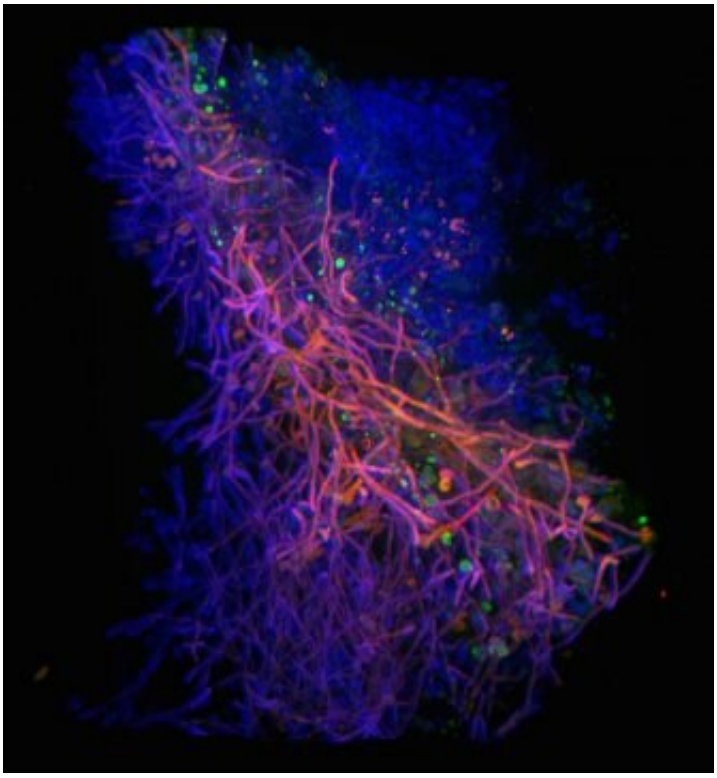
Study reveals how fungal biofilm structure impacts lung disease

September 23 2019, by Timothy Dean



Aspergillus fumigatusin vivo fungal lesion during murine infection. Aspergillus fumigatus (red) grows in compact fungal lesions or biofilms within airways during invasive pulmonary aspergillosis resulting in lesions that have little available oxygen. The host cells (blue) attack the invading fungal mass, but different strains of A. fumigatus differentially grow within the low-oxygen environment of the infected airways and ultimately alter the interaction with host cells and the progression of disease. Credit: Caitlin Kowalski and Joshua Kerkaert

Findings from an innovative new study led by researchers at Dartmouth's Geisel School of Medicine and published this week in *Nature Microbiology* reveal that the way in which human fungal pathogens form colonies can significantly impact their ability to cause disease.

Highly diverse and adaptable, these colonies, known as biofilms, allow invasive fungal pathogens such as Aspergillus fumigatus to grow and thrive, infecting the lungs of patients, even under demanding environmental circumstances.

"It's a type of infection that most people don't have to be concerned about, since our immune systems have evolved to allow us to be resistant to fungi in the environment," explains Robert Cramer, Ph.D., a professor of microbiology and immunology at Geisel and senior author on the study.

But for patients with diseases like cancer, who are on drugs or therapies that suppress their immune systems, the infections can be lethal. "Since fungi are some of our closest relatives genetically, the drugs we have for treatment are limited and very toxic," says Cramer. "The big challenge we face is trying to develop new therapies that target these infections in critically ill patients, that don't make them sicker but also can prevent these organisms from causing morbidity and mortality."

To this end, in the study the researchers sought to assess how an important environmental stressor impacts disease progression in invasive aspergillosis, a disease caused by the mold Aspergillus fumigatus, and to identify fungal genetic factors involved in this process.

"Our project was based on some previous work Robb had done, which showed that within the lesions in the lung where the fungus is growing there's actually very little oxygen available," says Caitlin Kowalski, Guarini '20, a Ph.D. candidate in the Cramer Lab at Geisel and first

author on the study. "This puts a lot of stress on the fungus, but some strains are able to grow in a hypoxic (oxygen deficient) environment better than others."

Collaborating with Jason Stajich, Ph.D., a genomics expert at the University of California-Riverside, the team used an experimental evolution approach, exposing the pathogen to low oxygen conditions to identify genes and mechanisms involved in low oxygen fitness. They then screened for and identified a specific mutation that caused key changes in gene function.

"Not only did the strain that we isolated end up growing better in low oxygen, it was better able to cause disease in a murine model of infection where we know (from previous studies) that the lungs become hypoxic," says Kowalski. "In the process we were able to ascribe function to a gene that was previously unknown to have any role in Aspergillus physiology and virulence."

Working with Carey Nadell, Ph.D., an assistant professor of biological sciences at Dartmouth College, Kowalski and her colleagues were also able to use advanced microscopy techniques that revealed differences in the strain's filamentous architecture.

"I think that's the other big takeaway from Caitlin's project, in addition to the novel gene finding," says Cramer. "That is, that the appearance of the organism can actually tell us something about how it's going to behave in the lung—in this case, how this particular morphology gives the organism the ability to be more virulent and to cause more host damage."

Understanding these characteristics is an important step in developing more effective therapies for patients. "For these strains that look different and cause more inflammation, we may need to incorporate

more host-targeted therapeutics—and our field is moving in this direction—to dampen down the immune response and allow antifungals more time to actually work," he explains.

Cramer credits the Burroughs Wellcome Fund, of which he is an Investigator in the Pathogenesis of Infectious Diseases, as a key source of support for the research.

"The fellowship allows me to take some risks with certain projects, where you're sort of in unchartered territory and you don't know what you're going to find," he says. "It paid off very handsomely in that it allowed us to generate some valuable data, which is already helping us secure other grant funding, such as from the NIH, that will help support Caitlin's career and our overall efforts to reduce the disease burden caused by this organism."

More information: Caitlin H. Kowalski et al, Fungal biofilm morphology impacts hypoxia fitness and disease progression, *Nature Microbiology* (2019). DOI: 10.1038/s41564-019-0558-7

Provided by The Geisel School of Medicine at Dartmouth

Citation: Study reveals how fungal biofilm structure impacts lung disease (2019, September 23) retrieved 1 May 2024 from https://medicalxpress.com/news/2019-09-reveals-fungal-biofilm-impacts-lung.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.