MICROBIOLOGY

Cultivating fungal research

Growing interest in host-fungal interactions has implications for human health and disease

By **Heidi H. Kong**[1] and **Julia A. Segre**[2]

Fungi cover epithelial surfaces of the human body, engaging in many mutualistic interactions with the host and other microbiota such as the more prevalent bacteria. These interactions are shaped by multiple factors, including host physiology and immunity, as well as nutrient competition. The beneficial effects of fungal colonization for hosts include resistance to pathogens and tuning of the immune system. Although health benefits continue to be explored, recent studies have revealed expanded roles of fungi in human disease, including inflammatory disorders and specific cancers. The global burden of fungal infections is also expanding, with increased numbers of at-risk patients and increased resistance to limited antifungal drugs. More fungal research is needed to overcome these unmet needs.

Fungi exist as single-celled yeast, multicellular molds, or dimorphic species occurring as both yeast and filamentous cells. *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, and *Candida* and *Malassezia* spp. are frequently studied yeast, whereas *Penicillium*, *Mucor*, and *Aspergillus* are well-known molds. As with many microbiota, fungi are classically recognized for their roles as human-associated pathogens. Candidal bloodstream infections are the most common form of fungal invasive disease, affecting about 1 in 10,000 people in the United States. Globally, cryptococcal meningitis contributes to a substantial burden of disease, particularly in HIV-positive individuals. The paucity of available antifungal treatments contributes to the morbidity and mortality of fungal infections. Classes of antifungals include azoles (e.g., fluconazole), echinocandins, and amphotericin B. However, fluconazole is the only antifungal drug available in many parts of the world. Additionally, some fungal diseases can be difficult to diagnose because of nonspecific patient symptoms, invasive tissue sampling, specific culture conditions, and identification requiring sophisticated techniques.

Recent studies have begun to explore how fungi are multifaceted in their potential to lead to beneficial as well as pathogenic outcomes for the host. Commensalism in the context of human fungi is exemplified by colonization resistance against pathogens. An example of a beneficial effect is the dominant human skin–associated *Malassezia*, which have adapted to their niche by making use of skin lipids as a nutrient, and then secreting antimicrobial products that deter bacterial pathogens (*1*). Another example of the importance of colonization resistance is *Candida albicans* commensalism in the gastrointestinal tract. In an evolutionary experiment, *C. albicans* strains acquired genetic mutations that enabled them to more stably colonize the mouse gastrointestinal tract. These evolved *C. albicans* strains provided protection against subsequent experimental challenges with different virulent fungi (*C. albicans, Aspergillus fumigatus*) and bacteria (*Staphylococcus aureus, Pseudomonas aeruginosa*) (*2*). However, these *C. albicans* strains evolved only in antibiotic-treated mice and were unable to stably colonize mice with endogenous gut bacteria, highlighting the genetic tradeoffs of adaptation to the host and competition within mixed microbial communities. Complementary studies demonstrated that mutations in transcription factors that regulate morphology are key determinants of the gut commensal fitness of *C. albicans* (*3*).

In addition to these direct host-microbial interactions, mouse gut colonization with *C. albicans* tuned host immunity, resulting in a systemic increase in fungal-specific T helper 17 (T_H17) $CD4^+$ T cells and interleukin-17 (IL-17)–responsive circulating neutrophils, which protected against more invasive bacterial and fungal, but not viral, infections (*4*). Ex vivo experiments showed that *C. albicans* elicited robust IL-17A and IL-22 responses from peripheral *C. albicans*– and *A. fumigatus*–specific T_H17 $CD4^+$ T cells from healthy human donors, demonstrating that *C. albicans* can modulate human immunity as well (*5*).

Given the complexity of host-microbial interactions, any alteration in the host or microbiota can result in infections, ranging from chronic chromoblastomycosis of the skin, dermatophyte nail infections, and acute vaginal yeast infections to potentially fatal mucormycosis in diabetics, candidal sepsis, and disseminated aspergillosis. Deficiencies in human immunity provide insight into the host-microbiota interplay. For example, patients with advanced HIV infections suffer from specific opportunistic fungal infections such as cryptococcal meningitis, mucosal candidiasis, and *Pneumocystis jirovecii* pneumonia. In patients receiving a hematopoietic stem cell transplant, candidal bloodstream infections were preceded by blooms of intestinal *Candida* spp. with altered bacterial communities, which could be used as biomarkers to identify and alter medical management (*6*). Additionally, the specificity of host-fungal immune interactions is reflected in patients with genetically defined primary immunodeficiency syndromes such as chronic granulomatous disease, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), or caspase recruitment domain–containing protein 9 (CARD9) deficiency, each of which renders patients susceptible to a specific fungal infection.

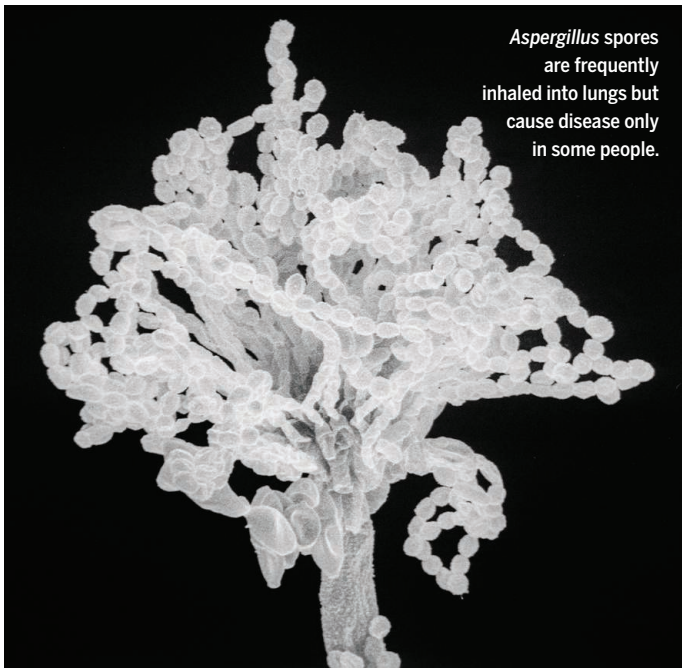
Other examples of host-specific fungal susceptibilities include mice deficient in the chemokine (C-X-C motif) receptor 1 (*Cxcr1*) gene, which have defective neutrophil killing of *Candida*, decreased survival, and higher fungal burden. This phenotype is similar to that of disseminated candidiasis patients and healthy donors with the *CXCR1-T276* allele who also demonstrate impaired neutrophil killing of *Candida* (*7*). Recurrent vulvovaginal candidiasis, a localized fungal infection, is estimated to affect more than 100 million women worldwide annually and has been linked with a functional variant in the *SIGLEC15* (sialic acid–binding immunoglobulin-like lectin 15) gene (*8*). Expressed on immune cells, SIGLEC15 can bind *C. albicans* and induces IL-17A and interferon-γ (IFN-γ) production, suggesting a role in anti–*C. albicans* immune responses. Host susceptibility contributes to the development of more persistent or severe fungal infections—for example, from dermatophytes or penetrating wounds. Studies of other single-nucleotide polymorphism (SNP) variants in immune-related genes that correlate with increased susceptibility to mucosal or life-threatening fungal infections hold promise for the future development of precision medicine approaches for risk stratification and preventive treatment of patients at the highest risk for fungal disease.

Inflammatory and autoimmune diseases are increasingly linked to alterations in fungal communities, particularly in ge-

[1]Cutaneous Microbiome and Inflammation Section, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD 20892, USA. [2]Microbial Genomics Section, Translational and Functional Genomics Branch, National Human Genome Research Institute, Bethesda, MD 20892, USA.
Email: konghe@mail.nih.gov; jsegre@nhgri.nih.gov

Downloaded from https://www.science.org at Chinese University of Hong Kong on August 31, 2021

Published by AAAS


Aspergillus spores are frequently inhaled into lungs but cause disease only in some people.

netically defined hosts. SNPs in *CARD9* and *CLEC7A* (C-type lectin domain–containing 7A), which encodes Dectin-1, have been associated with inflammatory bowel diseases in humans. Dectin-1 is a C-type lectin receptor (CLR) that recognizes β-glucan in fungal cell walls and, through CARD9, signals to induce inflammatory mediators and T_H1 and T_H17 cell differentiation. Mice deficient in Dectin-1 had more severe experimentally induced colitis with increased *C. tropicalis* burden, and a SNP in human *CLEC7A* is associated with more severe ulcerative colitis (*9*). Similarly, Crohn's disease patients have higher relative abundances of intestinal *Malassezia* compared with healthy controls, and oral gavage of *Malassezia* demonstrated worsening of experimental colitis in mice, again through activation of CARD9 signaling and downstream T_H1 and T_H17 cell polarization (*10*). Genetic ablation of $CX3CR1^+$ mononuclear phagocytes, which express antifungal CLRs, also exacerbated experimental colitis in mice. Furthermore, a missense mutation in *CX3CR1* in Crohn's disease patients has been associated with reduced immunoglobulin G (IgG) responses to fungi (*11*). These and other studies suggest that inflammatory diseases may result from host-fungal imbalances.

Although bacteria and viruses have been implicated in cancer, fungi typically have not been. Histologic observations revealed higher amounts of intratumoral fungi, particularly of *Malassezia*, infiltrating human pancreatic ductal adenocarcinomas (PDAs). Further investigation of mouse models of PDA demonstrated fungal translocation from the intestinal tract into the pancreas, increased burden of *Malassezia* accelerated PDA progression, and antifungal treatment slowed pancreatic cancer growth (*12*). The complement cascade integrates immune recognition and fungal killing with tumor development by stimulating proinflammatory pathways. Human tissue expression of mannose-binding lectin (MBL), which activates the complement cascade, was associated with worse survival in PDA patients. Similarly, PDA progression in mice depended on *Malassezia* stimulation of MBL, linking fungi, inflammation, and tumorigenesis. This study has prompted researchers to reconsider the potential relationships between fungi and broader human diseases.

Candida auris epitomizes the gravest concerns about an emerging fungal pathogen because it has evolved resistance to all classes of antifungal drugs, particularly azoles. Numerous countries have reported active outbreaks, with increasing cases of *C. auris* bloodstream infections. The high prevalence of resistance renders these infections difficult to treat, with resultant high mortality. Over the past decade, four distinct strains of *C. auris* have emerged independently on different continents. The origin of *C. auris* as a human pathogen has remained a mystery since it was first identified in 2009. The propensity of *C. auris* to colonize human skin for a long time, which is an atypical feature for non-*auris Candida* species, is of substantial concern because shedding from patients into the environment facilitates transmissions within health care facilities (*13*). The emergence of a new human fungal pathogen points to urgent unmet medical needs for new antifungal drugs and environmental disinfectants, genomic datasets that include fungal sequences to map global fungal diversity, and a coordinated global health response.

Investigations into the role of fungi in human health and disease are challenging. Despite a myriad of bacteria, fungi, and viruses existing together in and on humans, researchers tend to focus on a few microbial species because they are more tractable to study. Diverse culture conditions or inclusion of metabolically distinct forms of dimorphic fungi (*3*) may reveal different functions and interactions. In vivo systems also have limitations. For example, conventional laboratory mice have a lower fungal burden and different immune profiles than those of wild-type mice (*14*). Additionally, adaptation to stress—induced by, for example, culture conditions, passaging through mammalian hosts, antifungal pressures, high temperatures, or acidic pH—can lead to alterations in morphology, fungal capsule, and cell wall components. This can result in evasion or triggering of host immunity and radically altered genomes in fungal cells. Genomic plasticity in fungi, including loss of heterozygosity, copy number variation, and aneuploidy, underscores the importance of incorporating metagenomic analyses into studies of fungal community adaptation to different niches (*15*).

Fungal research is an area of considerable potential. This includes understanding how fungi are beneficial to human health and mining the multiple compounds produced by fungi that may benefit clinical medicine (for example, penicillin is derived from the fungal species *Penicillium* spp.). The emergence of multidrug-resistant *C. auris* has been postulated to be due in part to rising temperatures and to the widespread use of azoles in agriculture and in the clinic. Because these pressures on host-microbial homeostasis are likely to persist and evolve, the development of new antifungal drugs is critical to counteract outbreaks from existing and future pathogens. Advances in technology, such as targeted CRISPR-Cas9–mediated gene deletion for fungal mutagenesis, can provide precise tools for testing genetic hypotheses and elucidating fungal pathophysiology. Further advances will continue to improve our understanding of how fungi affect human health and disease. ■

REFERENCES AND NOTES

1. G. Wu *et al.*, *PLOS Genet.* **11**, e1005614 (2015).
2. G. H. W. Tso *et al.*, *Science* **362**, 589 (2018).
3. J. N. Witchley *et al.*, *Cell Host Microbe* **25**, 432 (2019).
4. T. Y. Shao *et al.*, *Cell Host Microbe* **25**, 404 (2019).
5. P. Bacher *et al.*, *Cell* **176**, 1340 (2019).
6. B. Zhai *et al.*, *Nat. Med.* **26**, 59 (2020).
7. M. Swamydas *et al.*, *Sci. Transl. Med.* **8**, 322ra10 (2016).
8. M. Jaeger *et al.*, *Sci. Transl. Med.* **11**, eaar3558 (2019).
9. I. D. Iliev *et al.*, *Science* **336**, 1314 (2012).
10. J. J. Limon *et al.*, *Cell Host Microbe* **25**, 377 (2019).
11. I. Leonardi *et al.*, *Science* **359**, 232 (2018).
12. B. Aykut *et al.*, *Nature* **574**, 264 (2019).
13. B. R. Jackson *et al.*, *J. Fungi* **5**, 58 (2019).
14. S. P. Rosshart *et al.*, *Science* **365**, eaaw4361 (2019).
15. A. Forche *et al.*, *mBio* **2**, e00129 (2011).

ACKNOWLEDGMENTS

The authors are supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (H.H.K.) and the National Human Genome Research Institute (J.A.S.).

10.1126/science.aaz8086

PHOTO: THE NATURAL HISTORY MUSEUM, LONDON/SCIENCE SOURCE

Downloaded from https://www.science.org at Chinese University of Hong Kong on August 31, 2021

Published by AAAS

Science

Cultivating fungal research

Heidi H. KongJulia A. Segre

Science, 368 (6489),

View the article online
https://www.science.org/doi/10.1126/science.aaz8086
Permissions
https://www.science.org/help/reprints-and-permissions

Downloaded from https://www.science.org at Chinese University of Hong Kong on August 31, 2021

Use of think article is subject to the Terms of service

Science (ISSN 1095-9203) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.
Copyright © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works