COVID-19 Research Watch
May 10, 2021

BIOENGINEERING

COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets

The pathogenesis of severe COVID-19 cases was further explored using the newly developed cross-body COVID-19 autopsy biobank, where samples of the COVID-19 victims’ lungs, heart, and liver tissue were collected for single cell and spatial analysis using RNA-seq protocols. This work was able to evaluate the effect of severe COVID-19 infections on distinct tissues and regions of the lung. The researchers noticed a decrease in AT2 cells and the presence of PATS and IPBLP-like cells in the lungs, which suggests that the cells were trying to re-establish alveolar epithelial cells lost during infection. The study elucidated the cell-specific inflammatory pathways upregulated during infection, which can help in the development of improved treatments. Spatial analysis also shows that there were high viral levels during the onset of the infection in the lungs. However, the researchers did not detect a large presence of viral RNA in the heart, liver, or kidney. The study can be improved with a widening atlas, as the current atlas has very few donors. Nonetheless, the methods outlined enable other researchers to study diverse diseases.

Nanotraps for the containment and clearance of SARS-CoV-2

Chen et al. developed a “Nanotrap” nanoparticle that could reduce infection by enhancing the clearance of SARS-CoV-2 viruses before they could infect cells. Polylactic acid and liposome-based particles were co-functionalization with 1) recombinant ACE2 proteins (the receptor target of SARS-CoV-2) or anti-SARS-CoV-2 neutralizing antibodies to sequester viruses and 2) phosphatidylserine ligands to enhance phagocytosis by macrophages. The particles demonstrated the ability to bind pseudotyped SARS-CoV-2 virus, be cleared by macrophages, and the binding of SARS-CoV-2 to ACE-2 receptors sites of host cells to reduce the extent of infection. Additionally, in living human lungs in an ex vivo lung perfusion system, the Nanotrap entirely inhibited pseudotyped SARS-CoV-2 infection. Storing the nanoparticles effectively at -20°C for six months demonstrated no damage for surface integrity and promise excellent stability over time. For these reasons, the team has demonstrated a great potential for clinical application.

Sentinel cells enable genetic detection of SARS-CoV-2 Spike protein (preprint)

In response to the demand for adaptable COVID-19 diagnostics and therapies, Weinberg et al. proposed the idea of engineered cells composed of a customizable receptor-transcription module capable of detecting and responding to the SARS-COV-2 Spike protein. These “sentinel cells” are cellular biosensors that utilize the previously established synthetic-Notch receptor (SynNotch), a two-part, user-defined mechanism composed of an extracellular epitope-specific binding domain that cleaves an intracellular transcription factor when activated, resulting in customizable gene expression. Weinberg et. al’s “SARSNotch” receptor consists of their de novo-designed Spike protein binder LCB1—the lead short protein sequence candidate found via computational analysis—coupled to a transcription factor encoded with a downstream TagBFP for activation visualization via FACS. LCB1-SARSNotch-sentinel cell functionality was with plate-bounded Spike proteins or spike-
protein expressing k562 cells. In both models, SARSNotch cells exhibited significantly higher Spike-detection sensitivity compared to cells with no SynNotch mechanism. Activation was found to be sensitive to a Spike concentration as low as .316 μg/ml and at a 1:10 K562 to sentinel cell ratio in models 1 and 2, respectively, with cells lacking SARSNotch displaying zero percent activation regardless of Spike or Spike-K562 relative concentrations. Detection sensitivity results were successfully reproduced in therapeutically-relevant SARSNotch T cells, and the SARSNotch cells were shown to not increase susceptibility to viral infection—two critical results in confirming potential for in vivo success as a medium for cell therapy. Also, SARSNotch exhibited drastic activation when present in adherent cell lines, pointing to SARSNotch’s potential use in vitro therapeutic development. In the end, Weinberg et al. have successfully demonstrated that their modified SynNotch and de novo Spike protein binder system can be adapted to encode any therapeutic output, such as SARS-COV-2 neutralizing proteins for a highly-sensitive cell therapy.

Single-cell analyses reveal SARS-CoV-2 interference with intrinsic immune response in the human gut

Triana et al. conducted single-cell RNA sequencing of SARS-CoV-2 infected intestinal organoids to better understand the antiviral response the virus triggers in human intestinal epithelial cells (hIECs). The authors identified a subpopulation of enterocytes in the colon and ileum as the primary target of SARS-CoV-2 in hIECs. They then studied the virus’s impact on angiotensin-converting enzyme 2 (ACE2) and cellular protease type II transmembrane serine protease 2 (TMPRSS2) expression levels, as well as proinflammatory and interferon (IFN)-mediated responses, in infected cells and uninfected bystander cells. Cells with high levels of ACE2 were not particularly susceptible to SARS-CoV-2 infection, demonstrating that infection was not associated with high levels of ACE2; however, levels of TMPRSS2 were high in cells susceptible to SARS-CoV-2. Furthermore, ACE2 expression was found to negatively correlate to the presence of SARS-CoV-2. SARS-CoV-2 infection downregulated ACE2 expression in infected colon and ileum cells, as well as ileum bystander cells, but it did not affect ACE2 regulation in colon bystander cells. The study also found that infection generated a strong proinflammatory NFκB/TNF-mediated response in infected cells, while the bystander cells demonstrated a strong production of interferon-stimulated genes (ISGs) mediated by type III IFNs. Although infected cells secreted the IFNs that signaled to the bystander cells in a paracrine manner, SARS-CoV-2 shut down the cells’ own IFN-mediated signaling, meaning that the infected cells were unable to produce ISGs themselves.

CLINICAL PRESENTATION AND MANAGEMENT

Obesity is a strong risk factor for short-term mortality and adverse outcomes in Mexican patients with COVID-19: a national observation study

This retrospective observational analysis of a cohort of 71,103 patients from Mexico between February and April of 2020, was conducted to understand obesity’s role in short-term mortality for patients suspected of having COVID-19. This cohort included 21.8% who received a positive SARS-CoV-2 results, 66.1% a negative test results, and 12.1% whose results were still pending. Overall, the case-fatality rate was found to be higher among patients with positive test result (9.2%) than those with negative or pending results (1.9% and 1.6%, respectively). Obesity was found to increase adjusted mortality risk in positively diagnosed patients (HR=2.47, 95% CI:2.04-2.98). In positive cases who had
both a comorbidity and obesity, such as asthma or hypertension, obesity increased the adjusted mortality risk of those patients and was higher than either obesity or the comorbidity alone. In addition, when obesity was observed in conjunction with other comorbidities, it was found to increase the risk of secondary outcomes such as pneumonia and ICU admission. As a result, the authors identify that obesity is a risk factor for short-term mortality of patients who have tested positive for SARS-CoV-2.

**SARS-CoV-2 and stroke characteristics: A report from the multinational COVID-19 stroke study group**

This study aimed to understand the risk of stroke, the severity of stroke, and the type of stroke that occurred in patients with COVID-19 across 32 countries and 136 tertiary centres. Among 432 patients, all of which were diagnosed with COVID-19, 57.6% were men, 24.1% were over 55 years old, 37.8% had symptoms of stroke, and 24.4% did not present with vascular risk. Additionally, 74.8% presented with acute ischemic stroke (AIS), 21.1% with intracranial haemorrhage (ICH), and 4.2% with cerebral venous or sinus thrombosis (CVST). Of the patients with acute ischemic stroke, 33% had large artery atherosclerosis, 27% had cardio-embolism, 44.5% had large vessel occlusion (LVO), and 10% had small artery occlusion. Overall, the study found that this cohort of AIS patients who were also diagnosed with COVID-19, were younger, more often male, and approximately one third had an asymptomatic SARS-CoV-2 infection as compared to available population-level information from before the COVID-19 pandemic. In addition, this cohort included fewer small artery occlusion and lacunar infarcts, and more LVO strokes, as compared to pre-pandemic population-level data.

**MODELS**

**Modeling of Future COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Rates and Nonpharmaceutical Intervention Scenarios — United States, April–September 2021**

Borchering et al. created models to assess the potential course of COVID-19 in the United States across four scenarios with different vaccination rates, effectiveness estimates, and quality and implementation of non-pharmaceutical interventions (NPIs). The data was collected through March 27, 2021 from the Johns Hopkins Center for Systems Science and Engineering Coronavirus Resource Center and federal databases, and they projected weekly reported cases, hospitalizations, and deaths, both nationally and by jurisdiction for April-September 2021. The expectation is that with high vaccination coverage and moderate NPI adherence, hospitalizations and deaths will likely remain low nationally, with a sharp decline in cases projected by July 1st, 2021. Lower NPI adherence could lead to substantial increases in severe COVID-19 outcomes, even with improved vaccination coverage, which could keep the United States from declining below 15,000 weekly cases through September.
NON-ClinICAL TRENDS

Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform

Mathur et al conducted an observational study looking at death, intensive care unit admission, and COVID-19 related hospitalization and infection among different minority ethnic adult populations in the United Kingdom. The data was collected from the OpenSAFELY platform electronic health record system, and there were 17,288,532 adults that were observed in this study in two waves (February-August 2020 and September-December 2020). The hazard ratio for testing positive for infection was increased in South Asian people (1.08), Black people (1.08), and people of mixed ethnicities (1.04), compared to White populations. The "other" ethnicity category actually had a decrease in this hazard ratio (.77) compared to White populations. The researchers postulate that this might have been due to minorities getting tested at more severe stages of disease due to a lack of access to testing. In the other metrics, the hazard ratio was higher for South Asian people, mixed people, Black people, and "other" compared to the White population. Similar results were found in wave 2, except that South Asian hazard risk increased and Black hazard risk decreased. They hypothesized that multigenerational South Asian households increased infection susceptibility and that increased exposure, in general, contributed to the risk of death for minority populations (rather than increased disease severity susceptibility). The researchers show vast ethnic inequality and suggests increased access to testing, clinical care, and understanding how comorbidities affect COVID-19 may be crucial in reducing health disparities among populations in the UK.

PHARMACEUTICAL INTERVENTIONS

COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study

Hall et al conducted a prospective cohort study to investigate the effectiveness of the BNT162b2 in healthcare workers who resided in the United Kingdom and were over 18 years of age. The participants were divided into two groups, the positive cohort and the negative cohort. The positive cohort consisted of individuals who had a positive antibody test or a history of infection which was indicated by previous positivity of antibody or PCR tests. The negative cohort consisted of participants who had a negative antibody test with no previous positive test. The sample size was of 22,324 individuals with 35% assigned to the positive cohort and 65% assigned to the negative cohort. The research team utilized a piecewise exponential hazard mixed-effects model to conduct their analysis. Upon conducting their analysis, the research team found that a single dose of BNT162b2 vaccine showed an effectiveness of 70% after the first dose and 85% 7 days after the two doses. These results show that the vaccine can prevent both asymptomatic and symptomatic infection in adults, as well as effectiveness against the dominant variant at the time of the study, B1.1.7.
TRANSMISSION PATTERNS

SARS-CoV-2 seroprevalence, and IgG concentration, and pseudovirus neutralizing antibody titres after infection, compared by HIV status: a matched case-control observational study

Spinelli et al measured SARS-CoV-2 IgG, neutralizing antibody titres, and antibody serum in people living with HIV who had previously received positive PCR tests. This study was a case-control observational study; IgG seroprevalence was 3.7% in people living with HIV compared to 7.4% in those who were not. With evidence of a past infection, those with HIV had an odds ratio 5.52 times higher for severe COVID-19 compared to those without HIV.

Although there were lower numbers of infections, there were more severe cases of COVID-19 in the HIV population. Neutralizing antibody titres were lower in people living with HIV. This indicated that there was a reduced immune response to the virus in people with HIV.

The low levels of seroprevalence for SARS-CoV-2 in the HIV population were attributed to greater caution, aid from additional social services (such as the Ryan White Care Program) which helped sustain shelter in place, as well as possibly lower levels of testing in these at-risk populations. One caveat to the study is that there were only seven cases of severe COVID-19 (five occurring in HIV patients), so further analysis is warranted.

Rapid Emergence and Epidemiologic Characteristics of the SARS-CoV-2 B.1.526 Variant — New York City, New York, January 1–April 5, 2021

Thompson et al. performed an analysis of the SARS-CoV-2 B.1.526 variant which was first identified in New York City in November 2020 and was considered a variant of interest. This is because the variant has a mutation (E484K) in the receptor binding domain, which weakens antibody neutralization in vitro. The NYC Department of Health and Mental Hygiene analyzed laboratory and epidemiologic data to understand cases of B.1.526 infection and the potential for reinfection/breakthrough infections. They used NYC resident samples collected between January 1 and April 5, 2021, and all samples underwent nucleic acid amplification tests with some undergoing whole genome sequencing as well (if their cycle threshold was under 32). The analysis suggested that the B.1.526 variant does not lead to more severe disease or increased risk for reinfection. However, the B.1.526 variant may be more transmissible, and people with the variant were much more likely to live in high-poverty neighborhoods (Bronx) and to identify as Black/African-American. Cases of another variant, B.1.1.7, were also compared, as it was found to be 19% of the samples while the B.1.256 variant represented 38% of the sample. People with the B.1.1.7 variant were more likely to be hospitalized than those without, but there were no other significant differences with the B.1.256 variant and non-variant cases. The authors concluded that whole genome sequencing and population-based surveillance data are highly important in characterizing SARS-CoV-2 variants.

Transmission Risk Among National Basketball Association Players, Staff, and Vendors Exposed to Individuals with Positive Test Results After COVID-19 Recovered During the 2020 Regular and Postseason

Mack et conducted a retrospective cohort study to investigate the case characteristics of individuals who have clinically recovered from SARS-CoV-2 infection but continued to have positive test results after discontinuing isolation, also known as a persistent positive case. The research team analysed data from the National Basketball Association (NBA) closed
campus occupational health program in Orlando Florida, which included that of NBA players, staff, and vendors between June 11, 2020 and October 19, 2020. The results of the study found that of the 3648 individuals who participated, 36 individuals had persistent positive test results. These 36 individuals participated in approximately 51 days of unmasked contact events each and no transmission events or secondary infections were detected following their contact. The authors identify that this population most likely has a healthier status than the general population, which could have confounded these results.

ADDITIONAL RESOURCES
UCSF Library COVID-19 Research and Information Resources
UCSF Institute for Global Health Sciences COVID-19 Resources
UC Davis One Health Institute COVID-19 FAQs
Harvard Viswanath Lab Myths vs Facts
Accesocovid.com

Note on this Document: This document was assembled by undergraduate and doctoral students attending the University of California, Los Angeles and the University of California, San Francisco with the intent of facilitating the rapid dissemination of information to the global community. Alyssa Bercasio, Sara Covin, Elsa Dubil, Maya Ganeshan, Tyler Hoffman, Brooke Jackson, Emily Lin, Disha Nangia, Emily Ng, Nico Pedroncelli, Ilia Vasilopoulos and and contributed to these summaries. This work is volunteer based.

References:
