Innate and adaptive immune responses to fungi in the airway

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Fungi are ubiquitous outdoors and indoors. Exposure, sensitization, or both to fungi are strongly associated with development of asthma and allergic airway diseases. Furthermore, global climate change will likely increase the prevalence of fungi and enhance their antigenicity. Major progress has been made during the past several years regarding our understanding of antifungal immunity. Fungi contain cell-wall molecules, such as β-glucan and chitin, and secrete biologically active proteases and glycosidases. Airway epithelial cells and innate immune cells, such as dendritic cells, are equipped with cell-surface molecules that react to these fungal products, resulting in production of cytokines and proinflammatory mediators. As a result, the adaptive arm of antifungal immunity, including T_H1-, T_H2-, and T_H17-type $CD4^+$ T cells, is established, reinforcing protection against fungal infection and causing detrimental immunopathology in certain subjects. We are only in the beginning stages of understanding the complex biology of fungi and detailed mechanisms of how they activate the immune response that can protect against or drive diseases in human subjects. Here we describe our current understanding with an emphasis on airway allergic immune responses. The gaps in our knowledge and desirable future directions are also discussed. (J Allergy Clin Immunol 2018;142:353-63.)

Key words: *Fungi, innate immunity, adaptive immunity, airway*

Abbreviations used

ABPM:	Allergic bronchopulmonary mycosis
AFRS:	Allergic fungal rhinosinusitis
AHR:	Airway hyperreactivity
CLR:	C-type lectin receptor
CRS:	Chronic rhinosinusitis
DC:	Dendritic cell
DC-SIGN:	Dendritic cell–specific intercellular adhesion molecule 3 grabbing nonintegrin
ILC2:	Group 2 innate lymphoid cell
MR:	Mannose receptor
PAR:	Protease-activated receptor
PRR:	Pattern recognition receptor
RAGE:	Receptor for advanced glycation end-products
SAFS:	Severe asthma with fungal sensitization
SPT:	Skin prick test
TLR:	Toll-like receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

Fungi are ubiquitous organisms that make their homes both indoors and outdoors.[1] Human subjects are constantly exposed to environmental fungal spores, often at levels 1000-fold greater than levels of grass and tree pollens.[2] Virtually everyone in the United States is exposed to *Alternaria* species antigens at home.[3] Molecular evidence suggests that animals and fungi have coevolved since diverging from plants more than 1 billion years ago.[4] Since then, the immune system has been crucial in establishing a close relationship between the host and fungi by "keeping the peace" at barrier surfaces.[5] In immunocompromised hosts fungi can colonize and infect the lungs and other organs, causing increases in morbidity and mortality. Alternatively, fungi and their products can cause exaggerated immune responses and pathologic changes in organs in certain subjects.

Although numerous environmental factors are associated with asthma and allergic diseases, allergen exposure likely plays a key role in triggering and exacerbating asthma and allergy symptoms.[6] In particular, exposure to airborne allergens derived from animals, arthropods, and molds is considered an important risk factor.[7-9] In human subjects an association between fungal exposure, sensitization, or both, in particular to *Alternaria* and *Aspergillus* species, and asthma is recognized in various countries.[2,10] For example, *Alternaria* species sensitivity is linked closely to the development of allergic asthma.[11-13] Severe asthma and life-threatening acute asthma exacerbations have also been associated with increased airborne exposure to *Alternaria* species.[14,15] Increased spore counts during crop harvest and after thunderstorms can contribute to asthma exacerbations as well.[16] Furthermore, water damage and other environmental effects lead to increased growth of fungi, such as *Stachybotrys chartarum*, compromising air quality and promoting airway inflammation.[17] In experimental animals the highly potent actions of *Alternaria* and *Aspergillus* species in stimulating innate and adaptive type 2 immunity have been recognized by a number of investigators.[18-25]

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Terms in boldface and italics are detailed in the glossary on page 354.

In the coming years, global climate change might increase the incidence of fungal sensitization and allergic airway diseases because increased fungal colonization of plants occurs at higher CO_2 levels.[26] Indeed, *Alternaria alternata* grown on plants in a high-CO_2 environment showed increased spore production and higher antigen content per spore.[27] Higher air temperature was correlated with more days that *Cladosporium* species spore counts exceeded the allergenic threshold.[28] The likelihood of an increasing effect of fungi on human health provides an incentive to learn more about the mechanisms of infection and immune response to fungi.

Alterations in the bacterial microbiome have a dramatic effect on host immunity and contribute to a number of immune-mediated diseases.[29] Fungi are naturally present in the mammalian intestine,[30] and recent sequencing technologies have expanded our understanding of fungal communities at barrier surfaces.[31] For example, intestinal fungal dysbiosis has been shown to influence gastrointestinal diseases, such as inflammatory bowel disease,[32] as well as allergic inflammation of the lungs.[33] Furthermore, a large number of fungal species have been found in sputum specimens from asthmatic patients.[34]

GLOSSARY

CHITIN: A long-chain polysaccharide similar to cellulose, chitin is a primary component of cell walls in fungi, exoskeletons of arthropods, insects, and the scales of fish and lissamphibians.

CpG SITES: Regions of DNA in which a cytosine nucleotide occurs next to a guanine nucleotide separated by only 1 phosphate. Methylation of the cytosine within a gene can turn the gene off.

CXCL10: A chemokine that elicits its effects by binding to the cell-surface chemokine receptor CXCR3, resulting in pleiotropic effects, including stimulation of monocyte, natural killer cell, and T-cell migration and modulation of adhesion molecule expression.

DUAL OXIDASE 1 (DUOX1): A member of the NADPH oxidase family. This protein generates hydrogen peroxide and thereby plays a role in the activity of thyroid peroxidase and lactoperoxidase and in lactoperoxidase-mediated antimicrobial defense at mucosal surfaces.

GALACTOMANNANS: Multifunctional macromolecular carbohydrates found in various albuminous or endospermic seeds.

GLUCAGON-LIKE PEPTIDE 1 (GLP-1): A 30-amino-acid peptide hormone produced in the intestinal epithelial endocrine L-cells by means of differential processing of proglucagon, the gene expressed in these cells.

β-GLUCAN: β-D-glucose polysaccharides found in the cell walls of bacteria, fungi, yeasts, algae, lichens, and plants, such as oats and barley.

GLYCOSIDASES: Also called glycoside hydrolases or glycosyl hydrolases, an enzyme that catalyzes the hydrolysis of glycosidic bonds in complex sugars, thus degrading oligosaccharides and glycoconjugates.

GM-CSF: Also known as colony-stimulating factor 2 (CSF2), a monomeric glycoprotein secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts, which functions as a cytokine. GM-CSF functions as a white blood cell growth factor and stimulates stem cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes.

IFN-γ: A type II interferon, IFN-γ is a cytokine that is required for innate and adaptive immunity against viral, bacterial, and protozoal infections. IFN-γ has been shown to be an important activator of macrophages and inducer of class II MHC molecule expression. IFN-γ is produced predominantly by natural killer (NK) and NKT cells as part of the innate immune response and by CD4 T_H1 and CD8 cytotoxic T lymphocyte effector T cells once antigen-specific immunity develops.

IL-12: A cytokine produced by dendritic cells, macrophages, neutrophils, and human B-lymphoblastoid cells (NC-37) in response to antigenic stimulation that has been shown to be required for differentiation of naive T cells into T_H1 cells.

IL-25: A proinflammatory cytokine that shares sequence similarity with IL-17 and has been shown to favor the T_H2-type immune response. IL-25 can induce NF-κB activation and stimulate IL-8 production.

IL-33: A member of the IL-1 family of cytokines that potently drives production of T_H2-associated cytokines.

MANNOPROTEINS: Antigenic proteins found in the yeast cell wall with many mannose groups attached.

OROSOMUCOID-LIKE 3 (ORMDL3): A gene on chromosome 17q21 highly linked to asthma that has been shown to upregulate airway smooth muscle proliferation, contraction, and Ca^{2+} oscillations in asthmatic patients.

REACTIVE OXYGEN SPECIES (ROS): A natural byproduct of oxygen metabolism that has a critical role in cell signaling and homeostasis. However, during times of environmental stress, ROS levels can increase significantly and cause damage to cell structures, which is known as oxidative stress.

THYMIC STROMAL LYMPHOPOIETIN (TSLP): An IL-2 family cytokine that stimulates maturation of T cells through activation of antigen-presenting cells, such as dendritic cells and macrophages. This cytokine is implicated in the T_H2-type immune response.

TLR1/TLR2 HETERODIMER: A complex in which TLR1 recognizes peptidoglycan and triacyl lipoproteins in combination with TLR2.

TLR2: A membrane surface receptor that recognizes many bacterial, fungal, viral, and certain endogenous substances and plays a fundamental role in pathogen recognition and the activation of innate immunity.

TLR3: A membrane surface receptor that recognizes double-stranded RNA associated with viral infection and induces activation of interferon regulatory factor 3 (IRF3), unlike all other Toll-like receptors that activate NF-κB.

TLR4: A transmembrane protein that belongs to the pattern recognition receptor family. Its activation leads to activation of the innate immune system through the intracellular signaling pathway NF-κB and inflammatory cytokine production. TLR4 recognizes LPS, which is a component present in many gram-negative bacteria and select gram-positive bacteria. Its ligands also include several viral proteins, polysaccharide, and a variety of endogenous proteins.

TLR9: An important receptor expressed in dendritic cells, macrophages, natural killer cells, and other antigen-presenting cells that preferentially binds bacterial and viral DNA and triggers signaling cascades that lead to a proinflammatory cytokine response.

TOLL LIKE RECEPTORS (TLRS): Members of the TLR family that play a fundamental role in pathogen recognition and activation of innate immunity.

UNFOLDED PROTEIN RESPONSE (UPR): A signaling network activated by stresses that compromise the endoplasmic reticulum (ER), which impair maturation, resulting in accumulation of misfolded proteins to alleviate this stress and restore ER homeostasis and promoting cell survival and adaptation. However, under irresolvable ER stress conditions, the UPR promotes apoptosis.

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