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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 mechanisms used by *A. fumigatus* to access these essential micronutrients during infection, highlighting points of vulnerability in these pathways that could represent targets for therapeutic intervention. Emerging evidence is also linking host genetics with susceptibility to aspergillosis [20]. Cunha et al. [21] review the contribution of neutrophils to anti-*Aspergillus* immunity, drawing attention to the importance of genetic variants in neutrophil function as risk factors for the development of this disease. Hand in hand with the genetic influence on neutrophil function is the regulation of neutrophil activity by cytokines. Gresnigt and van de Veerdonk [22] present an in-depth review of the contribution of IL-1 family cytokines to *Aspergillus* immunity and discuss how blockade of IL-1 may be beneficial in some instances.

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.

References

1. Samson RA, Varga J. What is a species in *Aspergillus*? Med Mycol. 2009;47(Suppl 1):S13–20. doi:10.1080/13693780802354011.
2. Latge JP, Steinbach WJ. *Aspergillus fumigatus* and aspergillosis. Washington, D.C.: Am Soc Microbiol; 2008.
3. Sherif R, Segal BH. Pulmonary aspergillosis: clinical presentation, diagnostic tests, management and complications. Curr Opin Pulm Med. 2010;16(3):242–50. doi:10.1097/MCP.0b013e328337d6de.
4. Hartmann T, Sasse C, Schedler A, Hasenberg M, Gunzer M, Krappmann S. Shaping the fungal adaptome–stress responses of *Aspergillus fumigatus*. Int J Med Microbiol. 2011;301(5):408–16. doi:10.1016/j.ijmm.2011.04.008.
5. Fortwendel JR. Ras-mediated signal transduction and virulence in human pathogenic fungi. Fungal Genet Biol. 2012;2(1):105. doi:10.4172/2165-8056.1000105.
6. Norton TS, Fortwendel JR. Control of Ras-mediated signaling in *Aspergillus fumigatus*. Mycopathologia. 2014;. doi:10.1007/s11046-014-9765-1.
7. Grahl N, Shepardson KM, Chung D, Cramer RA. Hypoxia and fungal pathogenesis: to air or not to air? Eukaryot Cell. 2012;11(5):560–70. doi:10.1128/EC.00031-12.
8. Losada L, Barker BM, Pakala S, Pakala S, Joardar V, Zafar N, et al. Large-scale transcriptional response to hypoxia in *Aspergillus fumigatus* observed using RNAseq identifies a novel hypoxia regulated ncRNA. Mycopathologia. 2014;. doi:10.1007/s11046-014-9779-8.
9. Bastidas RJ, Reedy JL, Morales-Johansson H, Heitman J, Cardenas ME. Signaling cascades as drug targets in model and pathogenic fungi. Curr Opin Investig Drugs. 2008;9(8):856–64.
10. Juvvadi PR, Lamoth F, Steinbach WJ. Calcineurin-mediated regulation of hyphal growth, septation, and virulence in *Aspergillus fumigatus*. Mycopathologia. 2014;. doi:10.1007/s11046-014-9794-9.
11. Ene IV, Bennett RJ. The cryptic sexual strategies of human fungal pathogens. Nat Rev Microbiol. 2014;12(4):239–51. doi:10.1038/nrmicro3236.
12. Varga J, Szigeti G, Baranyi N, Kocsube S, O'Gorman CM, Dyer PS. *Aspergillus*: sex and recombination. Mycopathologia. 2014;. doi:10.1007/s11046-014-9795-8.
13. Hogan LH, Klein BS, Levitz SM. Virulence factors of medically important fungi. Clin Microbiol Rev. 1996;9(4):469–88.
14. Latge JP. The pathobiology of *Aspergillus fumigatus*. Trends Microbiol. 2001;9(8):382–9.
15. Chotirmall SH, Mirkovic B, Lavelle GM, McElvaney NG. Immunoevasive *Aspergillus* virulence factors. Mycopathologia. 2014;. doi:10.1007/s11046-014-9768-y.
16. Gastebois A, Clavaud C, Aimanianda V, Latge JP. *Aspergillus fumigatus*: cell wall polysaccharides, their biosynthesis and organization. Future Microbiol. 2009;4(5):583–95. doi:10.2217/fmb.09.29.
17. Beauvais A, Fontaine T, Aimanianda V, Latge JP. *Aspergillus* cell wall and biofilm. Mycopathologia. 2014;. doi:10.1007/s11046-014-9766-0.
18. Staats CC, Kmetzsch L, Schrank A, Vainstein MH. Fungal zinc metabolism and its connections to virulence. Front Cell Infect Microbiol. 2013;3:65. doi:10.3389/fcimb.2013.00065.
19. Amich J, Calera JA. Zinc acquisition: a key aspect in *Aspergillus fumigatus* virulence. Mycopathologia. 2014;. doi:10.1007/s11046-014-9764-2.
20. Zaas AK. Host genetics affect susceptibility to invasive aspergillosis. Med Mycol. 2006;44(suppl 1):S55–60.

21. Cunha C, Kurzai O, Loffler J, Aversa F, Romani L, Carvalho A. Neutrophil responses to aspergillosis: new roles for old players. Mycopathologia. 2014;. doi:10.1007/s11046-014-9796-7.
22. Gresnigt MS, van de Veerdonk FL. The role of interleukin-1 family members in the host defence against *Aspergillus fumigatus*. Mycopathologia. 2014;. doi:10.1007/s11046-014-9776-y.
23. Arvanitis M, Anagnostou T, Fuchs BB, Caliendo AM, Mylonakis E. Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev. 2014;27(3):490–526. doi:10.1128/CMR.00091-13.
24. Guinea J, Bouza E. Current challenges in the microbiological diagnosis of invasive aspergillosis. Mycopathologia. 2014;. doi:10.1007/s11046-014-9763-3.
25. Sanguinetti M, Posteraro B. MALDI-TOF Mass spectrometry: any use for aspergilli? Mycopathologia. 2014;. doi:10.1007/s11046-014-9757-1.
26. Balajee SA, Gribskov JL, Hanley E, Nickle D, Marr KA. *Aspergillus lentulus* sp. nov., a new sibling species of *A. fumigatus*. Eukaryot Cell. 2005;4(3):625–32. doi:10.1128/EC.4.3.625-632.2005.
27. Alastruey-Izquierdo A, Alcazar-Fuoli L, Cuenca-Estrella M. Antifungal susceptibility profile of cryptic species of *Aspergillus*. Mycopathologia. 2014;. doi:10.1007/s11046-014-9775-z.
28. Howard SJ. Multi-resistant aspergillosis due to cryptic species. Mycopathologia. 2014;. doi:10.1007/s11046-014-9774-0.
29. Nedel WL, Pasqualotto AC. Treatment of infections by cryptic *Aspergillus* species. Mycopathologia. 2014;. doi:10.1007/s11046-014-9811-z.
30. Agarwal R. Burden and distinctive character of allergic bronchopulmonary aspergillosis in India. Mycopathologia. 2014;. doi:10.1007/s11046-014-9767-z.
31. Pashley CH. Fungal culture and sensitisation in asthma, cystic fibrosis and chronic obstructive pulmonary disorder: what does it tell us? Mycopathologia. 2014;. doi:10.1007/s11046-014-9804-y.
32. Davoudi S, Anderlini P, Fuller GN, Kontoyiannis DP. A long-term survivor of disseminated *Aspergillus* and Mucorales infection: an instructive case. Mycopathologia. 2014;. doi:10.1007/s11046-014-9785-x.