Advances Against Aspergillosis: Biology, Host response, Diagnosis and Treatment

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The genus Aspergillus is comprised of over 260 species, representing a group of saprophytic filamentous fungi that occupy a variety of environmental niches worldwide [1]. The conidia from these organisms are inhaled on a daily basis, which may result in allergic and/or infectious complications that can be life-threatening in vulnerable individuals. Aspergillosis is the name given to the spectrum of diseases caused by approximately 20 species within this genus [2, 3]. Research on aspergillosis has shown a progressive expansion over the past three decades, largely due to the rise in the number of immunocompromised individuals who are at risk for the infection. This has fueled the creation of an international meeting, Advances Against Aspergillosis, the purpose of which

is to bring together basic and translational scientists, along with clinicians and clinical investigators to discuss state-of-the-art advances in *Aspergillus* biology, immunopathogenesis, antifungal host defenses, and the challenges confronting the diagnosis and treatment of aspergillosis. This special issue of *Mycopathologia* showcases a series of invited papers that are based on presentations given at the 6th meeting of Advances Against Aspergillosis (AAA6), which was held in Madrid, Spain, in February 2014.

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Fungal Stress Response

We do not yet fully appreciate why A. fumigatus is the predominant Aspergillus species associated with human infection. However, accumulating evidence strongly implicates adaptive stress responses [4]. Several articles in this issue highlight advances in the understanding of stress response pathways that support the ability of A. fumigatus to flourish in the host environment. The Ras signaling pathway provides a link between environmental cues and changes in cell physiology in a variety of species [5]. The manuscript by Norton and Fortwendel examines how post-translational modifications influence spatiotemporal regulation of Ras proteins in A. fumigatus and reveals the importance of this pathway to polarized invasive growth [6]. During infection, A. fumigatus must also adapt to the oxygen-limited environment of host tissues [7]. Losada et al. [8] report the

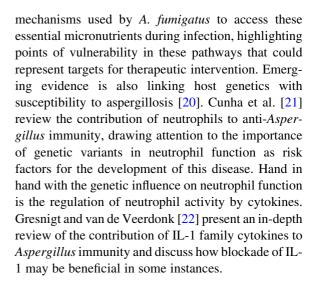


results of a study to determine the genome-wide expression profile of A. fumigatus exposed to a hypoxic environment. Using RNA-seq technology, the authors expand previous microarray data on the hypoxia transcriptome and provide intriguing evidence for the existence of a novel hypoxia-regulated non-coding RNA [8]. Another central mediator of eukaryotic stress responses is the calcium/calmodulin-activated protein phosphatase calcineurin, which controls a pathway that regulates drug tolerance, morphogenesis, and virulence in a variety of pathogenic fungi, including A. fumigatus [9]. Juvvadi et al. [10] present an overview of this pathway in A. fumigatus, integrating structural organization of the calcineurin complex with functions in germination, hyphal growth, cell wall homeostasis, and virulence. Sexual reproduction in pathogenic fungi is thought to enhance many of these adaptive stress responses by promoting genetic variation [11]. Varga et al. [12] review recent advances in delineating the extent and significance of sexual reproduction in clinically relevant Aspergillus species, including the potential for recombination events that could impact the evolution of antifungal drug resistance or the transfer of genes involved in mycotoxin production or virulence.

Pathogenesis and Host Response

The complexity of the pathogenesis of Aspergillus is illustrated by the plethora of virulence factors and fungus-host interactions that influence disease outcome [13, 14]. Some virulence factors are important for the organism to evade the host's immune response. For example, the manuscript by Chotirmall et al. [15] provides an update on the immunoevasive properties of A. fumigatus, including new data on the mechanism by which gliotoxin impacts airway colonization in the context of cystic fibrosis. The cell wall of A. fumigatus is the major interface between the fungus and the host immune system [16]. The manuscript by Beauvais reviews the structural organization of the A. fumigatus cell wall and highlights changes in cell wall composition during the transition from conidia to hyphae that are responsible for activating host immune cells during infection [17].

How then does the host protect itself from infection? One established mechanism involves sequestration of metal ions that are essential for microbial growth [18]. Amich and Calera [19] discuss the



Diagnosis and Treatment

Reliable early diagnosis of aspergillosis continues to be a challenge for the clinician because of nonspecific signs of infection, as well as limitations in the sensitivity or specificity of current diagnostic methods [23]. Guinea and Bouza [24] address these current issues and present evidence to support improved diagnosis with newer technologies, such as lateral flow techniques, and DNA technology. Sanguinetti and Posteraro [25] highlight the advantages and limitations of the emerging technology of MALDI-TOF mass spectrometry for the identification and antifungal susceptibility testing of pathogenic aspergilli in the clinical mycology laboratory. The discovery of cryptic species of Aspergillus [26], and the potential for differing susceptibilities to antifungal compounds, has brought to the forefront the importance of accurate species identification. Alastruey-Izquierdo et al. [27] review the clinical relevance of these cryptic species, emphasizing their epidemiology and antifungal drug susceptibility profiles. The importance of accurate susceptibility testing as a way to guide patient care is further illustrated in the review by Howard [28], which explores the increasing frequency of multi-resistant cryptic species as etiologic agents of aspergillosis. Nedel and Pasqualotto [29] further highlight the complexities of identification and the importance of the susceptibility of cryptic species of Aspergillus to antifungal drugs and emphasize the paucity of organized clinical data on how to manage these unusual, yet emerging causes of aspergillosis.



The impact of chronic aspergillosis syndromes in various parts of the world was a theme of emphasis at AAA6. Agarwal [30] discusses the significant burden of allergic bronchopulmonary aspergillosis (ABPA) in India and provides a practical diagnostic and treatment algorithm. In a thoughtful review by Pashley, the role of *Aspergillus* sensitization and the methods of *Aspergillus* detection are discussed in the context of patients with asthma, cystic fibrosis, or chronic obstructive lung disease [31]. The difficulties associated with the chronic treatment of patients with aspergillosis are illustrated by the paper of Davoudi et al. [32] where they present a case of a long-term survivor of a mixed infection with *Aspergillus* and Mucorales requiring lifelong antifungal therapy.

Aspergillus, once considered a relatively minor etiologic agent, is now recognized as a major cause of fungal infection. The papers in this issue highlight the culmination of excellent studies into the basic biology of A. fumigatus and the problems confronting the diagnosis and treatment of aspergillosis. These advances are a cause for optimism. Since the technologies for addressing complex questions in biological research continue to evolve at a rapid pace, their impact on the field of aspergillosis is expected to improve patient care through the acceleration of new drug target discovery, the development of new modalities of diagnosis, and an increased understanding of the pathogenesis of A. fumigatus. The next few years are likely to see major new advances in this field, and we look forward to hearing about these discoveries at the next Advances Against Aspergillosis meeting.

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Conflict of interest D. S. A., D. P. K, and K. V. C. were members of the scientific planning committee of the 6th Advances Against Aspergillosis that was held in Madrid, Spain, February 27 to March 1, 2014.

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