (145)	Hypersensitivity pneumonitis‡ Aspergilloma (137)
Type IV	T cells	Lymphokines	2–3 days	T-cell and macrophage activation	Tuberculosis, contact dermatitis (146, 147)	ABPA (133–137) Hypersensitivity pneumonitis (135, 136)

\*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 least 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 boidiini* 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 (GA<sup>2</sup>LEN (92)), the

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

Allergen	Genus	Accession Number	MW (kDa)	Biological Function	Cross-reactive with*	Ref.
Alt a 1	<i>Alternaria alternata</i>	U82633	30	Unknown	NF	(69)
Asp f 1	<i>Aspergillus fumigatus</i>	M83781	18	Ribotoxin	NF	(68, 69, 148)
Asp f 3	<i>A. fumigatus</i>	U58050	19	Peroxisomal protein	<i>Candida boidiini</i>	(73)
Asp f 11	<i>A. fumigatus</i>	AJ006689	24	Cyclophilin	Asp f 27, Mala s 6, Cyclophilins of <i>Candida albicans</i> , <i>Saccharomyces cerevisiae</i> , <i>Homo sapiens</i>	(75, 149)
Asp f 29	<i>A. fumigatus</i>	AJ937745	13	Thioredoxin	Asp f 28, Mala s 13, <i>H. sapiens thioredoxin</i>	(72, 76)
Asp f 34	<i>A. fumigatus</i>	AM496018	20	Phi A cell wall protein	NF	(150)
Cla h 8	<i>Cladosporium herbarum</i>	AJ181916	28	Mannitol dehydrogenase	Alt a 8	(151)
Pen o 18	<i>Penicillium oxalicum</i>	AF243425	34	Vacuolar serine protease	Cla h 18, Asp f 18	(152)
Mals s 6	<i>Malassezia sympodialis</i>	AJ011956	17	Cyclophilin	Asp f 11, Asp f 27, Asp f 28, <i>H. sapiens cyclophilin</i>	(75)
Mala s 11	<i>M. sympodialis</i>	AJ548421	23	MnSOD	Asp f 6, <i>H. sapiens</i> MnSOD	(60, 74, 85)

\*NF: not found.

These allergens are considered species specific and unique (69). Many phylogenetically highly conserved allergens react also with their human counterpart.

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* diagnosis of allergy based on skin tests as well as any *in vitro* diagnosis of allergy based on the determination of allergen-specific IgE depends on the quality of the material used for testing. Although standardized extracts approved by the FDA are available for some allergenic sources (94, 95), no fungal extracts have been approved to date. This is not astonishing because, in contrast to pollens or insect venoms, which represent allergenic sources more or less 'standardized' by nature as a feature of their biological function, fungi as allergenic source are extremely complex. Problems encountered in the standardization of fungal extracts derive from different patterns of allergens produced by different clinical isolates (96), batch to batch variations (97), time-dependent liberation of IgE-binding components during fungal growth (98), instability of the extracts due to protease content (99), culture conditions and medium used to grow the fungus and, of course, the extraction procedures (100). Moreover, fungi produce cell-bound, secreted and intracellular allergens (101), making it impossible to produce consistent extracts containing the three types of allergens in a single run. Therefore, even commercial extracts for skin tests provided by different suppliers deliver discrepant results (102). In clinical routine, fungal sensitization is normally assessed *in vitro* by determination of serum IgE levels with ImmunoCAPs, still considered the 'gold standard' for the *in vitro* diagnosis of allergy (103). Unfortunately, the ImmunoCAP manufacturer does not provide the extracts used to produce the *in vitro* test system as skin test solution, hampering a direct comparison of the skin test reactivity of a commercial extract with the serum IgE levels determined with the corresponding ImmunoCAP. This would be extremely important because (fungal) extracts con-

tain the so-called cross-reactive carbohydrate determinants to which about 20% or more of the sensitized patients generate specific antiglycan 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](http://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



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 (123) 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 stratum 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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