Allergology International 64 (2015) 321–331

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Sensitization to fungal allergens: Resolved and unresolved issues

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ARTICLE INFO

Article history:
Received 29 April 2015
Received in revised form
1 May 2015
Accepted 7 May 2015
Available online 9 June 2015

Keywords:
Allergen
Allergy
Cross-reactivity
Fungi
Molecular-based allergy diagnostics

Abbreviations:
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

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.05.007

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

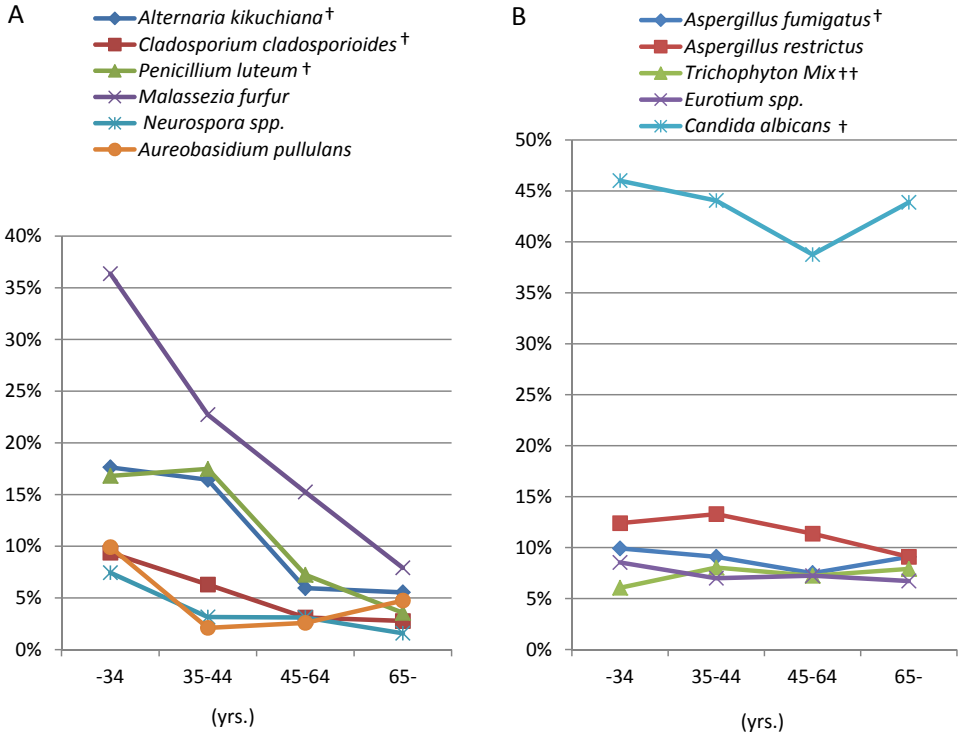

Fig. 1. Frequencies of positivity (%) to intradermal testing using fungal extracts among 1288 adult patients with asthma at Sagamihara National Hospital. Frequencies of sensitization to fungi shown in fig. A show statistically significant decrease trend with age (p trend<0.001 for all six fungi), and 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.