are safe and effective for both sexes [5]. Most likely, this virus will be maintained in the environment as a seasonal pathogen, much like the 2009 H1N1 influenza pandemic virus, with long-term implications for public health. In the meantime, investigating sex differences in the immune response to SARS-CoV-2 infection has the potential to provide therapeutic insights and contribute to precision medical interventions that do not assume that we can all be treated identically to be protected equally.

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References

Spotlight
Candida auris Mannans and Host Interplay
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Candida auris, a multidrug-resistant fungal pathogen, is responsible for the recent global outbreaks in hospitalized and long-term care patients with significant mortality. A new study by Bruno et al. delineates innate host immune responses against C. auris and identifies critical roles for fungal mannans and mannoproteins.

Candida auris causes healthcare-associated infections across the globe, often resulting in high mortality. Since its discovery, C. auris has spread to all major continents, causing hospital outbreaks, travel-related infections, and sustained colonization and infections in long-term care residents [1,2]. C. auris, alongside Candida dubosshaemulonii, Candida haemulonii, and Candida haemulonii var. vulnere, belongs to a particular clade of multidrug-resistant yeasts whose pathogenic potential is not well understood [3]. C. auris has presented many challenges for healthcare professionals, including the lack of facile diagnostic tests, decontamination of the organism from animate and inanimate surfaces, and a rapid acquisition of resistance to antifungal drugs. Although quick identification methods have now become available, frontline laboratories need point-of-care tests to detect C. auris. There is almost no information about the likely ecological niche of the yeast, which adversely impacts environmental containment and remediation. A recent report on pan-resistant C. auris strains further raises public health concerns [4]. Thus, there are urgent unmet healthcare needs for better diagnostics and therapeutics to deal with this problematic pathogen.

Fungal mannans (α-mannose polysaccharides) are among the three major components of the cell wall beside glucans and glycogens. As immunodominant molecules, mannans of Candida species are critical mediators of pathogen–host interplay and represent attractive targets for the development of diagnostic reagents and drugs [5]. Mannans from various pathogenic Candida species are hypothesized to be unique in their structure as defined by their oligomannosyl side chains. Recently, the unique structure of C. auris mannan was described and compared with that of Candida albicans and C. haemulonii, and showed preferential binding to IgG and mannose-binding lectins, suggesting the critical roles of C. auris mannans in host–pathogen interactions [6].

A new study by Bruno and colleagues delineates the specific role of C. auris mannans and mannoproteins in the innate immune response [7]. This investigative team used C. auris strains from all five clades and laboratory strains of C. albicans in a voluminous study. In a novel set of experiments, the authors exposed human peripheral blood mononuclear cells (PBMCs) to fungi followed by RNA sequence (RNA-seq) analysis and measurement of protein expression, which showed that all clades of C. auris caused higher expression of TNFα, IL-6, and IL-1β. C. albicans cell-wall β-glucans play a critical role in interactions with immune cells [7]. In an important differentiation, C. auris cell wall β-glucans were found to cause initial
but not sustained elevation of PBMC gene expression and cytokine stimulation in the present study. Instead, C. auris mannans, opsonized by human serum, caused notable stimulation of PBMC proinflammatory and anti-inflammatory cytokines, suggesting this cell wall component is crucial for host–pathogen interactions. The effect was variable in isolates from five C. auris clades, which carry significant single-nucleotide polymorphisms (SNPs) [2]. The unique finding with C. auris mannans is notable as both fungal β-glucans and mannans are reported as comparatively proficient in the stimulation of PBMC cytokine production [8]. C. auris was recognized and phagocytosed more efficiently compared to C. albicans by mouse bone-marrow-derived macrophages (BMDMs). However, C. auris failed to kill phagocytes at the rate observed for C. albicans, which authors attributed to a lack of glucose competition and filamentation in C. auris [7]. This explanation is in disagreement with recent reports on filamentation in C. auris, and shared regulatory pathways for yeast–hyphae transition in C. albicans and C. auris [9].

Bruno et al. found that C. auris mannans comprise acid-stable, long side-chains containing linked α-1,2-mannose, α-1,3-mannose, and β-1,2-mannose. C. auris mannans also contain two distinct, acid-labile side-chains of α-1,2-mannose-phosphate (M-α-1-phosphate) side chains [8]. Bruno and colleagues have revealed a substantial role for macrophage mannose receptor (MMR) and complement receptor 3 (CR3) in the recognition of these specific mannoproteins and the subsequent induction of cytokines [7]. Abbreviations: BMDM, bone-marrow-derived macrophage; IL, interleukin; PBMC, peripheral blood mononuclear cell; TNF, tumor necrosis factor.

The difference in mortality was not attributable to adaptive and innate cytokines, which were elicited at comparable levels in infected mice by both Candida species. Several recent studies on C. auris mouse models report the variable course of the experimental disease in immunocompetent, immunodeficient, and immunocompromised mice [10,11]. Future inclusion of such models will expand our understanding of the role of C. auris mannans and mannoproteins in systemic candidiasis. Also, genetically modified C. auris strains might provide additional insights into pathogen–host interplay. This approach remains well established for other Candida species and Aspergillus fumigatus [5]. Additionally, in future immunological studies, when attempting to compare C. auris and C. albicans, the results should be interpreted with caution. It is crucial to mention that C. albicans is a commensal, and its surface determinants have shared evolutionary history with the human immune system. Moreover, cell-wall mannans of commensal yeasts such as C. albicans and Saccharomyces klimentiae. Interactions with a Key Role for Fungal Mannans.

Figure 1. Possible Course of Phagocyte–Candida auris Interactions with a Key Role for Fungal Mannans. (A) Interactions between C. auris and phagocytes. Following recognition, budding yeasts are phagocytosed and first locate into an intracytoplasmic large vesicle termed a ‘phagosome’. Rapidly, either the yeast is lysed, thanks to the fusion of lysosomes (white and small vesicles) with the phagosome, or it escapes lysis. C. auris cells disseminate via the blood vessels to cause a potentially fatal bloodstream/deep-seated infection. (B) Host immune system–C. auris interplay. The C. auris cell surface harbors mannoproteins with specific α-1,2-mannose-phosphate (M-α-1-phosphate) side chains [8]. Bruno and colleagues have revealed a substantial role for macrophage mannose receptor (MMR) and complement receptor 3 (CR3) in the recognition of these specific mannoproteins and the subsequent induction of cytokines [7]. Abbreviations: BMDM, bone-marrow-derived macrophage; IL, interleukin; PBMC, peripheral blood mononuclear cell; TNF, tumor necrosis factor.
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Overall, Bruno et al. [2020] identified C. haemulonii as a new pathogenic yeast isolated from the external ear canal of New York subcluster susceptible to antifungal combination therapy [2020]. C. haemulonii is a novel species that exhibits distinct characteristics from other Candida species, such as its ability to cause disease in immunocompromised individuals. The study also highlighted the importance of recognizing this species in clinical settings to improve patient outcomes.


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Spotlight

The Mystery of MIS-C Post-SARS-CoV-2 Infection

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Following emergence of the coronavirus disease 2019 (COVID-19) pandemic, a surge in the life-threatening illness now termed ‘multisystem inflammatory syndrome in children’ (MIS-C) has raised questions about the unique effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children and adolescents. Two important new studies by Consiglio et al. and Gruber et al. have begun to shine light on the immune drivers of this enigmatic disease.

Early in the COVID-19 pandemic, epidemiological data offered reassuring evidence that children are largely spared of severe sequelae of SARS-CoV-2. Although that remains true, the severe MIS-C syndrome occurs in an estimated two per 100 000 children, based on New York State numbers [1], and primarily affects school-aged children approximately 4–6 weeks after the peak of total COVID-19 cases in a given region. Since April 2020, over 1000 cases of MIS-C have been confirmed by the Centers for Disease Control in the USA alone, and the clinical features of disease are now well established. MIS-C is characterized by fever and multiorgan dysfunction (including gastrointestinal, cardiovascular, cutaneous, neurologic, respiratory, nephrologic, hepaticologic) with the need for hospitalization in an intensive care unit in up to 80% of patients and a mortality rate of 2% [2,3]. Most children respond well to anti-inflammatory drugs (steroids, intravenous immunoglobulin, and various biologics) and supportive therapy, though a systematic evaluation of best treatments is currently lacking. To date, the pathophysiology of MIS-C remains enigmatic.

Due to a common presentation with rash, myocardial involvement, and coronary aneurysms, MIS-C has been compared extensively with Kawasaki disease (KD) [3]. Nevertheless, MIS-C is distinct from KD in several important epidemiological and clinical regards. Compared with KD patients, MIS-C patients are generally older (median of 8–11 years for MIS-C and 3 years for KD), predominantly Hispanic/Latino or Black (whereas KD is more prevalent in patients of Asian descent), and feature more pronounced abdominal symptoms, leukopenia, and elevated B-type natriuretic peptide, troponin, C-reactive protein, and ferritin [3–6]. Similarly to classical KD, MIS-C is thought to be a postinfectious inflammatory episode that is not known to recur, and no cases of MIS-C have been reported in multiple children from the same family. The unpredictable development of MIS-C in otherwise healthy children remains poorly understood, and further research is urgently needed.

What do we know about MIS-C immunopathology? Large clinical studies have consistently pointed to upregulation of systemic inflammatory cytokines in MIS-C as in other cytokine storm syndromes. Serum profiling