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Invited review article

Sensitization to fungal allergens: Resolved and unresolved issues

Yuma Fukutomi*, Masami Taniguchi

Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan

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HD, house dust; ECRHS, European Community Respiratory Health Survey; Abs, antibodies; CRD, component-resolved diagnostics; MA, molecular-based allergy; WHO/IUIS, World Health Organization and International Union of Immunological Societies; ABPM, allergic bronchopulmonary mycosis; ABPA, allergic bronchopulmonary aspergillosis; AD, atopic dermatitis; PMP, peroxisomal membrane protein; MnSOD, Manganese superoxide dismutase; SAP, secreted aspartyl proteinase

ABSTRACT

Exposure and sensitization to fungal allergens can promote the development and worsening of allergic diseases. Although numerous species of fungi have been associated with allergic diseases in the literature, the significance of fungi from the genera *Alternaria, Cladosporium, Penicillium*, *Aspergillus*, and *Malassezia* has been well documented. However, it should be emphasized that the contribution of different fungal allergens to allergic diseases is not identical, but species-specific.

Alternaria and *Cladosporium* species are considered to be important outdoor allergens, and sensitization and exposure to species of these genera is related to the development of asthma and rhinitis, as well as epidemics of asthma exacerbation, including life-threatening asthma exacerbation. In contrast, xerophilic species of *Penicillium* and *Aspergillus,* excluding *Aspergillus fumigatus,* are implicated in allergic diseases as indoor allergens. *A. fumigatus* has a high capacity to colonize the bronchial tract of asthmatic patients, causing severe persistent asthma and low lung function, and sometimes leading to allergic bronchopulmonary aspergillosis. *Malassezia* are common commensals of healthy skin, although they are also associated with atopic dermatitis, especially on the head and neck, but not with respiratory allergies.

Despite its importance in the management of allergic diseases, precise recognition of species-specific IgE sensitization to fungal allergens is often challenging because the majority of fungal extracts exhibit broad cross-reactivity with taxonomically unrelated fungi. Recent progress in gene technology has contributed to the identification of specific and cross-reactive allergen components from different fungal sources. However, data demonstrating the clinical relevance of IgE reactivity to these allergen components are still insufficient.

Introduction

Fungi can have adverse effects on human health, causing infection, IgE-mediated allergy, non-IgE-mediated hypersensitivity, and toxicity/irritation. The incidence of fungal diseases has risen rapidly over the last two decades, and fungal allergy is one of the common health problems/medical conditions worldwide. It is estimated that there are approximately 1.5 million species of fungi, and numerous fungal species have been described as causes of allergic diseases in the literature.[1,2] The pathogenic significance of fungi from the genera *Alternaria, Cladosporium, Penicillium, Aspergillus,* and *Malassezia* has been well described in the literature. The significance of *Candida*, and *Trichophyton* have also been discussed, but still controversial. However, it should be emphasized that the contribution of fungi to allergic diseases is species-specific, with different fungal species leading to allergic diseases with distinct presentations, which also vary according to the route and specific episode of fungal allergen exposure. This review focuses on the allergenicity of common environmental and commensal fungi in humans, and on the species-specific clinical relevance of these fungal allergens in allergic diseases.

Outdoor environmental fungi

Cladosporium and *Alternaria*, which display some lesional variations, are two of the major genera of outdoor airborne fungi worldwide.[3–6] The outdoor concentration of fungal species from these genera has been associated with epidemics of asthma

* Corresponding author. Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, 18-1 Sakuradai, Minami-ku, Sagamihara, Kanagawa 252-0392, Japan.
E-mail address: y-fukutomi@sagamihara-hosp.gr.jp (Y. Fukutomi).
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exacerbation.[4,7–9] A survey of outdoor airborne fungi in Sagamihara city in Japan[10] demonstrated that *Cladosporium* and *Alternaria* were the predominant genera, followed by *Epicoccum* spp., *Aureobasidium* spp., *Curvularia* spp., and *Ulocladium* spp. Detection of *Cladosporium* revealed two seasonal peaks, during the rainy season (June) and the autumn (September to October), whereas *Alternaria* was detected from April to October, but most frequently in the rainy season (June).[10]

Indoor environmental fungi

Although there also is some lesional variation, *Cladosporium, Penicillium,* and *Aspergillus* spp. are reported to be the most common indoor airborne fungi.[3,11–17] However, in the case of *Cladosporium,* because the indoor concentration is highly correlated with the outdoor concentration,[13] the primary source of *Cladosporium* is considered to be the outdoor environment. A recent environmental survey in Japan used an air sampler to investigate the profile of indoor airborne fungal spores.[18] The frequencies of isolates of *Cladosporium* spp., *Penicillium* spp., *Aspergillus* section *restricti*, and *Aspergillus versicolor* were 100, 78, 84, and 59%, respectively. Among all the isolated fungal species, the highest number of spores was detected for *Aspergillus conicus*, a species of *Aspergillus* section *restricti.* House dust (HD) also contains fungi, and the profile of fungi in HD is similar but not identical to that of airborne. In Japan, the profile of fungal spores isolated from HD was characterized by high frequencies of *Eurotium* spp. (88%), *A. versicolor* (90%), *and Aspergillus* section *restricti* (87%), and a relatively low frequency of *Penicillium* spp.(30%).[18] The abundance of *Aspergillus* and *Penicillium* spores in the indoor environment may be explained by the finding that although optimal fungal growth requires high humidity, some xerophilic species of the genera *Aspergillus* and *Penicillium* are able to survive in a dry environment.[14,19]

Prevalence of fungal sensitization

The prevalence of fungal sensitization displays wide geographical variation.[20,21] Data from the European Community Respiratory Health Survey (ECRHS) demonstrated that among adults aged 20–44 years in the general population, the prevalence of positive skin tests using *Alternaria* and *Cladosporium* extracts ranged from 0.2 to 14.4 %, and 0–11.9%, respectively.[21]

The frequencies of positivity to fungal allergens among adult patients with asthma at Sagamihara National Hospital in Japan are shown in Fig. 1. Sensitization to *Malassezia*, *Alternaria,* and *Cladosporium* tended to decrease with age, which is in accordance with the general recognition that atopic asthma is more common in younger patients.[22] However, the frequency of *Aspergillus fumigatus* did not decrease with age, most likely because sensitization to this species is associated with severe persistent asthma with long disease duration.[23] A notable proportion of the patients, approximately 10–15%, were positive for common indoor environmental xerophilic fungi, in particular, *Aspergillus restrictus*, and *Eurotium* spp. The frequencies of positive skin tests for these fungi did not change with age, highlighting the potential significance of these indoor fungal species in middle-aged and elderly patients. This finding is similar to that of a study by Chou *et al.*[24] Although *Candia* exhibits markedly high frequencies of positivity, the majority of affected patients have negative serum IgE tests for *Candida* (data not shown).

Cross-reactivity of fungal allergens

Measurement of serum IgE antibodies (Abs) from crude extract and/or a skin prick test using crude extract has been traditionally performed as the standard test for diagnosis of allergies. However, because of cross-reactivity between crude allergen extracts from

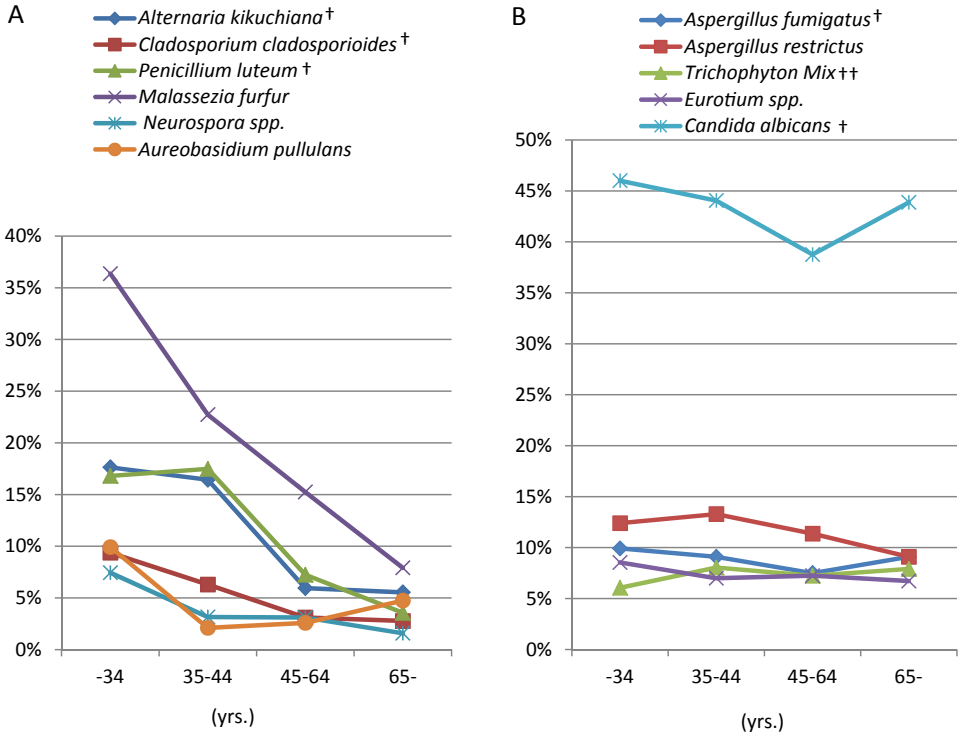

Fig. 1. Frequencies of positivity (%) to intradermal testing using fungal extracts among 1288 adult patients with asthma at Sagamihara National Hospital. Frequencies of sensitization to fungi shown in fig. A show statistically significant decrease trend with age (p trend<0.001 for all six fungi), and those to fungi shown in fig. B do not show any change with age. †extracts purchased from Torii Pharmaceutical (Japan); †† and from HollisterStier (USA). Other fungal extracts were cultured in-house.

different fungi,[25] apparent sensitization to crude fungal extracts does not always indicate genuine sensitization. Species-specific IgE reactivity is difficult to confirm using crude extracts alone, and this represents a major problem for the evaluation of IgE tests in clinical practice. More recently, allergenic molecules (allergen components) that are either purified from their native sources or produced as recombinant proteins, have been introduced into the battery of tests available for the diagnosis of allergic diseases.[26–28] Molecular-based allergy (MA) diagnostics,[29] formally known as component-resolved diagnostics (CRD),[30,31] is an approach used to map the allergen sensitization of a patient at a molecular level, using purified natural or recombinant allergenic molecules instead of allergen extracts. One of the most important implications of MA diagnostics is its ability to distinguish genuine sensitization from sensitization due to cross-reactivity, following evaluation of the sensitization profile to specific allergens and pan-allergens.[29]

This review focuses on specific and cross-reactive allergens from seven genera of common allergenic fungi. Cross-reactivity between fungal allergens is largely explained by taxonomic relationships between genera/species. Fig. 2 depicts the taxonomic relationships among all the allergenic fungi registered in the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee database (http://www.allergen.org/).

Alternaria

Alternaria alternata, which commonly grows on vegetation, is the most common species of the genus *Alternaria*, and it is the major environmental allergen associated with asthma[32–35] and allergic rhinitis.[36] *Alternaria* spp. are generally considered to be outdoor fungi,[15,37] although they also exist in indoor environments.[38,39] Airborne outdoor *Alternaria* spores are detectable from May to November, with the highest levels occurring in cultivated areas containing grassland and grain.[40,41] A study using personal air samplers and nasal air samplers demonstrated that a greater number of spores were inhaled in an outdoor than an indoor environment, an effect that was accentuated by physical activity.[42] Spores from *Alternaria* spp. are larger than those from most other fungi, at approximately 20–40 μm in diameter,[7] and tend to be easily trapped in the nasal cavity. However, it has been reported that spores on cereal crops and grass may be broken into small fragments, presumably because of mechanized harvesting.[7,43,44]

The clinical significance of *A. alternata* as the respiratory allergen has been well documented. Studies have revealed a strong association between sensitization to *Alternaria* spp. and the presence of asthma[32,33,35,45–47] or allergic rhinitis,[36] as well as the severity of asthma.[48–50] In addition, sensitization and exposure to *Alternaria* has been associated with epidemics of severe asthma exacerbation,

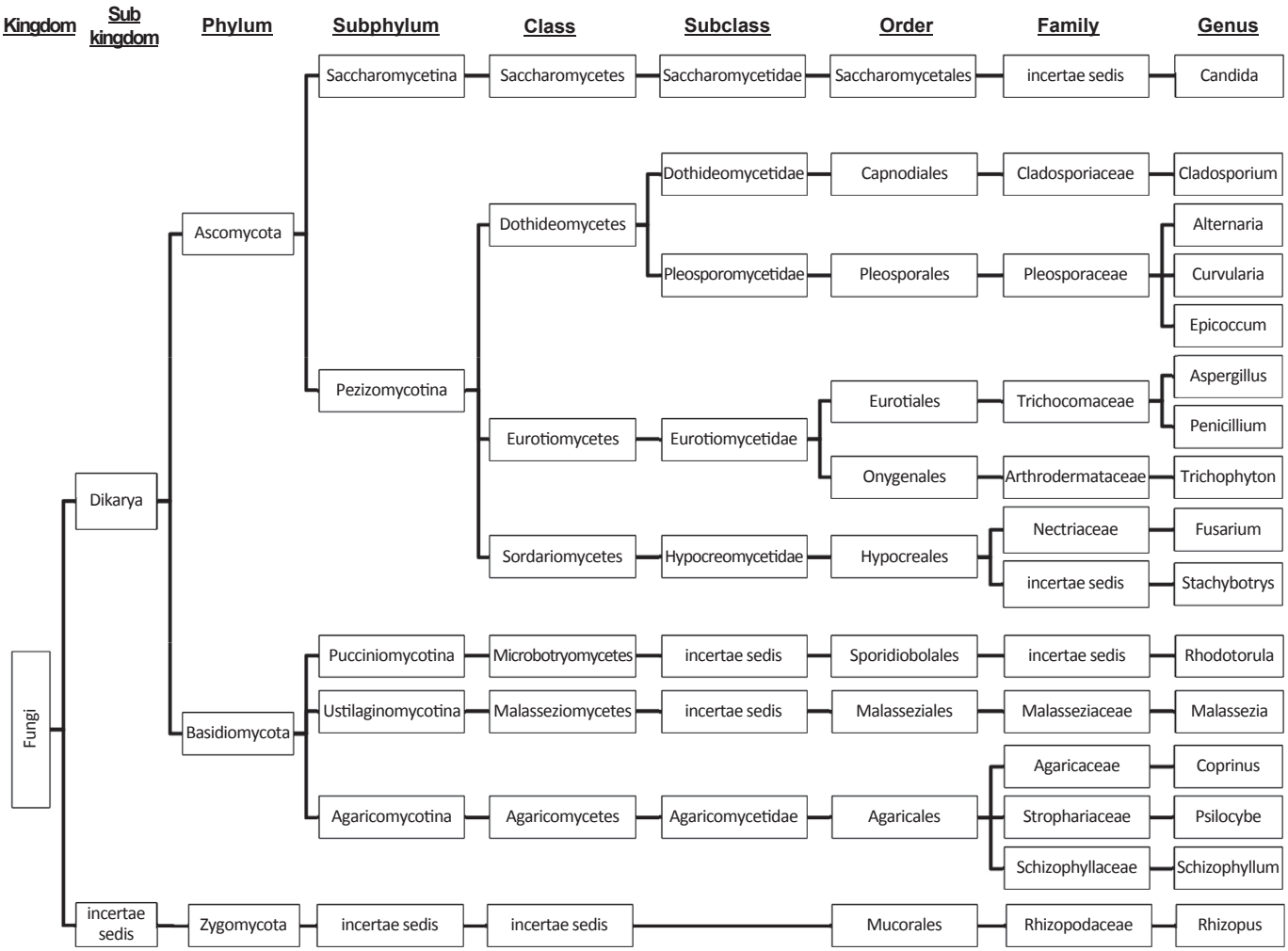

Fig. 2. Taxonomic relationships of allergenic fungi registered in the WHO/IUIS Allergen Nomenclature Sub-committee database (http://www.allergen.org/). Classification on the basis of Dictionary of the Fungi, 10th Edition, Wallingford, UK: CABI Publishing (http://www.speciesfungorum.org/).

including respiratory arrest.[51,52] Thunderstorms appear to be contributory factor to high levels of fungal spores and epidemics of asthma exacerbation.[4] Before a thunderstorm, an increase in air temperature and ozone concentration is observed, which is accompanied by a substantial increase in spore concentrations.[5] A study in the UK in patients with *Alternaria* sensitization revealed a correlation between fragmented *Alternaria* spores, presumably caused by mechanized harvesting, and epidemics of acute asthma exacerbation after thunderstorms.[7] Data from asthmatic patients identified in the ECRHS also demonstrate that sensitization to *Alternaria* is associated with a higher risk of asthma attacks during May to August in Southern Europe, and during July and August in Northern Europe.[53]

Alternaria can occur in indoor environments, especially under humid conditions, such as cervices in bathrooms and walls with dew condensation.[17] However, the clinical relevance of *Alternaria* spp. as indoor fungi has not been deeply studied. Because indoor *Alternaria* concentrations are strongly influenced by outdoor concentrations,[13] the independent contribution of indoor *Alternaria* concentrations is difficult to determine. However, a recent birth cohort study in Boston revealed a significant relationship between indoor dust-borne *Alternaria* at the age of 2–3 months and the frequency of wheezes, by one year old even after adjustment for outdoor airborne *Alternaria* concentrations.[54] These data suggest that *Alternaria* in HD may be an important environmental allergen, in particular, for children.[38]

Although many allergenic proteins have been identified and approved by the WHO–IUIS Allergen Nomenclature Sub-committee (Table 1), Alt a 1 is considered to be only specific allergen component for the genuine *Alternaria* (or Pleosporaceae family) allergy.[55–59] Spore germination promotes the release of allergens, including Alt a 1, from *A. alternata*.[60] A recent study using immunogold electron microscopy demonstrated that Alt a 1 was mainly localized in the cell wall of airborne spores, which may explain the high clinical relevance of Alt a 1 as a respiratory allergen.[61] Alt a 1 has been reported to cross-react with homologous fungal proteins from members of the Pleosporaceae family such as *Stemphylium*, *Ulocladium*, and *Curvularia*.[1,59,62] In contrast, allergenic proteins other than Alt a 1 exhibit a high sequence similarity with homologous proteins from taxonomically unrelated fungi. Thus, the diagnostic and clinical relevance of allergenic proteins other than Alt a 1 with respect to *Alternaria* allergy is unclear.

Cladosporium

Cladosporium is one of the most abundant genera of environmental fungi worldwide, and *Cladosporium herbarum* is one of the most common species to be isolated. Similar to *Alternaria*, *Cladosporium* is generally recognized as an outdoor fungus,[4,15] but it is frequently detected in indoor environments.[38,39,63] A strong correlation between indoor and outdoor *Cladosporium* concentrations has also been reported.[39,64] The clinical relevance of *Cladosporium* as a respiratory allergen resembles that of *Alternaria*,[65–67] whereas the contribution of this genus to the pathogenesis of asthma appears to be a little weaker than that of *Alternaria*. Data from the ECHRS indicate that the prevalence of positive skin prick tests for *Cladosporium* is 1.7% (ranging from 0 to 11.9%), which is lower than that for *Alternaria* (3.3%, ranging from 0.2 to 14.4%).[21] The threshold concentration for evoking allergic symptoms is estimated to be 3,000 spores/m^3 air for *Cladosporium*, which is substantially higher than that for *Alternaria* (100 spores/m^3 air).[43,68] The size of *Cladosporium* spores varies over a wide range, between 3 and 70 × 2–56 μm.[69]

Although many allergenic proteins have been identified and approved by the WHO–IUIS Allergen Nomenclature Subcommittee (Table 2), no specific major allergen components have been identified for *Cladosporium* allergies. With the exception of Cla h 8, all of the registered allergens are cross-reactive minor allergens.[1] Cla h 8, an NADP-dependent mannitol dehydrogenase, is recognized by 57% of *Cladosporium herbarum*-sensitized patients,[70] and it has 75% sequence similarity with Alt a 8, an NADP-dependent mannitol dehydrogenase from *A. alternata*.[71] Presumably due to the cross-reactive nature of identified *Cladosporium* allergens, monosensitization to *Cladosporium* appears to be relatively rare.[72]

Penicillium

Penicillium is the blue or blue-green mold found on fruits and vegetables, and it is used for the production of blue mold cheese. While *Penicillium* is frequently isolated both in indoor and outdoor environments,[13,15] many studies have focused on the significance of *Penicillium* as an indoor mold allergen.[11,73,74] Indoor environmental factors, including inadequate heating and ventilation, the presence of pets, water leaks, and low sun exposure, are known to increase the concentrations of airborne *Penicillium*.[14] Results for *Alternaria* and *Cladosporium* spp. indicate that indoor concentrations are highly correlated with outdoor concentrations, whereas for *Penicillium* spp. this correlation is not always observed.[13] A birth cohort study in Connecticut and western Massachusetts evaluated the effect of exposure to specific genera of indoor airborne fungi, collected with a portable air sampler, on the incidence of respiratory symptoms. Although *Cladosporium* (61%) were most frequent followed by *Penicillium* (41%), airborne levels of *Cladosporium* were not related to an increased risk of wheeze. In contrast, the highest concentration of *Penicillium* was associated with a higher rate of incident wheeze (RR, 2.15, 95%Cis, 1.34–3.46), and persistent cough

Table 1
Allergenic proteins from fungi of genus *Alternaria* approved by WHO/IUIS Allergen Nomenclature Sub-committee.

Species	Allergen	Biological activity	Molecular weight
Alternaria alternata	Alt a 1		16.4 and 15.3 band (30 non-red)
	Alt a 3	Heat shock protein 70	
	Alt a 4	Disulfide isomerase	57
	Alt a 5	Ribosomal protein P2	11
	Alt a 6	Enolase	45
	Alt a 7	YCP4 protein	22
	Alt a 8	Mannitol dehydrogenase	29
	Alt a 10	Aldehyde dehydrogenase	53
	Alt a 12	Acid ribosomal protein P1	11
	Alt a 13	Glutathione-S-transferase	26
	Alt a 14	Manganese superoxide dismutase	24 kDa (reducing)
	Alt a 15	Serine protease	58 kD

Table 2
Allergenic proteins from fungi of the genus *Cladosporium* approved by the WHO/IUIS Allergen Nomenclature Sub-committee.

Species	Allergen	Biological activity	Molecular weight
Cladosporium cladosporioides	Cla c 9	Vacuolar serine protease	36
	Cla c 14	Transaldolase	36.5
Cladosporium herbarum	Cla h 2		45
	Cla h 5	Acid ribosomal protein P2	11
	Cla h 6	Enolase	46
	Cla h 7	YCP4 protein	22
	Cla h 8	Mannitol dehydrogenase	28
	Cla h 9	Vacuolar serine protease	
	Cla h 10	Aldehyde dehydrogenase	53
	Cla h 12	Acid ribosomal protein P1	11

(RR, 2.06, 95%Cis, 1.31–3.24).[75] Another cross-sectional study by the same authors confirmed the association of sensitization and exposure to indoor airborne *Penicillium* with wheeze and the severity of asthma.[76]

Although numerous allergens from different *Penicillium* species have been identified and approved by the WHO–IUIS Allergen Nomenclature Sub-committee (Table 3), no species- or genus-specific major allergen components have been documented for *Penicillium* allergies. The major allergens from *Penicillium* spp. are alkaline and vacuolar serine proteases, which are referred to as group 13 and group 18 allergens, respectively.[1,77,78] These proteases exhibit high sequence similarity with homologous allergens from *A. fumigatus* (Asp f 13, Asp f 18). A study in Taipei demonstrated that 17% of asthmatic patients are positive to purified Pen ch 13 by IgE-immunoblotting, and the frequency of positivity increases with age, reaching 42% among patients aged over 70 years, indicating that *Penicillium* is of higher relevance to adult asthma than childhood asthma.[24] Because of the cross-reactive nature of identified *Penicillium* allergens, mono-sensitization to *Penicillium* appears to be relatively rare.[72] Hypersensitivity pneumonitis induced by *Penicillium* species has also been reported.[79–81]

Aspergillus

The genus *Aspergillus* includes more than one hundred species that are distributed ubiquitously in the environment. Human disorders caused by the *Aspergillus* include allergic asthma and/or rhinitis, allergic bronchopulmonary mycosis (ABPM),[82] allergic rhinosinusitis,[83,84] hypersensitivity pneumonitis,[85–87] aspergilloma,[88] and invasive aspergillosis. ABPM is a pulmonary hypersensitivity disease characterized by sensitization to fungi, uncontrolled asthma, recurrent transient radiographic infiltrate, peripheral and pulmonary eosinophilia, and bronchiectasis.[6,82,89,90] *A. fumigatus* is the most common causal pathogen for ABPM. In addition, it is frequently isolated from the respiratory tract of patients with asthma who do not meet the criteria for allergic bronchopulmonary aspergillosis (ABPA),[23,91] and also from patients with respiratory diseases other than asthma, including cystic fibrosis,[92] chronic obstructive pulmonary disease,[93] tuberculosis-related fibrocavity disease,[94,95] and occasionally in the respiratory tract of healthy individuals.[23] The pathogenic capacity of *A. fumigatus* is related to its pronounced thermotolerance,[96] which enables them to grow at human body temperature, and its small spore size (approximately 2–3 μm),[97] which enables transfer to the terminal airways. Despite its importance as a fungus that colonizes the human respiratory tract, *A. fumigatus* is not a dominant species in either indoor or outdoor environments. The most common environmental fungal species among the genus *Aspergillus* is not *A. fumigatus*, but *Aspergillus niger, A. restrictus, A. versicolor,* and *Aspergillus ochraceous.*[18,38,64,74] Studies have demonstrated that the clinical relevance of the association between exposure to indoor *Aspergillus* spp. and the risk of asthma[12,74,98] resembles that of *Penicillium* spp., which is a closely related fungus in the taxonomical classification.

Several studies have found that IgE sensitization to *A. fumigatus* and/or colonialization of *A. fumigatus* in the respiratory tract of asthmatic patients is associated with reduced lung function[23,91,99] and severe disease.[100] The possible role of antifungal therapy in the treatment of fungal allergic asthma has also been reported.[101] Another study demonstrated that although *A. fumigatus* is not abundant in the indoor environment, isolation of this species from sputum was related to higher airborne concentrations of the fungus in the homes of asthmatic patients, suggesting that the home environment should also be considered as a source of fungal exposure.[102] Therefore, housing intervention may be necessary for the management of fungal allergen-sensitized severe asthma.[14]

Numerous allergens from *Aspergillus* have been identified and approved by the WHO–IUIS Allergen Nomenclature Sub-committee (Table 4). Some of these allergen components are species- or genus-specific, while others are pan-allergens that display cross-reactivity beyond the family or order. Asp f 1 has been identified as an 18-kD allergen of mitogillin family, which is almost identical to restrictocin cloned from *A. restrictus*,[103] and is a species-specific major allergen for *A. fumigatus*.[104] The Asp f 1 allergen is not

Table 3
Allergenic proteins from fungi of the genus *Penicillium* approved by the WHO/IUIS Allergen Nomenclature Sub-committee.

Species	Allergen	Biological activity	Molecular weight
Penicillium brevicompactum	Pen b 13	Alkaline serine protease	33
	Pen b 26	Acidic ribosomal prot. P1	11
Penicillium chrysogenum	Pen ch 13	Alkaline serine protease	34
	Pen ch 18	Vacuolar serine protease	32
	Pen ch 20	N-acetyl-glucosaminidase	68
	Pen ch 31	Calreticulin	
	Pen ch 33		16
	Pen ch 35	Transaldolase	36.5
Penicillium citrinum	Pen c 3	Peroxysomal membrane protein	18
	Pen c 13	Alkaline serine protease	33
	Pen c 19	Heat shock protein P70	70
	Pen c 22	Enolase	46
	Pen c 24	elongation factor 1 beta	
	Pen c 30	Catalase	97
	Pen c 32	Pectate lyase	40
Penicillium crustosum	Pen cr 26	60S acidic ribosomal phosphoprotein P1	11 kDa
Penicillium oxalicum	Pen o 18	Vacuolar serine protease	34

Table 4
Allergenic proteins from fungi of the genus *Aspergillus* approved by the WHO/IUIS Allergen Nomenclature Sub-committee.

Species	Allergen	Biological activity	Molecular weight
Aspergillus flavus	Asp fl 13	Alkaline serine protease	34
Aspergillus fumigatus	Asp f 1	Mitogillin family	18
	Asp f 2		37
	Asp f 3	Peroxysomal protein	19
	Asp f 4		30
	Asp f 5	Metalloprotease	40
	Asp f 6	Mn superoxide dismutase	26.5
	Asp f 7		12
	Asp f 8	Ribosomal protein P2	11
	Asp f 9		34
	Asp f 10	Aspartate protease	34
	Asp f 11	Peptidyl-prolyl isomerase	24
	Asp f 12	Heat shock protein P90	90
	Asp f 13	Alkaline serine protease	34
	Asp f 15		16
	Asp f 16		43
	Asp f 17		
	Asp f 18	Vacuolar serine protease	34
	Asp f 22	Enolase	46
	Asp f 23	L3 ribosomal protein	44
	Asp f 27	Cyclophilin	18
	Asp f 28	Thioredoxin	13
	Asp f 29	Thioredoxin	13
	Asp f 34	PhiA cell wall protein	20
Aspergillus niger	Asp n 14	Beta-xylosidase	105
	Asp n 18	Vacuolar serine protease	34
	Asp n 25	3-phytase B	66–100
Aspergillus oryzae	Asp o 13	Alkaline serine protease	34
	Asp o 21	TAKA-amylase A	53
Aspergillus versicolor	Asp v 13	Extracellular alkaline serine protease	43 kDa

present in spores, being produced after germination and growth of the fungi,[105] and it is almost undetectable in HD extracts.[106] Thus, respiratory sensitization to airborne Asp f 1 in the indoor environment seems to be uncommon, and patients who develop antibody responses to Asp f 1 have been exposed to *A. fumigatus* which has germinated in their respiratory tract.[106] A specific mAb-based ELISA for Asp f 1 has been shown to be a useful tool for standardization and quality control of *A. fumigatus* allergenic products.[107] Asp f 2 is a species-specific major allergen of *A. fumigatus*, with a frequency of sensitization of 96%,[100,108–110] while Asp f 4 is another well-described specific allergen, with a frequency of sensitization of 92%.[111] On the contrary, Asp f 3[112], Asp f 6[113], Asp f 8[114], Asp f 12[115], Asp f 22[116], and Asp f 27[117], which correspond to peroxisomal membrane protein (PMP), manganese superoxide dismutase (MnSOD), ribosomal protein P2, heat shock protein 90, enolase, and cyclophilin from *A. fumigatus*, exhibit high similarity and identity with homologous proteins from fungi of genera other than *Aspergillus*.[112,118,119] While many studies[111,120–122] have focused on the clinical relevance of sensitization to panels of the *A. fumigatus* allergic proteins, Asp f 1, f 2, f 3, f 4, and f 6, as diagnostic markers of ABPA, the results are controversial.[90]

Although some allergenic molecules, such as Asp f 9[113] and the more recently identified Asp f 34[123], have a relatively high sequence specificity for *A. fumigatus* and a high prevalence of sensitization among the ABPA population, indicating that these allergens are of clinical importance, the number of studies demonstrating their clinical relevance has been limited to date. Asp n 14 and Asp n 25 from *A. niger*, and Asp o 21 from *Aspergillus orizae* have been identified as allergenic proteins causing occupational respiratory allergies.

It is important to recognize that most of the allergenic components from *A. fumigatus* have been identified using sera from patients with ABPA. The importance of other allergenic proteins from the genus *Aspergillus* as environmental respiratory allergens has not been well studied. According to clinical data from the author's hospital, the concordance between positive intradermal tests to *A. fumigatus* and *A. restrictus* is low (data not shown), which indicates that current techniques for serum IgE or skin tests using extracts from *A. fumigatus* may not be used for the diagnosis of sensitization to environmental *Aspergillus*.

Malassezia

Malassezia yeasts (formally known as *Pityrosporum orbiculare/ovale*) are commensals of healthy human skin, but are also associated with pityriasis versicolor, seborrheic dermatitis, and atopic dermatitis.[124,125] All the species within the genus, with the exception of *Malassezia pachydermatis*, are lipid-dependent due to their inability to initiate *de novo* synthesis of C_{14} or C_{16} fatty acids.[126] Thus, *Malassezia* spp. do not exist in the external atmosphere. Although many species have been identified within the genus, the most commonly detected species on healthy human skin are *Malassezia sympodialis, M. globose,* and *Malassezia restricta*.

Malassezia spp allergens have been described as important exacerbating factors for atopic dermatitis (AD), in particular, head and neck-type adult AD, but they have not been associated with respiratory allergies. Studies have demonstrated the strong correlation between specific IgE Abs to *Malassezia* and the presence of AD,[127–129] as well as between IgE Abs to *Malassezia* and the severity of AD[130–132] and dermatitis on head and neck.[131,133] The frequency of sensitization to *Malassezia* among the head and neck-type AD population is relatively high, ranging from 55% to 68%.[132,134,135] Improvements in head and neck-type AD after antifungal therapy have been documented.[136–138] Similar to healthy individuals, *M. sympodialis, M. globose,* and *M. restricta* are also commonly detected species on the skin of AD patients. However, in contrast to the strong IgE response of AD patients to *Malassezia*, a study reported that the population density of *Malassezia* on lesional AD skin was lower than non-lesional AD or healthy skin.[139] Furthermore, a more recent study indicated that non-*Malassezia* yeast microbiota of AD patients is more diverse than that of healthy individuals.[140]

Many allergenic proteins from fungi of the genus *Malassezia* have been identified and approved by the WHO/IUIS Allergen Nomenclature Sub-committee (Table 5). *Malassezia* species produce complex allergens that contain both common and species-specific allergen sequences.[141,142] It is hypothesized the variation in *Malassezia* microflora on the skin surface of AD patients is reflected by the heterogeneity of sensitivity to *Malassezia* spp of each AD patient. Thus, serum IgE Ab tests using a mixture of *M. sympodialis, M. globose*, and *M. restricta* are commercially available and used in clinical practice. Crude extracts of *Malassezia* spp. also contain allergenic proteins that exhibit high sequence similarity to proteins from fungi of genera other than *Malassezia*, including PMP (Mala f 2, and 3),[118] cyclophiline (Mala s 6),[117,143,144] heat shock protein 70 (Mala s 10),[145] MnSOD (Mala s 11),[145] and thioredoxin (Mala s 13).[146] As a result, cross-reactivity is observed between crude extracts of *Malassezia* spp. and those of fungi from genera other than *Malassezia*. Mannan, a polysaccharide, is also known to be associated with IgE cross-reactivity beyond the genus.[147] In contrast, Mala s 1, 7, 8, and 9 are considered to be specific allergens with unique sequences.[129,144,148,149]

Casagrande *et al*. investigated the frequency of sensitization to a panel of recombinant *M. sympodialis* allergens (rMala s 1 and 5–9) in 51 patients with atopic eczema who were positive for IgE Abs to crude *M. sympodialis* (ImmunoCAP m70). Analysis by ELISA indicated that the frequencies of positivity for IgE Abs to rMala s 1, 5, 6, 7, 8, and 9 were 39, 47, 55, 10, 31, and 61%, respectively, indicating that Mala s 1, 5, 6 and 9 are the predominant allergenic components.[129]

Candida

Candida is a genus of yeasts, with many species being commensals of the skin, and the gastrointestinal and genitourinary tracts. *Candida albicans* is the most frequently isolated species and many studies have suggested that it plays a role in the pathogenesis of allergic diseases. However, the clinical significance of *C. albicans* as an allergen causing allergic diseases remains controversial. Many studies have shown the association between IgE sensitization to *C. albicans*, and the presence and severity of AD.[150–153] In addition, *C. albicans* is more frequent in the gastrointestinal tract of patients

Table 5
Allergenic proteins from fungi of the genus *Malassezia* approved by the WHO/IUIS Allergen Nomenclature Sub-committee.

Species	Allergen	Biological activity	Molecular weight
Malassezia furfur	Mala f 2	Peroxysomal membrane protein	21
	Mala f 3	Peroxysomal membrane protein	20
	Mala f 4	Mitochondrial malate dehydrogenase	35
Malassezia sympodialis	Mala s 1		
	Mala s 5		
	Mala s 6	Cyclophilin	
	Mala s 7		
	Mala s 8		
	Mala s 9		
	Mala s 10	Heat shock protein 70	86
	Mala s 11	Manganese superoxide dismutase	23
	Mala s 12	Glucose-methanol-choline (GMC) oxidoreductase	67
	Mala s 13	Thioredoxin	13

with AD compared with healthy controls.[151,154] However, because of the significant cross-reactivity between *C. albicans* and *Malassezia* allergens,[155,156] the clinical relevance of specific IgE sensitization to *C. albicans*, independent from that to *Malassezia*, also remains a matter of debate.

The clinical significance of *C. albicans* as a causal allergen for respiratory allergies is much less clear than for AD.[157] *C. albicans* is frequently isolated from the respiratory tract. However, a study in patients with cystic fibrosis demonstrated that although sensitization to and colonialization of *C. albicans* was common, colonialization and sensitization were not correlated.[92] While some asthmatic patients who are IgE-sensitized to *C. albicans* experience an immediate bronchial response after inhalation of *C. albicans* extract,[158] its specific significance beyond fungal cross-reactivity is yet to be clarified. Asero *et al.* reported on the clinical features of adult patients with respiratory allergies monosensitized to *C. albicans*.[159] The proportion of males and females was equally distributed, the mean age was 58 years old, which was higher than atopic controls, and 44% had nasal polyposis. The same author demonstrated that the higher frequency of sensitization to *C. albicans* in patients with nasal polyposis compared with the general subjects with respiratory allergy.[160] One study examined the association between recurrent vaginal candidiasis and atopy in women. Atopy, defined by the presence of allergic respiratory diseases or a positive skin prick test to at least one allergen, was associated with recurrent vaginal candidiasis, whereas specific IgE to *C. albicans* was not.[161] Other studies have revealed an association between IgE sensitization to *C. albicans* and chronic urticaria,[162] as well as a high frequency of sensitization to *C. albicans* in eosinophilic esophagitis.[163]

Several allergenic proteins from fungi of the genus *Candida* have been approved by the WHO/IUIS Allergen Nomenclature Subcommittee. Cand a 1 is a 40-kD alcohol dehydrogenase from *C. albicans*. Using sera from 30 asthmatic patients with a positive skin test and IgE Abs to *C. albicans*, IgE immunoblotting of *C. albicans* extract showed that Cand a 1 had the highest frequency, being recognized by 23 (77%) patients.[164] Cand a 3 is 20-kD peroxisomal protein, which has 62% sequence identity with a hypothetical protein (YDR533c) from *Saccharomyces cerevisiae*.[165] Nine (56%) of 16 asthmatic sera with positive serum IgE Abs tests to *C. albicans* displayed positivity to Cand a 3 in IgE immunoblotting. Cand b 2 is a 20-kD peroxisomal membrane protein from *Candida boidnii,* which displays cross-reactivity with PMP from *A. fumigatus*, Asp f 3 [112]. Secreted aspartyl proteinase (SAP; formally known as *C. albicans* acid protease) is an extracellular hydrolytic enzyme secreted by *C. albicans* and some pathogenic *Candida* species, and it is a key determinant of the virulence of *C. albicans*.[166] Akiyama *et al.* demonstrated that the significance of SAP as an allergen for respiratory and mucosal allergy after conjunctival and bronchial provocation with the purified SAP enzyme.[167,168] Isolated late skin and bronchial responses to purified SAP were also observed for nonatopic asthmatics whose peripheral blood mononuclear cells released IL-5 upon incubation with purified SAP, which indicated the possible role of SAP as a T-cell allergen for nonatopic asthma.[169]

Trichophyton

Fungi in the genus *Trichophyton* are known as the causal pathogen of dermatophytosis, a fungal infection of the skin, hair, and nails. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the most common pathogens in the genus. Although *Trichophyton* spp. are only found at low concentrations in indoor and outdoor environments, sensitization to *Trichophyton* is relatively common among the general atopic population.[72] This is attributed to the high prevalence of dermatophytosis in the general population.[170–172]

High levels of IgE Abs to *Trichophyton* are found in patients with trichophytosis, regardless of atopy,[173,174] indicating that *Trichophyton* infection, not respiratory exposure, is the major determinant of an IgE response to *Trichophyton*. However, it has been suggested that tinea infection/sensitization plays a role in the pathogenesis of asthma and rhinitis.[175–178] In a placebo-controlled clinical trial by Ward *et al.*, an improvement in asthma symptoms, peak flow, and steroid use was observed among patients with late-onset asthma who had tinea infection after oral fluconazole treatment.[179] However, the route of exposure to *Trichophyton* allergens in such *Trichophyton*-infected patients has not been identified. A few reports have suggested the possible role of inhaled *Trichophyton* in the pathogenesis of asthma or rhinoconjunctivitis among subjects without *Trichophyton* infection.[180] Occupational exposure to airborne *Trichophyton* in nail dust has been shown to induce nasal and eye symptoms in chiropodists.[181] Sensitization to *Trichophyton* is also reported to be a risk factor for more severe disease among the general asthmatic population.[182]

Some allergenic proteins from fungi of the genus *Trichophyton* have been identified and approved by the WHO/IUIS Allergen Nomenclature Sub-committee. Tri t 1 is a 30-kD, exo 1,3-beta-glucanase that causes an immediate hypersensitivity skin reaction. It is a major allergen of *Trichophyton tonsurans*, with the prevalence of sensitization being 73% (22 of 30) in patients with asthma rhinitis or urticaria who were sensitized to *Trichophyton* extract.[183–185] Tri t 4 is an 83-kD serine protease that is associated with delayed hypersensitivity skin reactions, but can also cause immediate hypersensitivity skin reactions.[186] Tri r 2, from the *T. rubrum* species, is as a 29-kD serine protease that elicits immediate and delayed-type hypersensitivity skin reactions in different individuals.[187,188] Tri r 4, an 85-kD serine protease, has also been identified but it does not elicit skin test reactivity.[188]

Conclusion

The clinical and diagnostic relevance of allergens from seven common genera of fungi has been reviewed. Recent progress in gene technology has greatly contributed to the identification of species-specific and cross-reactive allergic molecules from different allergenic fungal sources. However, data verifying the clinical and diagnostic relevance of IgE reactivity to these allergens are insufficient. Recent studies from Japan have suggested the possible contribution of other fungal allergen sources, including *Schizophyllum commune*[189,190] and *Bjerkandera adusta*[191] from basidiomycetous fungi,[192,193] to the pathogenesis of respiratory allergy, cough, and ABPM. Data regarding the species-specific impact of these fungi on the general allergic population are also needed.

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Conflict of interest

The authors have no conflict of interest to declare.

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