

Pathogenesis of *Aspergillus fumigatus* in Invasive Aspergillosis

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INTRODUCTION

Aspergillus species are ubiquitous, saprophytic fungi that play a significant role in global carbon and nitrogen recycling. Although their primary ecological niche is soil or decaying vegetation, aspergilli produce small, hydrophobic conidia that disperse easily into the air and can survive a broad range of environmental conditions. The genus *Aspergillus*, which includes almost 200 species, has a tremendous impact on public health both beneficially as the workhorse of industrial applications and negatively as plant and human pathogens (71). Several *Aspergillus* species are utilized for their rich enzymatic profile in the industrial production of foods and pharmaceuticals. For example, *Aspergillus niger* is used for the industrial production of citric acid, amylases, pectinases, phytases, and proteases; *A. terreus* is used for the cholesterol-lowering drug lovastatin; and *A. oryzae* is used for the fermentation of soybeans and rice into soy sauce and sake, respectively. Aspergilli also have a less reputable side in the agricultural industry.

Aspergillus section *Flavi*, particularly *A. flavus* and *A. parasiticus*, can contaminate several common crops with aflatoxin, a highly toxic carcinogen with immunosuppressive properties (228, 230). The consumption of contaminated crops can cause serious illness or death and is a common problem in developing countries.

The Human Pathogen *A. fumigatus*

Among the human pathogenic species of *Aspergillus*, *A. fumigatus* is the primary causative agent of human infections, followed by *A. flavus*, *A. terreus*, *A. niger*, and the model organism, *A. nidulans* (54, 135). Aspergilli cause a wide range of human ailments depending on the immune status of the host (54, 107). In individuals with altered lung function such as asthma and cystic fibrosis patients, aspergilli can cause allergic bronchopulmonary aspergillosis, a hypersensitive response to fungal components. Noninvasive aspergillomas may form following repeated exposure to conidia and target preexisting lung cavities such as the healed lesions in tuberculosis patients. Invasive aspergillosis (IA) is perhaps the most devastating of *Aspergillus*-related diseases, targeting severely immunocompromised patients. Those most at risk for this life-threatening disease are individuals with hematological malignancies such

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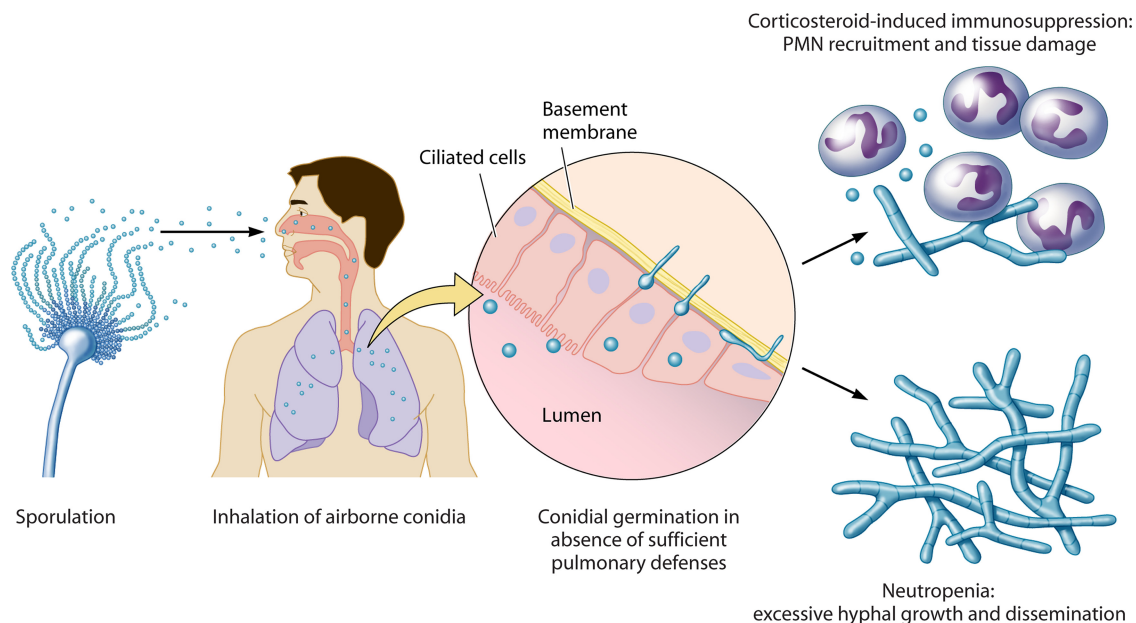


FIG. 1. Infectious life cycle of *A. fumigatus*. *Aspergillus* is ubiquitous in the environment, and asexual reproduction leads to the production of airborne conidia. Inhalation by specific immunosuppressed patient groups results in conidium establishment in the lung, germination, and either PMN-mediated fungal control with significant inflammation (corticosteroid therapy) or uncontrolled hyphal growth with a lack of PMN infiltrates and, in severe cases, dissemination (neutropenia).

as leukemia; solid-organ and hematopoietic stem cell transplant patients; patients on prolonged corticosteroid therapy, which is commonly utilized for the prevention and/or treatment of graft-versus-host disease in transplant patients; individuals with genetic immunodeficiencies such as chronic granulomatous disease (CGD); and individuals infected with human immunodeficiency virus (54, 97, 126, 133, 148, 162, 227). Mortality rates range from 40% to 90% in high-risk populations and are dependent on factors such as host immune status, the site of infection, and the treatment regimen applied (114). The severity and increased incidence of IA necessitate a better understanding of the interplay between host and fungus that contributes to *A. fumigatus* pathogenesis (130). Pathogenesis and virulence are terms used here in the context of altered host immune function, as this organism is inherently an opportunistic pathogen, and disease pathology and progression are the result of both fungal growth and the host response. In this review, we will thus discuss the pathogenic potential of *A. fumigatus* as a progression of the infectious life cycle within the context of these immunodeficiencies.

Invasive Aspergillosis

Infectious life cycle. Aspergilli are predominantly saprophytes, growing on dead or decaying matter in the environment. The infectious life cycle of *Aspergillus* begins with the production of conidia (asexual spores) that are easily dispersed into the air, ensuring ubiquity in both indoor and outdoor environments (Fig. 1) (65, 137). The primary route of human infection is via the inhalation of these airborne conidia, followed by conidial deposition in the bronchioles or alveolar spaces. In healthy individuals, conidia that are not removed by mucociliary clearance encounter epithelial cells or alveolar

macrophages, the primary resident phagocytes of the lung. Alveolar macrophages are primarily responsible for the phagocytosis and killing of *Aspergillus* conidia as well as the initiation of a proinflammatory response that recruits neutrophils (one type of polymorphonuclear cell [PMN]) to the site of infection. Conidia that evade macrophage killing and germinate become the target of infiltrating neutrophils that are able to destroy hyphae. The risk of developing IA results primarily from a dysfunction in these host defenses in combination with fungal attributes that permit *A. fumigatus* survival and growth in this pulmonary environment (176). Although other host responses have been associated with disease resistance, for this review, we will focus on fungal interactions with the primary innate components that are most important for fungal defense.

Risk factors and pathology. The primary host immunodeficiencies that are responsible for the increased risk of IA are neutropenia and corticosteroid-induced immunosuppression, and the pathological consequences of IA under these immunosuppressive conditions differ, as described previously for patients and animal models (9, 17, 53, 192). Prolonged neutropenia is classically defined as the most dominant risk factor for IA and is often the result of highly cytotoxic therapies such as cyclophosphamide, which is used for transplant patients or those with hematological diseases. Cyclophosphamide, a DNA-alkylating agent, binds to DNA and interferes with cellular replication, depleting circulating white blood cells including neutrophils. In neutropenic patients and animal models of chemotherapy-induced neutropenia, IA is characterized by thrombosis and hemorrhage from rapid and extensive hyphal growth (41, 192). The lack of inflammatory infiltrates, despite the production of tumor necrosis factor alpha (TNF- α), results

