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.

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disparities in communication before, though biases persist in online formats [10]. And despite the difficulty of comparing virtual and in-person conferences, we must reach a clear understanding of the unique benefits provided by face-to-face and virtual interaction so that these can be appropriately balanced at future conferences.

Assuredly, the coming months will see continued experimentation with virtual conference structures, and new challenges will surface. Already, the scientific community is recognizing how easily cyber security and enhanced accessibility options are overlooked. Many digital platforms now provide enhanced security options, but it remains incumbent on organizers to ensure adequate accessibility, for instance including captioning and/or sign language interpretation for all audiences, which our workshop failed to provide.

New technology and the challenges of the SARS-Cov-2 pandemic have changed the landscape in which we work and communicate as scientists. Our survey found 97% of respondents would participate in another virtual meeting, suggesting that the community is ready to embrace new forms of attendance. Meeting organizers must similarly adopt new conference models, commit resources to enhancing the virtual experience, share effective strategies, and accelerate science communication while broadening participation through innovative uses of technology. Our experience shows that virtual conference models should be tailored to specific meeting objectives and continuously refined following careful examination, but also suggests that investment in creative virtual meeting delivery has significant payoffs for the scientific community.

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Spotlight

Sex-biased Immune Responses Following SARS-CoV-2 Infection

Rebecca L. Ursin,[1,4] Janna R. Shapiro,[2,4] and Sabra L. Klein [1,2,3,*]

Males are disproportionately affected by severe disease and death from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In their recent article, Takahashi *et al*. found sex differences in immune responses to SARS-CoV-2 and the predictors of disease progression. These findings contribute to elucidating the mechanisms that underlie the male bias in severe disease and death from coronavirus disease 2019 (COVID-19).

The world just crossed a grim milestone, with over 1 million deaths due to COVID-19. The USA alone just surpassed 200 000 deaths, with an additional 200 000 projected by the end of 2020[i]. While there are promising vaccine and therapeutic clinical trials, we desperately need to complement these initiatives with a deeper understanding of the immune responses that protect but that also cause pathology during SARS-CoV-2 infection. This goal is complicated by the fact that the virus does not impact everyone similarly, with age and comorbidities, such as obesity, diabetes, and heart conditions serving as risk factors for severe COVID-19 infection [1]. Biological sex is another factor influencing disease severity. SARS-CoV-2 causes significantly more hospitalizations, intensive

care unit (ICU) visits, and deaths in males than in females, across diverse countries and age groups. Globally, for every 10 hospitalizations of adult females there are 13 in males. And most strikingly, for every 10 deaths in females, there are 14 in males[ii]. It is important to note that both sex and gender contribute to disparities in COVID-19 outcomes; the former describing our biological predisposition (i.e., sex chromosome complement, sex steroid hormones, and reproductive tissues) and the latter referring to the social and behavioral characteristics (i.e., heath-seeking behaviors, mask wearing, and occupation) [1].

In their recent article, Takahashi *et al*. explore the immunopathogenic phenotypes exhibited by males and females in a cohort of 98 hospitalized SARS-CoV-2-positive patients, as compared to a control group of uninfected healthcare workers (HCWs) [2]. The first study of 39 patients not admitted to the ICU was used to assess baseline immune parameters, while repeated sampling from the larger cohort was used to assess longitudinal differences. Analysis of 71 plasma cytokines and chemokines adjusted for age and body mass index (BMI) revealed few differences between male and female patients. In unadjusted analysis, both male and female patients had higher frequencies of total and intermediate monocytes than healthy controls, while the proportion of nonclassical monocytes was higher in male than in female patients and HCWs of either sex. High frequencies of nonclassical monocytes in males were associated with lower T cell frequencies and were positively correlated with levels of CCL5, a chemokine important for recruiting T cells to inflammatory sites. Female patients had a higher proportion of activated ($CD38^+HLA\text{-}DR^+$) and terminally differentiated ($PD\text{-}1^+TIM\text{-}3^+$) T cells than female HCWs, particularly in the $CD8^+$ T cell compartment. Clinical scores at repeated time points were used to classify patients as stabilized or deteriorated. Among males, a greater deterioration was positively correlated with age and BMI and negatively correlated with activated and terminally differentiated $CD8^+$ T cells. Among females, disease progression was associated with the innate cytokines IL-15 and TNSF10 (TRAIL). The authors conclude that their findings demonstrate key sex differences in COVID-19 disease dynamics and provide a rationale for the pursuit of sex-specific strategies for prevention, care, and treatment of COVID-19.

Focusing on genetic differences, one small case series identified loss-of-function variants of the pattern-recognition receptor Toll-like receptor 7 (TLR7) in male patients requiring mechanical ventilation [3]. Upon stimulation *in vitro* with imiquimod, a TLR7 agonist, peripheral blood mononuclear cells isolated from the patients showed no increase in *TLR7* mRNA expression, decreased expression of transcripts in the type I interferon (IFN) pathway, and decreased production of IFN-γ, as compared to healthy controls. *TLR7* is X-linked and is known to escape X-inactivation [4], suggesting a mechanism whereby men expressing a single copy of *TLR7* are at increased risk of severe disease compared to women expressing two copies. This conclusion would also support the findings in the current paper, whereby greater T cell activation in females may result from greater induction of TLR7. A larger study performed shotgun RNA sequencing from nasopharyngeal swabs collected from 430 infected individuals and 54 controls [5]. Analysis revealed 19 genes where the sex difference in expression could be attributed to infection with SARS-CoV-2, including downregulation of B cell activity and natural killer cell-activating receptors in males, coupled with an upregulation of transcripts that inhibit NFκB signaling.

A recent article reports that at least 10% of 987 patients with severe disease had neutralizing IgG autoantibodies against IFN-ω and/or IFN-α, which were associated with low serum IFN levels *in vivo* and inhibited the ability of IFN-α2 to block SARS-CoV-2 from infecting Huh7.5 cells *in vitro* [6]. These autoantibodies were not found in any of 663 patients with mild or asymptomatic disease and are estimated to be present in 0.33% (0.015–0.67%) of the general population. Strikingly, 94% of the patients with neutralizing autoantibodies were male, providing yet another mechanism for the observed male bias in severe disease and death. Among COVID-19 patients with mild disease, a male sex bias exists during the recovery phase of COVID-19 where males produce more robust anti-SARS-CoV-2-spike protein antibodies and greater neutralizing antibodies than females. Because Takahashi *et al.* saw no sex difference in antibody titers at baseline, this points to a potential difference in antibody kinetics between the sexes [7].

Takahashi *et al.* provide insight into the underlying immunological mechanisms that contribute to sex differences in COVID-19. Most published reports describe heterogeneity of the immune responses to SARS-CoV-2, without analytical consideration of the host demographic factors that could be involved. The data in Takahashi *et al.* illustrate that host demographic factors, including sex, explain heterogeneity in the immune responses to SARS-CoV-2, which could provide novel insights into targetable factors that could mitigate disease. Pre-existing conditions, age, BMI, sex, and other intrinsic factors can all drastically alter how a viral pathogen is recognized, the magnitude and efficacy of innate and adaptive immune responses, and ultimately disease outcomes. Sex-specific treatment of all diseases, not just viruses and not just SARS-CoV-2, need to be further investigated and implemented. Furthermore, sex-disaggregated data in vaccine and therapeutic trials are crucial for developing interventions that

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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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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