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are safe and effective for both sexes [8]. 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.

Resources

[i] www.cdc.gov/coronavirus/2019-ncov/covid-data/forecasting-us.html

[ii] https://globalhealth5050.org/

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https://doi.org/10.1016/j.tim.2020.10.002

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Spotlight

Candida auris Mannans and Pathogen–Host Interplay

Vishnu Chaturvedi [1,*] Robert J. Linhardt,[2] and Nicolas Papon[3,4]

***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 duobushaemulonii, Candida haemulonii*, and *Candida haemulonii* var. *vulnera*, 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 (D-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

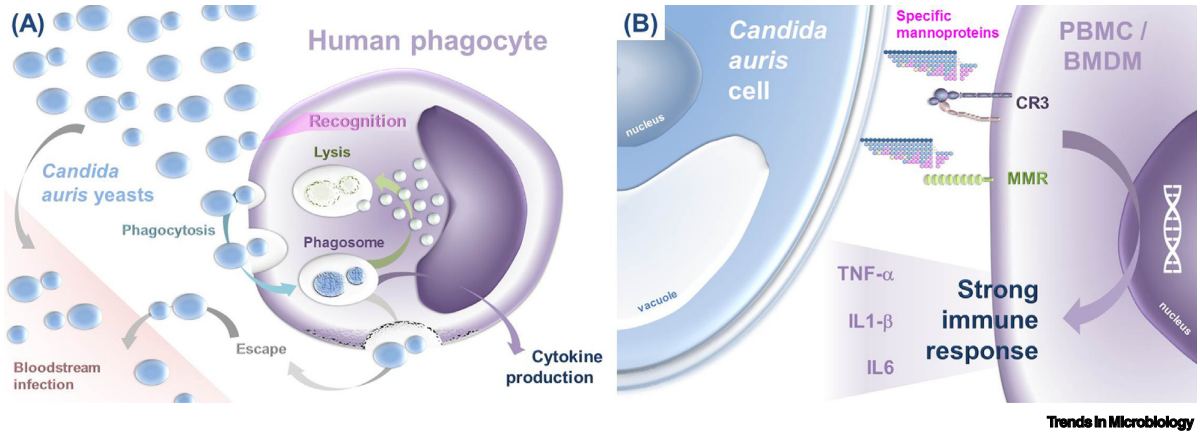

Figure 1. Possible Course of Phagocyte–*Candida auris* Interactions with a Key Role for Fungal Mannans. (A) Interactions between *C. auris* and phagocytes. Following recognition, budding yeasts are phagocytosed and first locate into an intracytoplasmic large vesicle termed a 'phagosome'. Rapidly, either 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.

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) [7]. *C. auris* recognition by the pattern-recognition receptor (PRR) and associated signaling pathways showed that macrophage mannose receptor (MMR) and CR3 are important for cytokine induction, similar to reports for other *Candida* species [5]. Strikingly, these experiments also suggested that there are additional mannan-recognizing receptors besides MMR for anti-*C. auris* cytokine induction. The authors expanded *in vitro* experimental findings by further comparisons in a new model for *C. auris* systemic candidiasis. Immunocompetent C57BL/6j mice were infected with *C. albicans* and *C. auris*. *C. auris*-infected mice survived longer than mice infected with *C. albicans*. 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*

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cerevisiae also provide protective immunity against intestinal injury and infection [12]. Overall, Bruno *et al*. establish a benchmark for future examination of host immune defense against *C. auris* infection. Apparently, *C. auris* is a new entrant in the human ecosystem, and features of its life cycle and pathogenic potential remain unknown. *C. auris* mannan, now established as a unique immunodominant molecule, could be the tool and target for fruitful insights into pathogen–host interplay (Figure 1).

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https://doi.org/10.1016/j.tim.2020.10.003

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Spotlight

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

Nina N. Brodsky [1,2], Anjali Ramaswamy [1] and Carrie L. Lucas [1,*]

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, nephrological, hepatologic) 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 aneurisms, 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