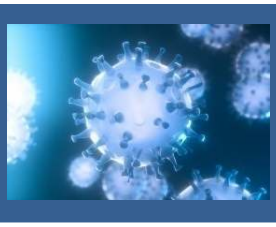
COVID-19

Jul 01 – 07, 2021



RESEARCH PUBLICATIONS

Publication Date: Jul 07, 2021

Genomic epidemiology of SARS-CoV-2 in the UAE reveals novel virus mutation, patterns of co-infection and tissue specific host immune response

Abstract

To unravel the source of SARS-CoV-2 introduction and the pattern of its spreading and evolution in the United Arab Emirates, meta-transcriptome sequencing of 1067 nasopharyngeal swab samples were conducted, which were collected between May 9th and Jun 29th, 2020 during the first peak of the local COVID-19 epidemic. Global clade distribution and eleven novel genetic variants were identified that were almost absent in the rest of the world and that defined five subclades specific to the UAE viral population. Cross-settlement human-to-human transmission was related to the local business activity. Perhaps surprisingly, at least 5% of the population were co-infected by SARS-CoV-2 of multiple clades within the same host. We also discovered an enrichment of cytosine-to-uracil mutation among the viral population collected from the nasopharynx, that is different from the adenosine-to-inosine change previously reported in the bronchoalveolar lavage fluid samples and a previously unidentified upregulation of APOBEC4 expression in nasopharynx among infected patients, indicating the innate immune host response mediated by ADAR and APOBEC gene families could be tissue-specific. The genomic epidemiological and molecular biological knowledge reported here provides new insights for the SARS-CoV-2 evolution and transmission and points out future direction on host–pathogen interaction investigation.

Reference

https://www.nature.com/articles/s41598-021-92851-3

The molecular basis for SARS-CoV-2 binding to dog ACE2

Abstract

SARS-CoV-2 can infect many domestic animals, including dogs. Herein, it was shown that dog angiotensin-converting enzyme 2 (dACE2) can bind to the SARS-CoV-2 spike (S) protein receptor binding domain (RBD), and that both pseudotyped and authentic SARS-CoV-2 can infect dACE2-expressing cells. The crystal structure of RBD in complex with dACE2 were solved and found that the total number of contact residues, contact atoms, hydrogen bonds and salt bridges at the binding interface in this complex are slightly fewer than those in the complex of the RBD and human ACE2 (hACE2). This result is consistent with the fact that the binding affinity of RBD to dACE2 is lower than that of hACE2. We further show that a few important mutations in the RBD binding interface play a pivotal role in the binding affinity of RBD to both dACE2 and hACE2. Our work reveals a molecular basis for cross-species transmission and potential animal spread of SARS-CoV-2, and provides new clues to block the potential transmission chains of this virus.

Reference

https://www.nature.com/articles/s41467-021-24326-y

User experience analysis of AbC-19 Rapid Test *via* lateral flow immunoassays for self-administrated SARS-CoV-2 antibody testing

Abstract

Lateral flow immunoassays are low cost, rapid and highly efficacious point-of-care devices, which have been used for SARS-CoV-2 antibody testing by professionals. However, there is a lack of understanding about how self-administered tests are used by the general public for mass testing in different environmental settings. The purpose of this study was to assess the user experience (UX) (including usability) of a self-testing kit to identify COVID-19 antibodies used by a representative sample of the public in their cars, which included 1544 participants in Northern Ireland. The results based on 5-point Likert ratings from a post-test questionnaire achieved an average UX score of 96.03% [95% confidence interval (CI) 95.05–97.01%], suggesting a good degree of user experience. The results of the Wilcoxon rank sum tests suggest that UX scores were

independent of the user's age and education level although the confidence in this conclusion could be strengthened by including more participants aged younger than 18 and those with only primary or secondary education. The agreement between the test result as interpreted by the participant and the researcher was 95.85% [95% CI 94.85–96.85%], Kappa score 0.75 [95% CI 0.69–0.81] (indicating substantial agreement). Text analysis via the latent Dirichlet allocation model for the free text responses in the survey suggest that the user experience could be improved for blood-sample collection, by modifying the method of sample transfer to the test device and giving clearer instructions on how to interpret the test results. The overall findings provide an insight into the opportunities for improving the design of SARS-CoV-2 antibody testing kits to be used by the general public and therefore inform protocols for future user experience studies of point-of-care tests.

Reference

https://www.nature.com/articles/s41598-021-93262-0

SARS-CoV-2-specific immune response in COVID-19 convalescent individuals

Abstract

Blood was collected from coronavirus disease 2019 (COVID-19) convalescent individuals and investigated SARS-CoV-2-specific humoral and cellular immunity in these discharged patients. Follow-up analysis in a cohort of 171 patients at 4–11 months after the onset revealed high levels of IgG antibodies. A total of 78.1% (164/210) of the specimens tested positive for neutralizing antibody (NAb). SARS-CoV-2 antigen peptide pools-stimulated-IL-2 and -IFN-γ response can distinguish COVID-19 convalescent individuals from healthy donors. Interestingly, NAb survival was significantly affected by the antigen peptide pools-stimulated-IL-2 response, -IL-8 response, and -IFN-γ response. The antigen peptide pools-activated CD8+ T cell counts were correlated with NAb. The antigen peptide pools-activated natural killer (NK) cell counts in convalescent individuals were correlated with NAb and disease severity. Our data suggested that the development of NAb is associated with the activation of T cells and NK cells. Our work provides a basis for further analysis of the protective immunity to SARS-CoV-2 and for understanding the pathogenesis of COVID-19. It also has implications for the development of an effective vaccine for SARS-CoV-2 infection.

Reference

https://www.nature.com/articles/s41392-021-00686-1

Informing selection of drugs for COVID-19 treatment through adverse events analysis

Abstract

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic and there is an urgent need for safe and effective drugs for COVID-19 treatment. Since developing a new drug is time consuming, many approved or investigational drugs have been repurposed for COVID-19 treatment in clinical trials. Therefore, selection of safe drugs for COVID-19 patients is vital for combating this pandemic. The goal was to evaluate the safety concerns of drugs by analyzing adverse events reported in post-market surveillance. We collected 296 drugs that have been evaluated in clinical trials for COVID-19 and identified 28,597,464 associated adverse events at the system organ classes (SOCs) level in the FDA adverse events report systems (FAERS). Z-scores of SOCs were calculated that statistically quantify the relative frequency of adverse events of drugs in FAERS to quantitatively measure safety concerns for the drugs. Analyzing the Z-scores revealed that these drugs are associated with different significantly frequent adverse events. The results suggest that this safety concern metric may serve as a tool to inform selection of drugs with favorable safety profiles for COVID-19 patients in clinical practices. Caution is advised when administering drugs with high Z-scores to patients who are vulnerable to associated adverse events.

Reference

https://www.nature.com/articles/s41598-021-93500-5

Clinical characterization of dysautonomia in long COVID-19 patients

Abstract

Increasing numbers of COVID-19 patients, continue to experience symptoms months after recovering from mild cases of COVID-19. Amongst these symptoms, several are related to neurological manifestations, including fatigue, anosmia, hypogeusia, headaches and hypoxia. However, the involvement of the autonomic nervous system, expressed by a dysautonomia, which can aggregate all these neurological symptoms

has not been prominently reported. Here, it was hypothesized that dysautonomia, could occur in secondary COVID-19 infection, also referred to as “long COVID” infection. 39 participants were included from December 2020 to January 2021 for assessment by the Department of physical medicine to enhance their physical capabilities: 12 participants with COVID-19 diagnosis and fatigue, 15 participants with COVID-19 diagnosis without fatigue and 12 control participants without COVID-19 diagnosis and without fatigue. Heart rate variability (HRV) during a change in position is commonly measured to diagnose autonomic dysregulation. In this cohort, to reflect HRV, parasympathetic/sympathetic balance was estimated using the NOL index, a multiparameter artificial intelligence-driven index calculated from extracted physiological signals by the PMD-200 pain monitoring system. Repeated-measures mixed-models testing group effect were performed to analyze NOL index changes over time between groups. A significant NOL index dissociation over time between long COVID-19 participants with fatigue and control participants was observed ($p = 0.046$). A trend towards significant NOL index dissociation over time was observed between long COVID-19 participants without fatigue and control participants ($p = 0.109$). No difference over time was observed between the two groups of long COVID-19 participants ($p = 0.904$). Long COVID-19 participants with fatigue may exhibit a dysautonomia characterized by dysregulation of the HRV, that is reflected by the NOL index measurements, compared to control participants. Dysautonomia may explain the persistent symptoms observed in long COVID-19 patients, such as fatigue and hypoxia.

Reference

https://www.nature.com/articles/s41598-021-93546-5

The signal pathways and treatment of cytokine storm in COVID-19

Abstract

Coronavirus Disease 2019 (COVID-19) pandemic has become a global crisis and is more devastating than any other previous infectious disease. It has affected a significant proportion of the global population both physically and mentally, and destroyed businesses and societies. Current evidence suggested that immunopathology may be responsible for COVID-19 pathogenesis, including lymphopenia, neutrophilia, dysregulation of monocytes and macrophages, reduced or delayed type I interferon

(IFN-I) response, antibody-dependent enhancement, and especially, cytokine storm (CS). The CS is characterized by hyperproduction of an array of pro-inflammatory cytokines and is closely associated with poor prognosis. These excessively secreted pro-inflammatory cytokines initiate different inflammatory signaling pathways via their receptors on immune and tissue cells, resulting in complicated medical symptoms including fever, capillary leak syndrome, disseminated intravascular coagulation, acute respiratory distress syndrome, and multiorgan failure, ultimately leading to death in the most severe cases. Therefore, it is clinically important to understand the initiation and signaling pathways of CS to develop more effective treatment strategies for COVID-19. Herein, we discuss the latest developments in the immunopathological characteristics of COVID-19 and focus on CS including the current research status of the different cytokines involved. We also discuss the induction, function, downstream signaling, and existing and potential interventions for targeting these cytokines or related signal pathways. We believe that a comprehensive understanding of CS in COVID-19 will help to develop better strategies to effectively control immunopathology in this disease and other infectious and inflammatory diseases.

Reference

https://www.nature.com/articles/s41392-021-00679-0

Publication Date: Jul 06, 2021

SARS-CoV-2 infection in the mouse olfactory system

Abstract

SARS-CoV-2 infection causes a wide spectrum of clinical manifestations in humans, and olfactory dysfunction is one of the most predictive and common symptoms in COVID-19 patients. However, the underlying mechanism by which SARS-CoV-2 infection leads to olfactory disorders remains elusive. Herein, it was demonstrated that intranasal inoculation with SARS-CoV-2 induces robust viral replication in the olfactory epithelium (OE), not the olfactory bulb (OB), resulting in transient olfactory dysfunction in humanized ACE2 (hACE2) mice. The sustentacular cells and Bowman's gland cells in the OE were identified as the major target cells of SARS-CoV-2 before invasion into olfactory sensory neurons (OSNs). Remarkably, SARS-CoV-2 infection triggers massive

cell death and immune cell infiltration and directly impairs the uniformity of the OE structure. Combined transcriptomic and quantitative proteomic analyses revealed the induction of antiviral and inflammatory responses, as well as the downregulation of olfactory receptor (OR) genes in the OE from the infected animals. Overall, our mouse model recapitulates olfactory dysfunction in COVID-19 patients and provides critical clues for understanding the physiological basis for extrapulmonary manifestations of COVID-19.

Reference

https://www.nature.com/articles/s41421-021-00290-1

First molecular-based detection of SARS-CoV-2 virus in the field-collected houseflies

Abstract

This is the first report of SARS-CoV-2 detection on field-collected Musca domestica housefly surface and tissue samples using the high-sensitive PCR assay which suggests the possible insect-borne transmission. The study was conducted in Shiraz city, southern Iran, in May and Jun 2020. Adult flies were sampled at the outdoor areas of two hospitals treating COVID-19 patients. Fly samples were first washed twice to remove the insect surface attached to SARS-CoV-2 virions. After that, the disinfected fly samples were homogenized. Fly surface washout and homogenate samples were tested using Taq Man real-time PCR assay for the SARS-CoV-2 virus. In a total of 156 houseflies, 75% of samples from the body washout samples were positive for SARS-CoV-2. Strikingly, 37% of the homogenized specimens were positive for the SARS-CoV-2, suggesting the possible infection of the insects or uptake of the virion to the insect metabolism. The other possibility is the houseflies up took the blood or blood fluids of the patients and the RNA of the SARS-CoV-2 survived in the insect body without replicating. Our preliminary findings suggest that the houseflies could transmit SARS-CoV-2 as a mechanical or biological vector especially during the warm seasons while increasing the population and activity of houseflies.

Reference

https://www.nature.com/articles/s41598-021-93439-7

Maternal outcomes and risk factors for COVID-19 severity among pregnant women

Abstract

Pregnant women may be at higher risk of severe complications associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may lead to obstetrical complications. A case control study was performed, comparing pregnant women with severe coronavirus disease 19 (cases) to pregnant women with a milder form (controls) enrolled in the COVI-Preg international registry cohort between March 24 and July 26, 2020. Risk factors for severity, obstetrical and immediate neonatal outcomes were assessed. A total of 926 pregnant women with a positive test for SARS-CoV-2 were included, among which 92 (9.9%) presented with severe COVID-19 disease. Risk factors for severe maternal outcomes were pulmonary comorbidities [aOR 4.3, 95% CI 1.9–9.5], hypertensive disorders [aOR 2.7, 95% CI 1.0–7.0] and diabetes [aOR2.2, 95% CI 1.1–4.5]. Pregnant women with severe maternal outcomes were at higher risk of caesarean section [70.7% (n = 53/75)], preterm delivery [62.7% (n = 32/51)] and newborns requiring admission to the neonatal intensive care unit [41.3% (n = 31/75)]. In this study, several risk factors for developing severe complications of SARS-CoV-2 infection among pregnant women were identified including pulmonary comorbidities, hypertensive disorders and diabetes. Obstetrical and neonatal outcomes appear to be influenced by the severity of maternal disease.

Reference

https://www.nature.com/articles/s41598-021-92357-y

Prolonged SARS-CoV-2 RNA virus shedding and lymphopenia are hallmarks of COVID-19 in cancer patients with poor prognosis

Abstract

Patients with cancer are at higher risk of severe coronavirus infectious disease 2019 (COVID-19), but the mechanisms underlying virus–host interactions during cancer therapies remain elusive. When comparing nasopharyngeal swabs from cancer and noncancer patients for RT-qPCR cycle thresholds measuring acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 1063 patients (58% with cancer), we found

that malignant disease favors the magnitude and duration of viral RNA shedding concomitant with prolonged serum elevations of type 1 IFN that anticorrelated with anti-RBD IgG antibodies. Cancer patients with a prolonged SARS-CoV-2 RNA detection exhibited the typical immunopathology of severe COVID-19 at the early phase of infection including circulation of immature neutrophils, depletion of nonconventional monocytes, and a general lymphopenia that, however, was accompanied by a rise in plasmablasts, activated follicular T-helper cells, and non-naive Granzyme B^+FasL^+, EomeshighTCF-1high, $PD\text{-}1^+CD8^+$ Tc1 cells. Virus-induced lymphopenia worsened cancer-associated lymphocyte loss, and low lymphocyte counts correlated with chronic SARS-CoV-2 RNA shedding, COVID-19 severity, and a higher risk of cancer-related death in the first and second surge of the pandemic. Lymphocyte loss correlated with significant changes in metabolites from the polyamine and biliary salt pathways as well as increased blood DNA from *Enterobacteriaceae* and *Micrococcaceae* gut family members in long-term viral carriers. We surmise that cancer therapies may exacerbate the paradoxical association between lymphopenia and COVID-19-related immunopathology, and that the prevention of COVID-19-induced lymphocyte loss may reduce cancer-associated death.

Reference

https://www.nature.com/articles/s41418-021-00817-9

Twelve-month specific IgG response to SARS-CoV-2 receptor-binding domain among COVID-19 convalescent plasma donors in Wuhan

Abstract

To investigate the duration of humoral immune response in convalescent coronavirus disease 2019 (COVID-19) patients, a 12-month longitudinal study was conducted through collecting a total of 1,782 plasma samples from 869 convalescent plasma donors in Wuhan, China and test specific antibody responses. The results show that positive rate of IgG antibody against receptor-binding domain of spike protein (RBD-IgG) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the COVID-19 convalescent plasma donors exceeded 70% for 12 months post diagnosis. The level of RBD-IgG decreases with time, with the titer stabilizing at 64.3% of the initial level by the 9th month. Moreover, male plasma donors produce more RBD-IgG than female, and

age of the patients positively correlates with the RBD-IgG titer. A strong positive correlation between RBD-IgG and neutralizing antibody titers is also identified. These results facilitate our understanding of SARS-CoV-2-induced immune memory to promote vaccine and therapy development.

Reference

https://www.nature.com/articles/s41467-021-24230-5

Prediction of individual COVID-19 diagnosis using baseline demographics and lab data

Abstract

The global surge in COVID-19 cases underscores the need for fast, scalable, and reliable testing. Current COVID-19 diagnostic tests are limited by turnaround time, limited availability, or occasional false findings. Here, a machine learning-based framework was developed for predicting individual COVID-19 positive diagnosis relying only on readily-available baseline data, including patient demographics, comorbidities, and common lab values. Leveraging a cohort of 31,739 adults within an academic health system, we trained and tested multiple types of machine learning models, achieving an area under the curve of 0.75. Feature importance analyses highlighted serum calcium levels, temperature, age, lymphocyte count, smoking, hemoglobin levels, aspartate aminotransferase levels, and oxygen saturation as key predictors. Additionally, we developed a single decision tree model that provided an operable method for stratifying sub-populations. Overall, this study provides a proof-of-concept that COVID-19 diagnosis prediction models can be developed using only baseline data. The resulting prediction can complement existing tests to enhance screening and pandemic containment workflows.

Reference

https://www.nature.com/articles/s41598-021-93126-7

Blood transcriptional biomarkers of acute viral infection for detection of pre-symptomatic SARS-CoV-2 infection: A nested, case-control diagnostic accuracy study

Abstract

Background: It was hypothesised that host-response biomarkers of viral infections might contribute to early identification of individuals infected with SARS-CoV-2, which is critical to breaking the chains of transmission. It was aimed to evaluate the diagnostic accuracy of existing candidate whole-blood transcriptomic signatures for viral infection to predict positivity of nasopharyngeal SARS-CoV-2 PCR testing.

Methods: A nested case-control diagnostic accuracy study was done among a prospective cohort of health-care workers (aged ≥18 years) at St Bartholomew's Hospital (London, UK) undergoing weekly blood and nasopharyngeal swab sampling for whole-blood RNA sequencing and SARS-CoV-2 PCR testing, when fit to attend work. We identified candidate blood transcriptomic signatures for viral infection through a systematic literature search. MEDLINE for articles were searched published between database inception and Oct 12, 2020, using comprehensive MeSH and keyword terms for “viral infection”, “transcriptome”, “biomarker”, and “blood”. Signature scores were reconstructed in blood RNA sequencing data and evaluated their diagnostic accuracy for contemporaneous SARS-CoV-2 infection, compared with the gold standard of SARS-CoV-2 PCR testing, by quantifying the area under the receiver operating characteristic curve (AUROC), sensitivities, and specificities at a standardised Z score of at least 2 based on the distribution of signature scores in test-negative controls. We used pairwise DeLong tests compared with the most discriminating signature to identify the subset of best performing biomarkers. Associations were evaluated between signature expression, viral load (using PCR cycle thresholds), and symptom status visually and using Spearman rank correlation. The primary outcome was the AUROC for discriminating between samples from participants who tested negative throughout the study (test-negative controls) and samples from participants with PCR-confirmed SARS-CoV-2 infection (test-positive participants) during their first week of PCR positivity.

Findings: 20 Candidate blood transcriptomic signatures of viral infection were identified from 18 studies and evaluated their accuracy among 169 blood RNA samples from 96 participants over 24 weeks. Participants were recruited between March 23 and March 31, 2020. 114 samples were from 41 participants with SARS-CoV-2 infection, and 55 samples were from 55 test-negative controls. The median age of participants was 36 years (IQR 27–47) and 69 (72%) of 96 were women. Signatures had little overlap of component genes, but were mostly correlated as components of type I interferon responses. A single blood transcript for IFI27 provided the highest accuracy for discriminating between test-negative controls and test-positive individuals at the time of their first positive SARS-CoV-2 PCR result, with AUROC of 0·95 (95% CI 0·91–0·99), sensitivity 0·84 (0·70–0·93), and specificity 0·95 (0·85–0·98) at a predefined threshold (Z score >2). The transcript performed equally well in individuals with and without symptoms. Three other candidate signatures (including two to 48 transcripts) had statistically equivalent discrimination to IFI27 (AUROCs 0·91–0·95).

Interpretation: The findings support further urgent evaluation and development of blood IFI27 transcripts as a biomarker for early phase SARS-CoV-2 infection for screening individuals at high risk of infection, such as contacts of index cases, to facilitate early case isolation and early use of antiviral treatments as they emerge.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00146-4/fulltext

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18 years or older: A randomized, double-blind, placebo-controlled, phase 1/2 trial

Abstract

Background: It was aimed to assess the safety and immunogenicity of an inactivated vaccine against COVID-19 in Chinese adults aged ≥18 years.

Methods: This is an ongoing randomized, double-blind, placebo-controlled, phase 1/2 clinical trial among healthy adults aged ≥18 years in Henan Province, China. Participants (n = 336 in 18–59 age group and n = 336 in ≥60 age group) were enrolled between April 12 and May 17 2020, and were equally randomized to receive vaccine or

placebo (aluminum hydroxide adjuvant) in a three-dose schedule of 2·5, 5, or 10 μg on days 0, 28, and 56. Another 448 adults aged 18–59 years were equally allocated to four groups (a one-dose schedule of 10 μg, and two-dose schedules of 5 μg on days 0 and 14/21/28) and received vaccine or placebo (ratio 3:1 within each group). The primary outcomes were 7-day post-injection adverse reactions and neutralizing antibody titres on days 28 and 90 after the whole-course vaccination. Trial registration: www.chictr.org.cn #ChiCTR2000031809.

Findings: The 7-day adverse reactions occurred in 4·8% to 32·1% of the participants in various groups, and most adverse reactions were mild, transient, and self-limiting. Twenty participants reported 68 serious adverse events which were judged to be unrelated to the vaccine. The 90-day post-injection geometric mean titres of neutralizing antibody ranged between 87 (95% CI: 61–125) and 129 (99–169) for three-dose schedule among younger and older adults; 20 (14–27), 53 (38–75), and 44 (32–61) in 5 μg days 0 and 14/21/28 groups, respectively, and 7 (6–9) in one-dose 10 μg group. There were no detectable antibody responses in all placebo groups.

Interpretation: The inactivated vaccine against COVID-19 was well tolerated and immunogenic in both younger and older adults. The two-dose schedule of 5 μg on days 0 and 21/28 and three-dose schedules on days 0, 28, and 56 could be further evaluated for long-term safety and efficacy in the phase 3 trials.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00290-X/fulltext

A selective sweep in the Spike gene has driven SARS-CoV-2 human adaptation

Abstract

The COVID-19 pandemic underscores the need to understand better animal-to-human transmission of coronaviruses and adaptive evolution within new hosts. Over 182,000 SARS-CoV-2 genomes were scanned for selective sweep signatures and found a distinct footprint of positive selection located around a non-synonymous change (A1114G; T372A) within the Spike protein receptor-binding domain (RBD), predicted to remove glycosylation and increase binding to human ACE2 (hACE2), the cellular receptor. This change is present in all human SARS-CoV-2 sequences but not closely

related viruses from bats and pangolins. As predicted, T372A RBD bound hACE2 with higher affinity in experimental binding assays. The reversion mutant (A372T) were engineered and found that A372 (WT-SARS-CoV-2) enhanced replication in human lung cells relative to its putative ancestral variant (T372), an effect which was 20x greater than the well-known D614G mutation. The findings suggest that this mutation likely contributed to SARS-CoV-2's emergence from animal reservoirs or enabled sustained human-to-human transmission.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00833-3

Investigating the impact of asymptomatic or mild SARS-CoV-2 infection on female fertility and *in vitro* fertilization outcomes: A retrospective cohort study

Abstract

Background: The current study aimed to investigate the impact of asymptomatic or mild severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on female fertility and laboratory and clinical outcomes in assisted reproductive technology (ART) treatments.

Methods: Patients undergoing ART treatments in the Reproductive Medicine Center, Tongji Hospital, Wuhan, from May 2020 to February 2021 were enrolled. Seventy of them were positive for serum SARS-CoV-2 antibodies (IgG and/or IgM), and 3973 patients had negative results. Propensity score matching with a ratio of 1:3 was performed, and there were 65 females in the case group and 195 females in the control group.

Findings: The ovarian reserves and ovarian responses between groups after matching were similar. The proportions of mature oocytes, damaged oocytes, fertilized oocytes, cleavage embryos, high-quality embryos, and available blastocysts were also similar, despite a slight decrease in the blastocyst formation rate in the case group. In addition, there were no significant differences in terms of the biochemical pregnancy rate, clinical pregnancy rate, early miscarriage rate, or implantation rate.

Interpretation: There is no evidence that a history of asymptomatic or mild SARS-CoV-2 infection in females may negatively affect female fertility, embryo laboratory outcomes, or clinical outcomes in ART treatments.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00293-5/fulltext

Publication Date: Jul 05, 2021

UVC disinfects SARS-CoV-2 by induction of viral genome damage without apparent effects on viral morphology and proteins

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a pandemic threat worldwide and causes severe health and economic burdens. Contaminated environments, such as personal items and room surfaces, are considered to have virus transmission potential. Ultraviolet C (UVC) light has demonstrated germicidal ability and removes environmental contamination. UVC has inactivated SARS-CoV-2; however, the underlying mechanisms are not clear. It was confirmed here that UVC 253.7 nm, with a dose of 500 μW/cm^2, completely inactivated SARS-CoV-2 in a time-dependent manner and reduced virus infectivity by 10–4.9-fold within 30 s. Immunoblotting analysis for viral spike and nucleocapsid proteins showed that UVC treatment did not damage viral proteins. The viral particle morphology remained intact even when the virus completely lost infectivity after UVC irradiation, as observed by transmission electronic microscopy. In contrast, UVC irradiation-induced genome damage was identified using the newly developed long reverse-transcription quantitative-polymerase chain reaction (RT-qPCR) assay, but not conventional RT-qPCR. The six developed long RT-PCR assays that covered the full-length viral genome clearly indicated a negative correlation between virus infectivity and UVC irradiation-induced genome damage (R2 ranging from 0.75 to 0.96). Altogether, these results provide evidence that UVC inactivates SARS-CoV-2 through the induction of viral genome damage.

Reference

https://www.nature.com/articles/s41598-021-93231-7

Understanding protection from SARS-CoV-2 using metabolomics

Abstract

The COVID-19 pandemic is still raging in most countries. Although the recent mass vaccination campaign has opened a new chapter in the battle against SARS-CoV-2, the world is still far from herd immunity. There is an urgent need to identify healthy people at high risk of contracting COVID-19, as well as supplements and nutraceuticals that can reduce the risk of infection or mitigate symptoms. In the present study, a metabolic phenotype that could protect individuals from SARS-CoV-2 infection or predispose them to developing COVID-19 was investigated. Untargeted metabolomics was performed on serum samples collected from 51 healthcare workers who were in good health at the beginning of the COVID-19 outbreak in Italy, and who were later exposed to the same risk of developing COVID-19. Half of them developed COVID-19 within three weeks of the blood collection. Our results demonstrate the presence of a specific signature associated with protection from SARS-CoV-2. Circulating monolaurin, which has well-known antiviral and antibacterial properties, was higher in protected subjects, suggesting a potential defensive role against SARS-CoV-2 infection; thus, dietary supplements could boost the immune system against this infection. In addition, our data demonstrate that people with higher levels of cholesterol are at higher risk of developing COVID-19. The present study demonstrates that metabolomics can be of great help for developing personalized medicine and for supporting public healthcare strategies. Studies with larger cohorts of subjects are necessary to confirm our findings.

Reference

https://www.nature.com/articles/s41598-021-93260-2

Monocyte-driven atypical cytokine storm and aberrant neutrophil activation as key mediators of COVID-19 disease severity

Abstract

Epidemiological and clinical reports indicate that SARS-CoV-2 virulence hinges upon the triggering of an aberrant host immune response, more so than on direct virus-induced cellular damage. To elucidate the immunopathology underlying COVID-19 severity, we perform cytokine and multiplex immune profiling in COVID-19 patients. It

was shown that hypercytokinemia in COVID-19 differs from the interferon-gamma-driven cytokine storm in macrophage activation syndrome, and is more pronounced in critical versus mild-moderate COVID-19. Systems modelling of cytokine levels paired with deep-immune profiling shows that classical monocytes drive this hyper-inflammatory phenotype and that a reduction in T-lymphocytes correlates with disease severity, with $CD8^+$ cells being disproportionately affected. Antigen presenting machinery expression is also reduced in critical disease. Furthermore, we report that neutrophils contribute to disease severity and local tissue damage by amplification of hypercytokinemia and the formation of neutrophil extracellular traps. Together our findings suggest a myeloid-driven immunopathology, in which hyperactivated neutrophils and an ineffective adaptive immune system act as mediators of COVID-19 disease severity.

Reference

https://www.nature.com/articles/s41467-021-24360-w

Pathophysiology of COVID-19-associated acute kidney injury

Abstract

Although respiratory failure and hypoxaemia are the main manifestations of COVID-19, kidney involvement is also common. Available evidence supports a number of potential pathophysiological pathways through which acute kidney injury (AKI) can develop in the context of SARS-CoV-2 infection. Histopathological findings have highlighted both similarities and differences between AKI in patients with COVID-19 and in those with AKI in non-COVID-related sepsis. Acute tubular injury is common, although it is often mild, despite markedly reduced kidney function. Systemic haemodynamic instability very likely contributes to tubular injury. Despite descriptions of COVID-19 as a cytokine storm syndrome, levels of circulating cytokines are often lower in patients with COVID-19 than in patients with acute respiratory distress syndrome with causes other than COVID-19. Tissue inflammation and local immune cell infiltration have been repeatedly observed and might have a critical role in kidney injury, as might endothelial injury and microvascular thrombi. Findings of high viral load in patients who have died with AKI suggest a contribution of viral invasion in the kidneys, although the issue of renal tropism remains controversial. An impaired type I interferon response has also been

reported in patients with severe COVID-19. In light of these observations, the potential pathophysiological mechanisms of COVID-19-associated AKI may provide insights into therapeutic strategies.

Reference

https://www.nature.com/articles/s41581-021-00452-0

Publication Date: Jul 02, 2021

Early and long term antibody kinetics of asymptomatic and mild disease COVID-19 patients

Abstract

Most patients infected with SARS-CoV-2 are asymptomatic or mildly symptomatic. However, the early and late antibody kinetics, and the association between antibody levels, clinical symptoms, and disease phase in these patients have not yet been fully defined. Confirmed SARS-CoV-2 patients and their household contacts were evaluated over a period four months. The evaluation procedure included symptom monitoring, viral load and serology analysis every ten days. A total of 1334 serum samples were collected from 135 patients and analyzed using three assays for IgG-N, IgG-S and IgM antibodies. Of the study participants, 97% were seropositive during the study, and two distinct clusters were identified. These clusters were significantly different in their inflammatory related symptoms. Peak IgG-S was 40.0 AU/ml for the non-inflammatory cluster and 71.5 AU/ml for the inflammatory cluster ($P = 0.006$), whereas IgG-N peaks were 4.3 and 5.87 ($P = 0.023$) respectively. Finally, a decision tree model was designed to predict the disease phase based on the serological titer levels, and had an overall accuracy of 80.7%. The specific profile of seroconversion and decay of serum antibodies can be used to predict the time-course from the acute infection.

Reference

https://www.nature.com/articles/s41598-021-93175-y

Mobility restrictions were associated with reductions in COVID-19 incidence early in the pandemic: Evidence from a real-time evaluation in 34 countries

Abstract

Most countries have implemented restrictions on mobility to prevent the spread of Coronavirus disease-19 (COVID-19), entailing considerable societal costs but, at least initially, based on limited evidence of effectiveness. It was asked whether mobility restrictions were associated with changes in the occurrence of COVID-19 in 34 OECD countries plus Singapore and Taiwan. The data sources were the Google Global Mobility Data Source, which reports different types of mobility, and COVID-19 cases retrieved from the dataset curated by Our World in Data. Beginning at each country's 100th case, and incorporating a 14-day lag to account for the delay between exposure and illness, we examined the association between changes in mobility (with January 3 to February 6, 2020 as baseline) and the ratio of the number of newly confirmed cases on a given day to the total number of cases over the past 14 days from the index day (the potentially infective 'pool' in that population), per million population, using LOESS regression and logit regression. In two-thirds of examined countries, reductions of up to 40% in commuting mobility (to workplaces, transit stations, retailers, and recreation) were associated with decreased cases, especially early in the pandemic. Once both mobility and incidence had been brought down, further restrictions provided little additional benefit. These findings point to the importance of acting early and decisively in a pandemic.

Reference

https://www.nature.com/articles/s41598-021-92766-z

A mass spectrometry-based targeted assay for detection of SARS-CoV-2 antigen from clinical specimens

Abstract

Background: The COVID-19 pandemic caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has overwhelmed health systems worldwide and highlighted limitations of diagnostic testing. Several types of diagnostic tests including

RT-PCR-based assays and antigen detection by lateral flow assays, each with their own strengths and weaknesses, have been developed and deployed in a short time.

Methods: Here, an immunoaffinity purification approach was described followed a by high resolution mass spectrometry-based targeted qualitative assay capable of detecting SARS-CoV-2 viral antigen from nasopharyngeal swab samples. Based on the discovery experiments using purified virus, recombinant viral protein and nasopharyngeal swab samples from COVID-19 positive patients, nucleocapsid protein was selected as a target antigen. An automated antibody capture-based workflow was then developed, coupled to targeted high-field asymmetric waveform ion mobility spectrometry (FAIMS) - parallel reaction monitoring (PRM) assay on an Orbitrap Exploris 480 mass spectrometer. An ensemble machine learning-based model for determining COVID-19 positive samples was developed using fragment ion intensities from the PRM data.

Findings: The optimized targeted assay, which was used to analyze 88 positive and 88 negative nasopharyngeal swab samples for validation, resulted in 98% (95% CI = 0.922–0.997) (86/88) sensitivity and 100% (95% CI = 0.958–1.000) (88/88) specificity using RT-PCR-based molecular testing as the reference method.

Interpretation: The results demonstrate that direct detection of infectious agents from clinical samples by tandem mass spectrometry-based assays have potential to be deployed as diagnostic assays in clinical laboratories, which has hitherto been limited to analysis of pure microbial cultures.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00258-9/fulltext

Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: A national prospective cohort study

Abstract

Background: Haematological malignancies and their treatments are likely to affect SARS-CoV-2 vaccine efficacy. It was aimed to evaluate serological response to BNT162b2 vaccine in patients with haematological malignancies by type of treatment.

Methods: The national prospective cohort study was done in Lithuania and assessed serological response to one and two BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine doses in healthy health-care workers and in patients with haematological malignancies. Eligible participants were aged 18 years or older, had received both vaccine doses, and had available biobanked blood samples from before vaccination and after the second dose. Biobanked samples and health data were obtained from Vilnius University Hospital Santaros Klinikos Biobank. Abbott Architect SARS-CoV-2 IgG Quant II chemiluminescent microparticle assay was used to quantify serum anti-SARS-CoV-2-S1 IgG antibody (anti-S1 IgG antibody) concentrations 0–10 days before the first BNT162b2 vaccine, on the day of second immunisation (around day 21), and 7 to 21 days after the second immunisation. Adverse events were assessed by a standardised questionnaire. Breakthrough infections were characterised clinically and by SARS-CoV-2 genotyping whenever possible. This study is registered with ClinicalTrials.gov, NCT04871165.

Findings: Between Jan 8 and April 21, 2021, 885 participants with haematological malignancies were included in the study. 857 patients were anti-S1 IgG seronegative at timepoint 0 and constituted the main analysis cohort. The age-matched comparison was made between 315 patients with haematological malignancies who were aged 18–60 years and 67 healthy health-care workers in the same age group. Patients aged 18–60 years with haematological malignancies had lower median anti-S1 IgG antibody responses after two BNT162b2 vaccine doses than did health-care workers of the same age group (median 6961 AU/mL [IQR 1292–20 672] vs 21 395 AU/mL [14 831–33 553]; p<0·0001). Compared with untreated patients with haematological malignancies (n=53; median 5761 AU/mL [629–16 141]), patients actively treated with Bruton tyrosine kinase inhibitors (BTKIs; n=44; 0 AU/mL [0–7]; p<0·0001), ruxolitinib (n=16; 10 AU/mL [0–45]; p<0·0001), venetoclax (n=10; 4 AU/mL [0–1218]; p=0·0005), or anti-CD20 antibody therapy (n=87; 17 AU/mL [1–2319]; p<0·0001) showed particularly poor anti-S1 IgG antibody responses following two BNT162b2 doses. Patients being treated with tyrosine kinase inhibitors (n=41; 10 537 AU/mL [IQR 2335–19 388]) or patients who received autologous haematopoietic stem-cell transplantation (HSCT; n=192; 6203 AU/mL [1451–16 834]) or allogeneic HSCT (n=122; 6304 AU/mL [1120–16 913]) were among the subgroups with the highest numerical responses. Nine SARS-CoV-2 infections and

three COVID-19 deaths were observed among fully vaccinated patients with haematological malignancies.

Interpretation: Patients with haematological malignancies mount blunted and heterogeneous antibody responses to the full course of BNT162b2 mRNA vaccination. Patients who are actively treated with BTKIs, ruxolitinib, venetoclax, or anti-CD20 antibody therapies seem to be the most negatively affected and might be left unprotected from SARS-CoV-2 infection. Breakthrough severe SARS-CoV-2 infections in fully vaccinated patients with haematological malignancies emphasise the importance of ongoing strict adherence to non-pharmacological interventions and household vaccination while SARS-CoV-2 is circulating in the community.

Reference

https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(21)00169-1/fulltext

Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): A prospective, multicentre cohort study

Abstract

Background: Although COVID-19 has greatly affected many low-income and middle-income countries, detailed information about patients admitted to the intensive care unit (ICU) is still scarce. Our aim was to examine ventilation characteristics and outcomes in invasively ventilated patients with COVID-19 in Argentina, an upper middle-income country.

Methods: In this prospective, multicentre cohort study (SATICOVID), we enrolled patients aged 18 years or older with RT-PCR-confirmed COVID-19 who were on invasive mechanical ventilation and admitted to one of 63 ICUs in Argentina. Patient demographics and clinical, laboratory, and general management variables were collected on day 1 (ICU admission); physiological respiratory and ventilation variables were collected on days 1, 3, and 7. The primary outcome was all-cause in-hospital mortality. All patients were followed until death in hospital or hospital discharge, whichever occurred first. Secondary outcomes were ICU mortality, identification of independent predictors of mortality, duration of invasive mechanical ventilation, and

patterns of change in physiological respiratory and mechanical ventilation variables. The study is registered with ClinicalTrials.gov, NCT04611269, and is complete.

Findings: Between March 20, 2020, and Oct 31, 2020, 1909 invasively ventilated patients were enrolled with COVID-19, with a median age of 62 years [IQR 52–70]. 1294 (67·8%) were men, hypertension and obesity were the main comorbidities, and 939 (49·2%) patients required vasopressors. Lung-protective ventilation was widely used and median duration of ventilation was 13 days (IQR 7–22). Median tidal volume was 6·1 mL/kg predicted bodyweight (IQR 6·0–7·0) on day 1, and the value increased significantly up to day 7; positive end-expiratory pressure was 10 cm H2O (8–12) on day 1, with a slight but significant decrease to day 7. Ratio of partial pressure of arterial oxygen (PaO2) to fractional inspired oxygen (FiO2) was 160 (IQR 111–218), respiratory system compliance 36 mL/cm H2O (29–44), driving pressure 12 cm H2O (10–14), and FiO2 0·60 (0·45–0·80) on day 1. Acute respiratory distress syndrome developed in 1672 (87·6%) of patients; 1176 (61·6%) received prone positioning. In-hospital mortality was 57·7% (1101/1909 patients) and ICU mortality was 57·0% (1088/1909 patients); 462 (43·8%) patients died of refractory hypoxaemia, frequently overlapping with septic shock (n=174). Cox regression identified age (hazard ratio 1·02 [95% CI 1·01–1·03]), Charlson score (1·16 [1·11–1·23]), endotracheal intubation outside of the ICU (ie, before ICU admission; 1·37 [1·10–1·71]), vasopressor use on day 1 (1·29 [1·07–1·55]), D-dimer concentration (1·02 [1·01–1·03]), PaO2/FiO2 on day 1 (0·998 [0·997–0·999]), arterial pH on day 1 (1·01 [1·00–1·01]), driving pressure on day 1 (1·05 [1·03–1·08]), acute kidney injury (1·66 [1·36–2·03]), and month of admission (1·10 [1·03–1·18]) as independent predictors of mortality.

Interpretation: In patients with COVID-19 who required invasive mechanical ventilation, lung-protective ventilation was widely used but mortality was high. Predictors of mortality in our study broadly agreed with those identified in studies of invasively ventilated patients in high-income countries. The sustained burden of COVID-19 on scarce health-care personnel might have contributed to high mortality over the course of our study in Argentina. These data might help to identify points for improvement in the management of patients in middle-income countries and elsewhere.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00229-0/fulltext

BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: A prospective, single-centre, longitudinal cohort study in health-care workers

Abstract

Background: Concurrent with the Pfizer–BioNTech BNT162b2 COVID-19 vaccine roll-out in Israel initiated on Dec 19, 2020, we assessed the early antibody responses and antibody kinetics after each vaccine dose in health-care workers of different ages and sexes, and with different comorbidities.

Methods: A prospective, single-centre, longitudinal cohort study was done at the Sheba Medical Centre (Tel-Hashomer, Israel). Eligible participants were health-care workers at the centre who had a negative anti-SARS-CoV-2 IgG assay before receiving the first dose of the intramuscular vaccine, and at least one serological antibody test after the first dose of the vaccine. Health-care workers with a positive SARS-CoV-2 PCR test before vaccination, a positive anti-SARS-CoV-2 IgG serology test before vaccination, or infection with COVID-19 after vaccination were excluded from the study. Participants were followed up weekly for 5 weeks after the first vaccine dose; a second dose was given at week 3. Serum samples were obtained at baseline and at each weekly follow-up, and antibodies were tested at 1–2 weeks after the first vaccine dose, at week 3 with the administration of the second vaccine dose, and at weeks 4–5 (*i.e.*, 1–2 weeks after the second vaccine dose). Participants with comorbidities were approached to participate in an enriched comorbidities subgroup, and at least two neutralising assays were done during the 5 weeks of follow-up in those individuals. IgG assays were done for the entire study population, whereas IgM, IgA, and neutralising antibody assays were done only in the enriched comorbidities subgroup. Concentrations of IgG greater than 0·62 sample-to-cutoff (s/co) ratio and of IgA greater than 1·1 s/co, and titres of neutralising antibodies greater than 10 were considered positive. Scatter plot and correlation analyses, logistic and linear regression analyses, and linear mixed models were used to investigate the longitudinal antibody responses.

Findings: Between Dec 19, 2020, and Jan 30, 2021, 4026 serum samples were obtained from 2607 eligible, vaccinated participants. 342 individuals were included in the enriched comorbidities subgroup. The first vaccine dose elicited positive IgG and neutralising antibody responses at week 3 in 707 (88·0%) of 803 individuals, and 264 (71·0%) of 372 individuals, respectively, which were rapidly increased at week 4 (ie, 1 week after the second vaccine dose) in 1011 (98·4%) of 1027 and 357 (96·5%) of 370 individuals, respectively. Over 4 weeks of follow-up after vaccination, a high correlation (r=0·92) was detected between IgG against the receptor-binding domain and neutralising antibody titres. First-dose induced IgG response was significantly lower in individuals aged 66 years and older (ratio of means 0·25, 95% CI 0·19–0·31) and immunosuppressed individuals (0·21, 0·14–0·31) compared with individuals aged 18·00–45·99 years and individuals with no immunosuppression, respectively. This disparity was partly abrogated following the second dose. Overall, endpoint regression analysis showed that lower antibody concentrations were consistently associated with male sex (ratio of means 0·84, 95% CI 0·80–0·89), older age (ie, ≥66 years; 0·64, 0·58–0·71), immunosuppression (0·44, 0·33–0·58), and other specific comorbidities: diabetes (0·88, 0·79–0·98), hypertension (0·90, 0·82–0·98), heart disease (0·86, 0·75–1·00), and autoimmune diseases (0·82, 0·73–0·92).

Interpretation: BNT162b2 vaccine induces a robust and rapid antibody response. The significant correlation between receptor-binding domain IgG antibodies and neutralisation titres suggests that IgG antibodies might serve as a correlate of neutralisation. The second vaccine dose is particularly important for older and immunosuppressed individuals, highlighting the need for timely second vaccinations and potentially a revaluation of the long gap between doses in some countries. Antibody responses were reduced in susceptible populations and therefore they might be more prone to breakthrough infections.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00220-4/fulltext

Temporal maturation of neutralizing antibodies in COVID-19 convalescent individuals improves potency and breadth to circulating SARS-CoV-2 variants

Abstract

Antibody titers against SARS-CoV-2 slowly wane over time. Here, how time affects antibody potency, was examined. To assess the impact of antibody maturation on durable neutralizing activity and protection against original SARS-CoV-2 and emerging variants of concern (VOCs), we analyzed receptor binding domain (RBD)-specific IgG antibodies in convalescent plasma taken 1-10 months after SARS-CoV-2 infection. Longitudinal evaluation of total RBD IgG and neutralizing antibody revealed declining total antibody titers, but improved neutralization potency per antibody to original SARS-CoV-2, indicative of antibody response maturation. Neutralization assays with authentic viruses revealed that early antibodies capable of neutralizing original SARS-CoV-2 had limited reactivity toward B.1.351 (501Y.V2) and B.1.1.28.1 (501Y.V3) variants. Antibodies from late convalescents exhibited increased neutralization potency to VOCs, suggesting persistence of cross-neutralizing antibodies in plasma. Thus, maturation of the antibody response to SARS-CoV-2 potentiates cross-neutralizing ability to circulating variants, suggesting that declining antibody titers may not be indicative of declining protection.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00259-4

Publication Date: Jul 01, 2021

Impact of SARS-CoV-2 variants on the total $CD4^+$ and $CD8^+$ T cell reactivity in infected or vaccinated individuals

Abstract

The emergence of SARS-CoV-2 variants with evidence of antibody escape highlight the importance of addressing whether the total $CD4^+$ and $CD8^+$ T cell recognition is also affected. Here, we compare SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells against the B.1.1.7, B.1.351, P.1, and CAL.20C lineages in COVID-19 convalescents and in recipients of the Moderna (mRNA-1273) or Pfizer/BioNTech (BNT162b2) COVID-19 vaccines. The total reactivity against SARS-CoV-2 variants is similar in terms of

magnitude and frequency of response, with decreases in the 10%–22% range observed in some assay/VOC combinations. A total of 7% and 3% of previously identified $CD4^+$ and $CD8^+$ T cell epitopes, respectively, are affected by mutations in the various VOCs. Thus, the SARS-CoV-2 variants analyzed here do not significantly disrupt the total SARS-CoV-2 T cell reactivity; however, the decreases observed highlight the importance for active monitoring of T cell reactivity in the context of SARS-CoV-2 evolution.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00204-4

Wisdom of crowds detects COVID-19 severity ahead of officially available data

Abstract

During the unfolding of a crisis, it is crucial to forecast its severity at an early stage, yet access to reliable data is often challenging early on. The wisdom of crowds has been effective at forecasting in similar scenarios. It was investigated whether the initial regional social media reaction to the emerging COVID-19 pandemic in three critically affected countries has significant relations with their observed mortality a month later. COVID-19 related regionally geolocated tweets were obtained from Italian, Spanish, and United States regions. The predictive power of the wisdom of the crowds was quantified using correlations and regressions of geolocated Tweet Intensity (TI) during the initial social media attention peak versus the cumulative number of deaths a month ahead. It was found that the intensity of initial COVID-19 related tweet attention at the beginning of the pandemic across Italian, Spanish, and United States regions is significantly related ($p < 0.001$) to the extent to which these regions had been affected by the pandemic a month later. This association is most striking in Italy as when at its peak of TI in late February 2020 only two of its regions had reported mortality. The collective wisdom of the crowds at early stages of the pandemic, when information on the number of infections was not broadly available, strikingly predicted the extent of mortality reflecting the regional severity of the pandemic almost a month later. The findings could underpin the creation of real-time novelty detection systems aimed at early reporting of the severity of crises impacting a territory leading to early activation of control measures at a stage when available data is extremely limited.

Reference

https://www.nature.com/articles/s41598-021-93042-w

The RNA sensor MDA5 detects SARS-CoV-2 infection

Abstract

Human cells respond to infection by SARS-CoV-2, the virus that causes COVID-19, by producing cytokines including type I and III interferons (IFNs) and proinflammatory factors such as IL6 and TNF. IFNs can limit SARS-CoV-2 replication but cytokine imbalance contributes to severe COVID-19. It was studied how cells detect SARS-CoV-2 infection. It was reported that the cytosolic RNA sensor MDA5 was required for type I and III IFN induction in the lung cancer cell line Calu-3 upon SARS-CoV-2 infection. Type I and III IFN induction further required MAVS and IRF3. In contrast, induction of IL6 and TNF was independent of the MDA5-MAVS-IRF3 axis in this setting. It was further found that SARS-CoV-2 infection inhibited the ability of cells to respond to IFNs. In sum, we identified MDA5 as a cellular sensor for SARS-CoV-2 infection that induced type I and III IFNs.

Reference

https://www.nature.com/articles/s41598-021-92940-3

The antiandrogen enzalutamide downregulates TMPRSS2 and reduces cellular entry of SARS-CoV-2 in human lung cells

Abstract

SARS-CoV-2 attacks various organs, most destructively the lung, and cellular entry requires two host cell surface proteins: ACE2 and TMPRSS2. Downregulation of one or both of these is thus a potential therapeutic approach for COVID-19. TMPRSS2 is a known target of the androgen receptor, a ligand-activated transcription factor; androgen receptor activation increases TMPRSS2 levels in various tissues, most notably prostate. It was shown here that treatment with the antiandrogen enzalutamide—a well-tolerated drug widely used in advanced prostate cancer—reduces TMPRSS2 levels in human lung cells and in mouse lung. Importantly, antiandrogens significantly reduced SARS-CoV-2 entry and infection in lung cells. In support of this experimental data, analysis of existing datasets shows striking co-expression of AR and TMPRSS2, including in

specific lung cell types targeted by SARS-CoV-2. Together, the data presented provides strong evidence to support clinical trials to assess the efficacy of antiandrogens as a treatment option for COVID-19.

Reference

https://www.nature.com/articles/s41467-021-24342-y

Massively scaled-up testing for SARS-CoV-2 RNA *via* next-generation sequencing of pooled and barcoded nasal and saliva samples

Abstract

Frequent and widespread testing of members of the population who are asymptomatic for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is essential for the mitigation of the transmission of the virus. Despite the recent increases in testing capacity, tests based on quantitative polymerase chain reaction (qPCR) assays cannot be easily deployed at the scale required for population-wide screening. Here, it was shown that next-generation sequencing of pooled samples tagged with sample-specific molecular barcodes enables the testing of thousands of nasal or saliva samples for SARS-CoV-2 RNA in a single run without the need for RNA extraction. The assay, which we named SwabSeq, incorporates a synthetic RNA standard that facilitates end-point quantification and the calling of true negatives, and that reduces the requirements for automation, purification and sample-to-sample normalization. SwabSeq was used to perform 80,000 tests, with an analytical sensitivity and specificity comparable to or better than traditional qPCR tests, in less than two months with turnaround times of less than 24 h. SwabSeq could be rapidly adapted for the detection of other pathogens.

Reference

https://www.nature.com/articles/s41551-021-00754-5

High-precision and cost-efficient sequencing for real-time COVID-19 surveillance

Abstract

COVID-19 global cases have climbed to more than 33 million, with over a million total deaths, as of September, 2020. Real-time massive SARS-CoV-2 whole genome sequencing is key to tracking chains of transmission and estimating the origin of

disease outbreaks. Yet no methods have simultaneously achieved high precision, simple workflow, and low cost. A high-precision, cost-efficient SARS-CoV-2 whole genome sequencing platform was developed for COVID-19 genomic surveillance, CorvGenSurv (Coronavirus Genomic Surveillance). CorvGenSurv directly amplified viral RNA from COVID-19 patients' Nasopharyngeal/Oropharyngeal (NP/OP) swab specimens and sequenced the SARS-CoV-2 whole genome in three segments by long-read, high-throughput sequencing. Sequencing of the whole genome in three segments significantly reduced sequencing data waste, thereby preventing dropouts in genome coverage. The precision of pipeline was validated by both control genomic RNA sequencing and Sanger sequencing. Near full-length whole genome sequences were produced from individuals who were COVID-19 test positive during April to June 2020 in Los Angeles County, California, USA. These sequences were highly diverse in the G clade with nine novel amino acid mutations including NSP12-M755I and ORF8-V117F. With its readily adaptable design, CorvGenSurv grants wide access to genomic surveillance, permitting immediate public health response to sudden threats.

Reference

https://www.nature.com/articles/s41598-021-93145-4

Immunological mechanisms of vaccine-induced protection against COVID-19 in humans

Abstract

Most COVID-19 vaccines are designed to elicit immune responses, ideally neutralizing antibodies (NAbs), against the SARS-CoV-2 spike protein. Several vaccines, including mRNA, adenoviral-vectored, protein subunit and whole-cell inactivated virus vaccines, have now reported efficacy in phase III trials and have received emergency approval in many countries. The two mRNA vaccines approved to date show efficacy even after only one dose, when non-NAbs and moderate T helper 1 cell responses are detectable, but almost no NAbs. After a single dose, the adenovirus vaccines elicit polyfunctional antibodies that are capable of mediating virus neutralization and of driving other antibody-dependent effector functions, as well as potent T cell responses. These data suggest that protection may require low levels of NAbs and might involve other immune effector mechanisms including non-NAbs, T cells and innate immune mechanisms.

Identifying the mechanisms of protection as well as correlates of protection is crucially important to inform further vaccine development and guide the use of licensed COVID-19 vaccines worldwide.

Reference

https://www.nature.com/articles/s41577-021-00578-z

Spatiotemporal analysis of COVID-19 outbreaks in Wuhan, China

Abstract

Few study has revealed spatial transmission characteristics of COVID-19 in Wuhan, China. It was aimed to analyze the spatiotemporal spread of COVID-19 in Wuhan and its influence factors. Information of 32,682 COVID-19 cases reported through March 18 were extracted from the national infectious disease surveillance system. Geographic information system methods were applied to analysis transmission of COVID-19 and its influence factors in different periods. It was found that decrease in effective reproduction number (Rt) and COVID-19 related indicators through taking a series of effective public health measures including restricting traffic, centralized quarantine and strict stay-at home policy. The distribution of COVID-19 cases number in Wuhan showed obvious global aggregation and local aggregation. In addition, the analysis at streets-level suggested population density and the number of hospitals were associated with COVID-19 cases number. The epidemic situation showed obvious global and local spatial aggregations. High population density with larger number of hospitals may account for the aggregations. The epidemic in Wuhan was under control in a short time after strong quarantine measures and restrictions on movement of residents were implanted.

Reference

https://www.nature.com/articles/s41598-021-93020-2

Ultrapotent antibodies against diverse and highly transmissible SARS-CoV-2 variants

Abstract

The emergence of highly transmissible SARS-CoV-2 variants of concern (VOC) that are resistant to therapeutic antibodies highlights the need for continuing discovery of

broadly reactive antibodies. Four receptor-binding domain targeting antibodies were identified from three early-outbreak convalescent donors with potent neutralizing activity against 23 variants including the B.1.1.7, B.1.351, P.1, B.1.429, B.1.526 and B.1.617 VOCs. Two antibodies are ultrapotent, with sub-nanomolar neutralization titers (IC50 0.3 to 11.1 ng/mL; IC80 1.5 to 34.5 ng/mL). We define the structural and functional determinants of binding for all four VOC-targeting antibodies and show that combinations of two antibodies decrease the *in vitro* generation of escape mutants, suggesting their potential in mitigating resistance development.

Reference

https://science.sciencemag.org/content/early/2021/06/30/science.abh1766

SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern

Abstract

A novel variant of concern (VOC) named CAL.20C (B.1.427/B.1.429), originally detected in California, carries spike glycoprotein mutations S13I in the signal peptide, W152C in the *N*-terminal domain (NTD), and L452R in the receptor-binding domain (RBD). Plasma from individuals vaccinated with a Wuhan-1 isolate-based mRNA vaccine or convalescent individuals exhibited neutralizing titers, which were reduced 2-3.5 fold against the B.1.427/B.1.429 variant relative to wildtype pseudoviruses. The L452R mutation reduced neutralizing activity of 14 out of 34 RBD-specific monoclonal antibodies (mAbs). The S13I and W152C mutations resulted in total loss of neutralization for 10 out of 10 NTD-specific mAbs since the NTD antigenic supersite was remodeled by a shift of the signal peptide cleavage site and formation of a new disulphide bond, as revealed by mass spectrometry and structural studies.

Reference

https://science.sciencemag.org/content/early/2021/06/30/science.abi7994

CORRESPONDANCE

Publication Date: Jul 06, 2021

Reactivation of IgA vasculitis after COVID-19 vaccination

Uncertainty persists as to the possibility that the COVID-19 vaccines might cause exacerbation of pre-existing autoimmune diseases. Here a case of reactivation of IgA vasculitis was reported, occurring after COVID-19 vaccination.

A woman aged 78 years with a history of IgA vasculitis with leukocytoclastic vasculitis, and renal and gastrointestinal involvement, had been in remission for 2 years with no immunosuppressant medication, before receiving the mRNA-1273 (Moderna) COVID-19 vaccine. At day seven post-vaccination, the patient had diarrhoea (6 times per day), and diffuse abdominal pain with acute onset. Her vaccines were up to date, including yearly influenza, and previous vaccinations had never caused an IgA vasculitis reactivation. She had not taken any new medication and showed no signs of any infection including SARS-CoV-2 before vaccination with mRNA-1273, at admission to hospital, or during hospitalisation. The patient's haemoglobin values decreased from 165 g/L to 143 g/L (normal range [N] 117–157 g/L) and laboratory tests including nasopharyngeal SARS-CoV-2 PCR test, large autoimmune panel, and infectious stool diarrhoea workup were in the normal range. However, the following tests were increased from pre-vaccine levels to 7 days post-vaccination: urea from 5·1 mmol/L to 10·2 mmol/L (N 2·9–6·4 mmol/L), creatinaemia from 96 µmol/L to 104 µmol/L (N 44–80 µmol/L), microhaematuria from 25 × 106/L to 150 × 106/L (N<26 × 106/L), C-reactive protein from 4 mg/L to 197 mg/L (N<10 mg/L), IgA from 2·25 g/L to 2·76 g/L (N 0·71–4·07 g/L), IgM from 0·19 g/L to 0·51 g/L (N 0·34–2·41 g/L), serum amyloid A from 10·2 mg/L to 2420 mg/L (N<6·4; appendix p 1). A CT scan showed sigmoid wall thickening with peripheral infiltration. The patient developed a palpable purpura in the hips and lower limbs. The patient was treated with methylprednisolone 1 mg/kg, and she improved rapidly with the disappearance of the purpura, gastrointestinal symptoms, and inflammatory syndrome, and improvement in renal function.

Taken together, these results might suggest a link between the increase in anti-SARS-CoV-2 spike IgA and the reactivation of pre-existing IgA vasculitis observed after

vaccination; however a coincidence cannot be ruled out. It remains to be established whether activation of autoreactive B cells following vaccination results from the pre-existing or de novo mobilisation of autoreactive B cells producing IgA (or both). For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00211-3/fulltext

Cytokine adsorption and ECMO in patients with COVID-19

The CYCOV trial by Alexander Supady and colleagues described extracorporeal membrane oxygenation (ECMO) support in patients with severe COVID-19 combined with cytokine adsorption. The authors conclude that cytokine adsorption during the first 72 h of ECMO support did not result in reduced interleukin (IL)-6 concentrations after 72 h, that cytokine adsorption was associated with an increased mortality risk within 30 days after initiation of ECMO, and that early cytokine adsorption should be avoided in patients with COVID-19 requiring venovenous ECMO support. Several comments can be made regarding these statements.

First, it was suggested that the most important limitation of the trial is that the patient models were unevenly grouped, notwithstanding the randomisation. The patients in the cytokine adsorption group were sicker: there were more patients with chronic multimorbidity in this group. These patients were started on mechanical ventilation right after hospital admission (number of days from hospital admission was equal to duration of non-invasive and invasive ventilation before ECMO), which also points to them being in a poorer condition. Some of them had been ventilated for 11 days until they were started on ECMO. This approach openly contradicts the European Extracorporeal Life Support Organisation (EuroELSO) recommendations for 3 days mean mechanical ventilation time before ECMO initiation. 7 days of mechanical ventilation is a direct contraindication for ECMO according to guidelines. It was considered that violation of this recommendation added to poor clinical outcomes of the patients who were sicker in the cytokine adsorption group. On the contrary, mean ventilation time in the control group was 4–8 days, which is maximally close to EuroELSO ECMO initiation guidelines. It is hardly a surprise that respiratory parameters were worse in the cytokine adsorption group: because these patients had lower ratio of the partial pressure of oxygen in

arterial blood to the fractional concentration of oxygen in inspired air (PaO_2/FiO_2) and lower arterial PaO_2, they required 5-times more norepinephrine. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00276-9/fulltext

Publication Date: Jul 02, 2021

Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma

Individuals with lymphoid malignancies are at risk of developing severe COVID-19 and are less likely to develop protective immune responses to SARS-CoV-2 vaccination than the general population because of disease-related or treatment-related immunosuppression. Data on vaccine responses in chronic lymphocytic leukaemia have shown antibody responses in 52–75% of individuals after the second dose. Vaccine responses after two doses in people with other lymphoid malignancies remain undefined.

In this interim analysis of the UK PROSECO study (a multicentre, prospective, observational study assessing COVID-19 vaccine immune responses in lymphoid malignancies [NCT04858568]), we report antibody levels before vaccination and 2 weeks after the first dose or 2–4 weeks after the second dose, or both, in participants with lymphoma recruited from general hospitals in Southampton, Nottingham, Leicester, Portsmouth and Oxford, UK. Participants were given either ChAdOx1 (AstraZeneca, Oxford, UK) or BNT162b2 (Pfizer-BioNTech, Puurs, Belgium) vaccines, with two doses given 10–12 weeks apart. IgG Antibodies against SARS-CoV-2 spike (S), receptor binding domain (RBD), and nucleocapsid (N) antigens were measured using a qualified electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA) and responses were reported in binding antibody units per mL (BAU/mL), and calibrated against the WHO COVID-19 international reference serum (National Institute for Biological Standards and Control number 20/136). Anti-S IgG concentrations of 0·55 BAU/mL or lower, anti-RBD IgG concentrations of 0·73 BAU/mL or lower, and anti-N IgG concentrations of 0·64 BAU/mL or lower were below the lower limit of detection. Participants with an anti-N IgG concentration of more than 6·60 BAU/mL were

considered to have had previous contact with SARS-CoV-2 and were excluded from the primary analysis. Antibody titres were compared with those in healthy volunteers recruited from the UK and Latvia who had received the vaccine as part of the government vaccine roll-out. Associations were calculated using the Mann-Whitney *U* test, with p values of 0·05 or lower being considered to be statistically significant. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(21)00199-X/fulltext

NEWS LETTER

Publication Date: Jul 01, 2021

Scientists identify long-sought marker for COVID vaccine success

Researchers developing the Oxford–AstraZeneca COVID-19 vaccine have identified biomarkers that can help to predict whether someone will be protected by the jab they receive. The team at the University of Oxford, UK, identified a 'correlate of protection' from the immune responses of trial participants — the first found by any COVID-19 vaccine developer. Identifying such blood markers, scientists say, will improve existing vaccines and speed the development of new ones by reducing the need for costly large-scale efficacy trials. New formulations of influenza vaccines, for instance, are generally judged by whether they trigger a strong enough antibody response against a viral protein in a relatively small number of people, instead of in large trials that look for reductions in rates of infection. Researchers and regulators hope to do the same with COVID-19 vaccines. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-021-01778-2

SPOT LIGHT

Publication Date: Jul 01, 2021

COVID-19 and the mental health of children with respiratory illness

Children and young people have been deeply affected by the COVID-19 pandemic. Lockdowns and new ways of living have necessitated massive adjustments. Despite heroic efforts from teachers, there has been a huge impact on education, and children lost the psychosocial benefits of being in school. News coverage is incessant, and polarised narratives and opinions are amplified in social media echo-chambers. In this report, co-authored with an adolescent from our clinic, we discuss the psychological impact of the COVID-19 pandemic on children and young people with respiratory problems.

Psychological problems in children during lockdowns include anxiety, depression, irritability, and boredom; lockdowns were also considered a contributing factor in some teenage suicides in the UK. Studies of children with chronic respiratory conditions are sparse: Parents of children with asthma and cystic fibrosis report heightened anxiety during the pandemic, but children adjusted well, perhaps reflecting their adaptation to the usual restrictions placed on their daily lives. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00319-2/fulltext