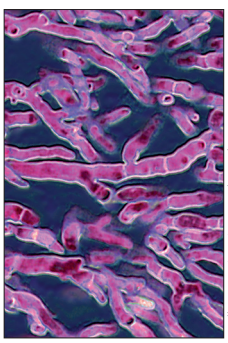
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

When disaster strikes fungi take control



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During 1 billion years of evolution, fungi have not only become masters of survival, but have actually leveraged disasters. 65 million years ago, when an asteroid strike wiped out 70% of all life on Earth by sending dusty debris into the atmosphere, fungi strived, taking advantage of the plants decaying due to the lack of sunlight. Back then, fungi infected and killed reptiles in their masses, potentially contributing to the extinction of the dinosaurs.[1] By contrast, fungi were not able to survive at the high body temperatures of mammals and thereby contributed to the succession of mammals as the new dominant species on Earth. Ever since then, fungi have maintained their integral role in the development of life.

Although fungi have made us who we are and have paved the way for human civilisation, they sometimes cause harm and can even kill humans.[1] Fungi often hit when humans suffer, causing outbreaks after tsunamis, hurricanes, and other natural disasters.[2] Where climate change negatively impacts us, fungi strive, quickly adapting to higher temperatures and becoming more virulent and potent; *Candida auris*, for example, is now emerging as a threat for humankind.[3] During the past decade, fungi have also come to our attention as a cause of deadly superinfections in patients with viral infection-associated acute respiratory failure.[4] We used to find these fungal superinfections mainly in patients with severe influenza, but the number of cases has been potentiated by the COVID-19 pandemic, with SARS-CoV-2 infecting more than 500 million individuals at a mortality rate of more than 1%.[5] Although mucormycosis[6] and candidiasis[5] have also been increasingly observed, COVID-19-associated pulmonary aspergillosis (CAPA) is the predominant fungal disease associated with high morbidity and mortality in patients with COVID-19 and acute respiratory failure.[5,7] Several immunological mechanisms have been hypothesised to contribute to the development of viral infection-associated pulmonary aspergillosis (VAPA),[4,5,8] but whether VAPA represents its own disease entity with a pathogenesis different to that of other forms of invasive pulmonary aspergillosis in the intensive care unit (ICU) setting is debated.

In *The Lancet Respiratory Medicine*, Simon Feys and colleagues[9] report results from the first study to use human lower respiratory tract samples to investigate epithelial and myeloid innate immunology in patients with influenza-associated pulmonary aspergillosis (IAPA) or CAPA. Using state-of-the-art techniques, including transcriptomics and proteomics on the bronchoalveolar lavage samples of more than 100 critically ill patients with influenza or COVID-19 with or without aspergillosis and RNAScope and spatial transcriptomics on the in vivo tracheobronchial biopsy samples from two patients with IAPA and two patients with CAPA, the authors identified a multilevel breach in antifungal immunity in patients with VAPA.[9]

First, they observed a downregulation of numerous genes with antifungal effector functions in patients with VAPA, implicating impairments in macrophages, monocytes, and neutrophils; the authors also found that patients with CAPA had significantly lower neutrophil cell fractions than did patients with COVID-19 only. Second, they visualised SARS-CoV-2-induced epithelial barrier disruption, facilitating tissue-invasive CAPA. Third, patients with VAPA had downregulated IFNγ signalling compared with patients with influenza or COVID-19 only, whereas only minor differences were observed in the concentrations of other major cytokines. Finally, the concentrations of several profibrotic growth factors were significantly increased in the bronchoalveolar lavage fluid from patients with IAPA versus influenza only and from patients with CAPA versus COVID-19 only, potentially contributing to the higher mortality observed in patients with VAPA versus monoinfections.[9]

Feys and colleagues should be applauded for their study that provides the foundation for future, functional research on the pathophysiology of VAPA. The identified multilevel breach in antifungal immunity, affecting the integrity of the epithelial barrier, the capacity to phagocytise and kill *Aspergillus* spores, and the ability to destroy *Aspergillus* hyphae, might also have implications for clinical management, including diagnosis (eg, novel diagnostic or prognostic biomarkers) and treatment (eg, the use of recombinant IFNγ as an adjuvant to antifungal treatment), which needs to be investigated in future studies.

In conclusion, when disaster hits, fungi are there to take advantage, with the potential to harm humans on multiple levels, such as by causing VAPA in those

requiring ICU admission. Recently, fungi have even been shown to translocate through the gut to trigger persistent inflammation after SARS-CoV-2 infection, potentially contributing to so-called long COVID in survivors.[10] Although the study by Feys and colleagues, which reports specific immunological mechanisms and pathogenetic characteristics, clearly strengthens the argument that VAPA represents its own disease entity, several questions remain to be answered. For example, what factors, other than COVID-19 treatment modalities and environmental exposures, might explain the wide variation in the incidence of VAPA observed between ICUs? To answer this question, the roles of host genetic predisposition and the respiratory mycobiome need to be studied further.

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