Clinical Commentary Review

Taxonomy of Allergenic Fungi

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The Kingdom Fungi contains diverse eukaryotic organisms including yeasts, molds, mushrooms, bracket fungi, plant rusts, smuts, and puffballs. Fungi have a complex metabolism that differs from animals and plants. They secrete enzymes into their surroundings and absorb the breakdown products of enzyme action. Some of these enzymes are well-known allergens. The phylogenetic relationships among fungi were unclear until recently because classification was based on the sexual state morphology. Fungi lacking an obvious sexual stage were assigned to the artificial, now-obsolete category, "Deuteromycetes" or "Fungi Imperfecti." During the last 20 years, DNA sequencing has resolved 8 fungal phyla, 3 of which contain most genera associated with important aeroallergens: Zygomycota, Ascomycota, and Basidiomycota. Advances in fungal classification have required name changes for some familiar taxa. Because of regulatory constraints, many fungal allergen extracts retain obsolete names. A major benefit from this reorganization is that specific immunoglobulin E (IgE) levels in individuals sensitized to fungi appear to closely match fungal phylogenetic relationships. This close relationship between molecular fungal systematics and IgE sensitization provides an opportunity to systematically look at cross-reactivity and permits representatives from each taxon to serve as a proxy for IgE to the group. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

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The Kingdom Fungi contains diverse eukaryotic organisms including molds, yeasts, mushrooms, bracket fungi, plant rusts, smuts, and puffballs. Fungi have a complex metabolism that differs from animals and plants; they secrete enzymes into their surroundings and absorb the breakdown products of enzyme action. Some of these enzymes are well-known allergens.[1]

True fungi have cell walls that contain chitin (with rare exceptions) and β-(1→3) and β-(1→6) glucans, unlike plant cell walls that contain cellulose, a β-(1→4) glucan, as the structural component.[2] Fungal surfaces have a wide array of molecules that are important targets for recognition by the innate immune system. In addition to β glucans, fungal cell walls contain chitin, mannans and mannoproteins, and galactomannans. Fungi may be unicellular such as yeast, but typically have a thread-like or tube-like body composed of hyphae, which range from 2 to 10 μm in diameter. Hyphae grow at their tips and frequently branch resulting in an interconnected network of hyphae called a mycelium.

Fungi reproduce by producing spores, many of which are adapted for airborne dispersal. Spores may be produced by either meiosis or mitosis. Spores produced by meiosis are associated with sexual reproduction (teleomorphic stage) and are produced in various structures that are characteristic of each fungal phylum. Among allergenic fungi, most spores produced by mitosis are formed on differentiated hyphae or conidiophores and are called conidia. These are associated with the anamorphic (asexual) stage of the life cycle.[3]

FUNGAL TAXONOMY

The phylogenetic relationships among fungi were unclear until recently. Classification was based on the sexual state morphology so fungi lacking an obvious sexual stage were assigned to an artificial, now-obsolete category, called the Deuteromycetes or Fungi Imperfecti. During the last 20 years, DNA sequencing has resolved 8 phyla of fungi, of which 3 are associated with the production of important aeroallergens (Figure 1).[4-7] As a result, the category Deuteromycetes has been discarded, and other fungus-like organisms such as slime molds (myxomycetes) and water molds (oomycetes) moved to other kingdoms.

Advances in classifying fungi have required name changes for some familiar taxa. For example, *Penicillium notatum* is now a defunct name and isolates formerly known by this name are now recognized as closely related species including *P. chrysogenum* and *P. rubens*. Because of regulatory constraints, many fungal allergen extracts have retained obsolete names.

Three phyla Zygomycota, Ascomycota, and Basidiomycota contain most genera of fungi that produce airborne fungal allergens (Figure 2).[4,8] A major benefit from this reorganization is that specific immunoglobulin E (IgE) levels in individuals

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Abbreviations used
IgE- Immunoglobulin E
IUIS- International Union of Immunological Societies

sensitized to fungi appear to closely match their phylogenetic relationships. This close relationship between molecular fungal systematics and IgE sensitization to fungal species provides a systematic way to look at cross-reactivity and permits representatives from each taxon to serve as a proxy for IgE to the group.[8,9]

The fungal genera described below each have species that produce substances that can adversely affect humans, causing allergic rhinitis and asthma among other disorders. A number of fungal-derived allergens have been identified from these species (Figure 3, Table E1, available in this article's Online Repository at www.jaci-inpractice.org) and are listed in the International Union of Immunological Societies (IUIS) nomenclature for allergens (see IUIS, Structural Database of Allergenic Proteins database, AllFam database, and Allergome database).[10] The noninfectious role of fungi is emphasized in this review.

Phylum Zygomycota

The phylum Zygomycota contains approximately 1000 species with 4 distinct evolutionary lines.[4] The largest and best studied is the subphylum Mucoromycotina that includes the agents of human mucormycosis (formerly zygomycosis).[11] Most species in the Mucoromycotina are saprobes commonly found in soil, compost, stored grain, fruit, vegetables, and dung. They form sporangia for asexual reproduction. Sporangiospores formed within a sporangium typically become airborne. This group is well known for producing abundant sporangia. Several species are used in food production and biotechnology, especially in cheese making and in the production of fermented foods.

Mucor. *Mucor racemosus* is a dimorphic, facultative anaerobic zygomycete, capable of vegetative growth in either a filamentous phase or as spherical yeasts. *M. racemosus* has been shown to induce sensitization in some individuals as demonstrated by skin-prick and provocation tests[9] as well as symptoms of asthma and rhinitis. In addition to homes, *Mucor* has been detected in schools,[12] hospitals,[13] and water-damaged buildings.[14]

Rhizopus. Species of *Rhizopus* are rapidly growing filamentous fungi that are characterized by the presence of rhizoids at the base of the sporangiophores. Colonies appear grayish because of abundant black sporangia.[15] The genus currently contains 10 species.[16] Several species are widely used in preparing fermented foods and in the pharmaceutical industry. Spores of *Rhizopus* tend to disperse in hot, dry weather.[17] *Rhizopus stolonifer*, commonly known as bread mold, is the most common species of *Rhizopus*. This species has been associated with allergy.[18] Allergens of both *R. stolonifer* (syn. *R. nigricans*) and *R. oryzae* have been characterized with both species showing multiple allergenic proteins.[18,19] In addition to IgE sensitization, reported health effects due to *Rhizopus* include rhinitis, asthma, fungal sinusitis, hypersensitivity pneumonitis, and infection.[20] Occupational exposure can occur among food handlers during the storage, transfer, and marketing of strawberries, peaches, cherries, corn, and peanuts.[21]

Phylum Ascomycota

The phylum Ascomycota is estimated to contain 65,000 species. Fungi in this phylum vary from single-celled yeasts to organisms with large fruiting bodies and grow in diverse habitats around the globe as saprobes, pathogens, and mutualistic symbionts. At least 30,000 species occur as the fungal symbionts of lichens.[22] Some cause devastating plant diseases including Dutch elm disease, chestnut blight, powdery mildews, *Alternaria* blight and leaf spot disease, and *Fusarium* head blight.[23] Many human pathogens are also in this phylum including *Aspergillus, Candida, Coccidioides, Histoplasma, Pneumocystis*, and *Trichophyton*.[24]

The defining characteristics are the meiotic ascospores, which are produced within asci (sing, ascus) and often occur in fruiting bodies. Some fruiting bodies are microscopic, whereas others such as morels and truffles are relatively large.[25] In many species, the ascospores are expelled from the asci after rain or during periods of high humidity. As a result, ascospores are often abundant in the air spora after rain. Conidia produced by many members of this phylum are dispersed by wind and often constitute a large component of the air spora; these include many well-known allergenic fungi.

Candida. *Candida albicans* is a yeast and one of the most prominent fungal members of the human microbiome.[26] It is also known to occur in soil and organic debris. *Candida* is known to cause clinically significant opportunistic infections such as thrush in infants, skin infections in diabetic patients, and sepsis in immunocompromised patients.[27,28] Sinonasal polyposis has been associated with hypersensitivity to *C. albicans*.[29] *Candida* is rarely found in surveys of airborne spores. The fungus has a major protein allergen (46 kD) and 15 minor allergens.[30]

Saccharomyces. *Saccharomyces cerevisiae*—baker's yeast or brewer's yeast—ferments sugars, releasing carbon dioxide (CO_2) and alcohol (ethanol) in the process.[31] *S. cerevisiae* exposure is associated with allergic rhinitis, asthma, and atopic dermatitis in sensitized individuals,[32,33] as well as hypersensitivity pneumonitis[34] and baker's asthma.[35] At least 9 allergens have been well characterized from *S. cerevisiae* (www.allergome.org).

Geotrichum. *Geotrichum* species, including *Geotrichum candidum*, can be found worldwide in soil, water, air, and sewage, as well as in plants, cereals, and dairy products. It is also part of the normal human microbiome, particularly in sputum and feces. *Geotrichum* is the causative agent of geotrichosis, an opportunistic infection facilitated by immunocompromised individuals and can present as bronchial, oral, vaginal, cutaneous, and alimentary infections.[36] Along with other molds, *Geotrichum* has been implicated in allergic symptoms in librarians.[37]

***Cladosporium* (obsolete *Fulvia* or *Hormodendrum*).** *Cladosporium* contains more than 750 species; some are the most common indoor and outdoor fungi.[38] Species of *Cladosporium* typically produce olive-green to brown or black colonies, and have pigmented conidia formed in simple or branched chains (Figure 2, *A*). Species of *Cladosporium* are commonly found on living and dead plant material. Many species are plant pathogens, whereas some parasitize fungi.[39]

Spores vary in size (5-40 × 3-13 μm), and they have a variety of shapes and cell numbers. The spores are wind-dispersed and are often extremely abundant in outdoor air. During summer, daily peaks may range from 2000 to 50,000 spores per cubic