Chemical Engineering Colloquium

December 1, 2021

12–12:50 p.m. | Goddard Hall, Room 227

Old Tricks for New Dogs: Genome-Wide Association to Uncover the Genetics of Pathogenicity-Associated Traits in Aspergillus Fumigatus

Dr. John Gibbons

Assistant Professor, Food Science, College of Natural Sciences

University of Massachusetts Amherst

Aspergillus fumigatus is a fungal pathogen responsible for the highest number of deaths and for the second highest number of infections of any fungal species. Estimates suggest that A. fumigatus infections result in ~100,000 annual deaths worldwide. A. fumigatus has evolved a collection of immune evasion and immune adaptation strategies that occur at the conidial and hyphal developmental stages. These strategies allow A. fumigatus to evade or survive macrophage phagocytosis, inhibit neutrophil and macrophage function, adhere to and acquire nutrients from host tissue, and resist antifungal drug treatment, hypoxic microenvironments, oxidative stress, and high temperature stress. These diverse immune evasion and immune adaptation strategies underscore the complex polygenic nature of A. fumigatus pathogenicity. To date, the vast majority of genes linked to functional roles in A. fumigatus pathogenicity and virulence have resulted from overexpression/ knockout mutants of candidate genes. However, the candidate gene approach is inherently biased towards genes with predicted functions, and can overlook genes that contribute to phenotypes but have no obvious functional connection. For this reason, our lab has developed a system to rapidly identify genes and genetic variants associated with A. fumigatus phenotypes using genome-wide association analysis. Using a collection of ~300 A. fumigatus isolates with fully sequenced genomes, we have identified genetic variants associated with (i) sensitivity to the antifungal drug triazole, (ii) the caspofungin paradoxical effect (the behavior of some strains to increase growth rate in the presence of high concentrations of the antifungal drug caspofungin), and (iii) growth rate at the human internal body temperature. In each study, we have validated the function of candidate genes by generating null mutants using a CRISPR/Cas9 approach. Our approach has the potential to discover novel genes and genetic variants that are associated with pathogenicity-associated traits, and has potential application for the development of new drug targets.

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