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The biology of pulmonary aspergillus infections

Adilia Warris*

University of Aberdeen, School of Medicine and Dentistry, Division of Applied Medicine, Institute of Medical Sciences, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK

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Summary Pulmonary aspergillus infections are mainly caused by *Aspergillus fumigatus* and can be classified based on clinical syndromes into saphrophytic infections, allergic disease and invasive disease. Invasive pulmonary aspergillosis, occurring in immunocompromised patients, reflects the most serious disease with a high case-fatality rate. Patients with cystic fibrosis and severe asthma might develop allergic bronchopulmonary aspergillosis, while saphrophytic infections are observed in patients with lung cavities mainly due to tuberculosis. Histopathologically, a differentiation can be made into angio-invasive and airway-invasive disease. If the host response is too weak or too strong, *Aspergillus* species are able to cause disease characterized either by damage from the fungus itself or through an exaggerated inflammatory response of the host, in both situations leading to overt disease associated with specific clinical signs and symptoms. The unraveling of the specific host — *Aspergillus* interaction has not been performed to a great extent and needs attention to improve the management of those clinical syndromes.

Introduction

The first reports of human *Aspergillus* infections were in 1842, at which time Bennet described the first case of aspergilloma complicating tuberculosis.[1] In the mid-20th century Cawley described the first case of invasive aspergillosis (IA) in a patient with chronic granulomatous disease,[2] followed several years later by a description of a neutropenic cancer patient suffering from pulmonary aspergillosis by Rankin.[3] These historic cases showed the different disease entities caused by *Aspergillus* species in particular hosts.

Aspergillus is a ubiquitous mold and can be found all around the world. Its hydrophobic conidia are easily dispersed into the air and their small diameter, of 2—4 microns, enables penetration deep into the respiratory tract upon inhalation. As a consequence, >90% of all invasive infections are located in the lungs. Depending on the host immune status, germination of the conidia might occur

* Tel.: +44 (0)1224437596; fax: +44 (0)1224437506.
E-mail address: a.warris@abdn.ac.uk

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followed by hyphal growth, and disease will develop. Of the 185 recognized species of *Aspergillus*, 20 are known to cause infections in humans. *Aspergillus fumigatus* accounts for about 65% of all invasive infections in humans and is the mostly encountered species in pulmonary infections. *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus* and *Aspergillus nidulans* are less frequently causes of invasive and pulmonary infections.[4–7]

Host-fungus interaction

Aspergillus species cause a wide range of disease as a function of the host response. The interplay between host and pathogen is depicted by the 'damage-response' framework of microbial pathogenesis by Casadevall and Pirofsky.[8] This framework shows that microbial pathogenesis is the outcome of the interaction between host and microorganism, that the pathological outcome is determined by the damage to the host, and that this damage can be the result of the microbial factors and/or the host response. For each microorganism, a specific curve can be drawn based on the basic parabolic curve of the 'damage-response' framework. The curve reflects the host damage as a result of the interaction with the extremes of the host response (from weak to strong).

If the host response is too weak or too strong, *Aspergillus* species are able to cause disease characterized by either damage by the fungus itself or by an exaggerated inflammatory response of the host, in both situations leading to overt disease. Phenotypically, clearly different disease entities are observed. Of note, *Aspergillus* species do not cause invasive disease in immunocompetent individuals.

The first line of host defense is directed against conidia, the infective form of the filamentous fungi, and consists of macrophages. The macrophages kill germinating spores intracellularly by mainly non-oxidative processes.[9] The second line of defense against mold infections is superoxide production by neutrophils, a powerful mechanism to kill the invasive hyphal structures of *Aspergillus* spp.[10] Consequently, when these cells are quantitatively or qualitatively impaired, the host becomes susceptible to the development of invasive pulmonary aspergillosis (IPA). Therefore, patients with neutropenia or dysfunction of neutrophils and/or macrophages, such as patients with hematologic malignancies, HSCT recipients, and patients with inherited immunodeficiencies, have an increased risk of developing IPA. Recognition is the first step in the innate host defense and two families of pattern recognition receptors (PRRs) have been identified to play an important role in the recognition of *A. fumigatus*. The C-type lectin receptor, Dectin-1, has been shown to be an important PRR in the interaction with fungi by recognizing β-glucan, and is involved in the phagocytosis of *A. fumigatus*.[11] In addition, it stimulates ROS production and release of pro-inflammatory cytokines including IL-17. Recognition of *A. fumigatus* by the Toll-like receptors (TLRs) 2 and 4 will lead to the release of inflammatory cytokines. Studies performed with knock-out mice, in which one of those PRRs were absent, have shown the importance of those PRRs in experimental IA [reviewed by Park & Mehrad,[12]]. Furthermore, genetic polymorphisms in the genes encoding Dectin-1, TLR4 or one of the TLRs forming heterodimers with TLR2 in humans, are an independent risk factor in addition to the underlying immunocompromised state in individual patients.[13–15] It is important to realize that the various morphologies of *A. fumigatus*, resting conidia, swollen conidia and hyphae, will induce different interactions with the host immune cells and might use its transition to hyphae to escape from the immune system. In general, the induction of a Th1 type response, characterized by IFN-gamma, TNF-alpha and Interleukin (IL)-12 production, is protective against the development of IA. In contrast, defense against IA is impaired by IL-4 and IL-10 [reviewed by Park & Mehrad,[12]]. A Th17 response characterized by the production of IL-17 and IL-22 can either be protective or detrimental depending on the underlying condition of the host.[16]

Classification of pulmonary aspergillosis

Invasive pulmonary aspergillosis can be classified histopathologically in angio-invasive and airway-invasive disease. Allergic bronchopulmonary aspergillosis (ABPA) differs from airway-invasive disease being a hypersensitivity reaction in which the conidia remain in the airway lumen. A classification based on clinical syndromes differentiates pulmonary aspergillosis in 3 disease entities; saphrophytic infections, allergic disease and invasive disease.[17–19] Saphrophytic infections are those that do not provoke a relevant immune response, as seen in colonization and aspergilloma. Extrinsic allergic alveolitis, ABPA and allergic asthma are the main clinical syndromes of an allergic signature. Invasive aspergillosis, occurring in immunocompromised patients, reflects the most serious disease with a high case-fatality rate, and can be further categorized into the following disease entities; acute angio-invasive aspergillosis as seen in mainly neutropenic patients and post hematopoietic stem cell transplant patients, acute bronchopneumonia in the mild to moderately immunocompromised patients, chronic necrotizing pulmonary aspergillosis as a complication of chronic obstructive pulmonary diseases and prolonged corticosteroid therapy and tracheobronchitis in particular in lung transplant patients. The classification of the clinical syndromes is useful for the recognition and early diagnosis of pulmonary aspergillosis. Furthermore, the usefulness of existing diagnostic modalities vary among these clinical syndromes and treatment may not be uniform.

Invasive pulmonary aspergillosis

The neutropenic host

Prolonged and profound neutropenia (absolute neutrophil count of $\leq$500/uL for $\geq$10 days) is the main risk factor for the development of IPA in children (and adults) with cancer and those receiving an HSCT. Incidence is highest in patients with AML, recurrent leukemia and allogeneic stem cell transplants, being upto 10%. Patients with ALL (although varies depending on the treatment protocol), non-Hodgkin lymphoma and autologous HSCT are considered to be at lower risk for IPA with a reported incidence $<$5%.[20–23]