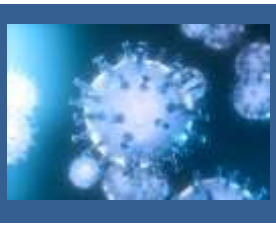
COVID-19

Apr 22-28, 2021



RESEARCH PUBLICATIONS

Publication Date: Apr 28, 2021

Kinetics and correlates of the neutralizing antibody response to SARS-CoV-2 infection in humans

Abstract

Understanding antibody-based SARS-CoV-2 immunity is critical for overcoming the COVID-19 pandemic and informing vaccination strategies. We evaluated SARS-CoV-2 antibody dynamics over 10 months in 963 individuals who predominantly experienced mild COVID-19. Investigating 2,146 samples, we initially detected SARS-CoV-2 antibodies in 94.4% individuals, with 82% and 79% exhibiting serum and IgG neutralization, respectively. Approximately 3% of individuals demonstrated exceptional SARS-CoV-2-neutralization, with these 'elite neutralizers' also possessing SARS-CoV-1 cross-neutralizing IgG. Multivariate statistical modeling revealed age, symptomatic infection, disease severity and gender as key factors predicting SARS-CoV-2 neutralizing activity. A loss of reactivity to the virus spike protein was observed in 13% individuals 10 months after infection. Neutralizing activity had half-lives of 14.7 weeks in serum versus 31.4 weeks in purified IgG, indicating a stable long-term IgG antibody response. Our results demonstrate a broad spectrum in the initial SARS-CoV-2-neutralizing antibody response, with sustained antibodies in most individuals for 10 months after mild COVID-19.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00191-8

SARS-CoV-2 outbreak in immune-mediated inflammatory diseases: The Euro-COVIMID multicentre cross-sectional study

Abstract

Background: The COVID-19 pandemic has raised numerous questions among patients with immune-mediated inflammatory diseases regarding potential reciprocal effects of COVID-19 and their underlying disease, and potential effects of immunomodulatory therapy on outcomes related to COVID-19. The seroprevalence of SARS-CoV-2 and factors associated with symptomatic COVID-19 in patients with immune-mediated inflammatory diseases are still unclear. The Euro-COVIMID study aimed to determine the serological and clinical prevalence of COVID-19 among patients with immune-mediated inflammatory diseases, as well as factors associated with COVID-19 occurrence and the impact of the pandemic in its management.

Methods: In this multicentre cross-sectional study, patients aged 18 years or older with a clinical diagnosis of rheumatoid arthritis, axial spondyloarthritis, systemic lupus erythematosus, Sjögren's syndrome, or giant cell arteritis were recruited from six tertiary referral centres in France, Germany, Italy, Portugal, Spain, and the UK. Demographics, comorbidities, treatments, and recent disease flares, as well as information on COVID-19 symptoms, were collected through a questionnaire completed by participants. SARS-CoV-2 serology was systematically tested. The main outcome was the serological and clinical prevalence of COVID-19. Factors associated with symptomatic COVID-19 were assessed by multivariable logistic regression, and incidence of recent disease flares, changes in treatments for underlying disease, and the reasons for treatment changes were also assessed. This study is registered with ClinicalTrials.gov, NCT04397237.

Findings: Between June 7 and Dec 8, 2020, 3136 patients with an immune-mediated inflammatory disease answered the questionnaire. 3028 patients (median age 58 years [IQR 46–67]; 2239 [73·9%] women and 789 [26·1%] men) with symptomatic COVID-19, serological data, or both were included in analyses. SARS-CoV-2 antibodies were detected in 166 (5·5% [95% CI 4·7–6·4]) of 3018 patients who had serology tests. Symptomatic COVID-19 occurred in 122 (4·0% [95% CI 3·4–4·8]) of 3028 patients, of whom 24 (19·7%) were admitted to hospital and four (3·3%) died. Factors associated with symptomatic COVID-19 were higher concentrations of C-reactive protein (odds

ratio 1·18, 95% CI 1·05–1·33; p=0·0063), and higher numbers of recent disease flares (1·27, 1·02–1·58; p=0·030), whereas use of biological therapy was associated with reduced risk (0·51, 0·32–0·82; p=0·0057). At least one disease flare occurred in 654 (21·6%) of 3028 patients. Over the study period, 519 (20·6%) of 2514 patients had treatment changes, of which 125 (24·1%) were due to the pandemic.

Interpretation: This study provides key insights into the epidemiology and risk factors of COVID-19 among patients with immune-mediated inflammatory diseases. Overall, immunosuppressants do not seem to be deleterious in this scenario, and the control of inflammatory activity seems to be key when facing the pandemic.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00112-0/fulltext

Temporal dynamics of viral load and false negative rate influence the levels of testing necessary to combat COVID-19 spread

Abstract

Colleges and other organizations are considering testing plans to return to operation as the COVID-19 pandemic continues. Pre-symptomatic spread and high false negative rates for testing may make it difficult to stop viral spread. Here, we develop a stochastic agent-based model of COVID-19 in a university sized population, considering the dynamics of both viral load and false negative rate of tests on the ability of testing to combat viral spread. Reported dynamics of SARS-CoV-2 can lead to an apparent false negative rate from ~ 17 to ~ 48%. Nonuniform distributions of viral load and false negative rate lead to higher requirements for frequency and fraction of population tested in order to bring the apparent Reproduction number (Rt) below 1. Thus, it is important to consider non-uniform dynamics of viral spread and false negative rate in order to model effective testing plans.

Reference

https://www.nature.com/articles/s41598-021-88498-9

Unraveling the stability landscape of mutations in the SARS-CoV-2 receptor-binding domain

Abstract

The interaction between the receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein and the ACE2 enzyme is believed to be the entry point of the virus into various cells in the body, including the lungs, heart, liver, and kidneys. The current focus of several therapeutic design efforts explores attempts at affecting the binding potential between the two proteins to limit the activity of the virus and disease progression. In this work, we analyze the stability of the spike protein under all possible single-point mutations in the RBD and computationally explore mutations that can affect the binding with the ACE2 enzyme. The mutation landscape of the receptor region was unraveled and assess the toxicity potential of single and multi-point mutations, generating insights for future vaccine efforts on mutations that might further stabilize the spike protein and increase its infectivity. We developed a tool, called SpikeMutator, to construct full atomic protein structures of the mutant spike proteins and shared a database of 3800 single-point mutant structures. The recent 65,000 reported spike sequences were analyzed across the globe and observed the emergence of stable multi-point mutant structures. Using the landscape, 7.5 million possible 2-point mutation combinations were searched and it was reported that the (R355D K424E) mutation produces one of the strongest spike proteins that therapeutic efforts should investigate for the sake of developing effective vaccines.

Reference

https://www.nature.com/articles/s41598-021-88696-5

Coiled-coil heterodimers with increased stability for cellular regulation and sensing SARS-CoV-2 spike protein-mediated cell fusion

Abstract

Coiled-coil (CC) dimer-forming peptides are attractive designable modules for mediating protein association. Highly stable CCs are desired for biological activity regulation and assay. Here, we report the design and versatile applications of orthogonal CC dimer-forming peptides with a dissociation constant in the low nanomolar range. In vitro stability and specificity was confirmed in mammalian cells by enzyme reconstitution,

transcriptional activation using a combination of DNA-binding and a transcriptional activation domain, and cellular-enzyme-activity regulation based on externally-added peptides. In addition to cellular regulation, coiled-coil-mediated reporter reconstitution was used for the detection of cell fusion mediated by the interaction between the spike protein of pandemic SARS-CoV2 and the ACE2 receptor. This assay can be used to investigate the mechanism of viral spike protein-mediated fusion or screening for viral inhibitors under biosafety level 1 conditions.

Reference

https://www.nature.com/articles/s41598-021-88315-3

Detect and destroy: CRISPR-based technologies for the response against viruses

Abstract

Despite numerous viral outbreaks in the last decade, including a devastating global pandemic, diagnostic and therapeutic technologies remain severely lacking. CRISPR-Cas systems have the potential to address these critical needs in the response against infectious disease. Initially discovered as the bacterial adaptive immune system, these systems provide a unique opportunity to create programmable, sequence-specific technologies for detection of viral nucleic acids and inhibition of viral replication. This review summarizes how CRISPR-Cas systems—in particular the recently discovered DNA-targeting Cas12 and RNA-targeting Cas13, both possessing a unique trans-cleavage activity—are being harnessed for viral diagnostics and therapies. We further highlight the numerous technologies whose development has accelerated in response to the COVID-19 pandemic.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00151-7

Notch4 signaling limits regulatory T-cell-mediated tissue repair and promotes severe lung inflammation in viral infections

Abstract

A cardinal feature of COVID-19 is lung inflammation and respiratory failure. In a prospective multi-country cohort of COVID-19 patients, we found that increased Notch4

expression on circulating regulatory T (Treg) cells was associated with disease severity, predicted mortality, and declined upon recovery. Deletion of Notch4 in Treg cells or therapy with anti-Notch4 antibodies in conventional and humanized mice normalized the dysregulated innate immunity and rescued disease morbidity and mortality induced by a synthetic analog of viral RNA or by influenza H1N1 virus. Mechanistically, Notch4 suppressed the induction by interleukin-18 of amphiregulin, a cytokine necessary for tissue repair. Protection by Notch4 inhibition was recapitulated by therapy with Amphiregulin and, reciprocally, abrogated by its antagonism. Amphiregulin declined in COVID-19 subjects as a function of disease severity and Notch4 expression. Thus, Notch4 expression on Treg cells dynamically restrains amphiregulin-dependent tissue repair to promote severe lung inflammation, with therapeutic implications for COVID-19 and related infections.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00139-4

Publication Date: Apr 27, 2021

Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms

Abstract

COVID-19 patients frequently develop neurological symptoms, but the biological underpinnings of these phenomena are unknown. Through single cell RNA-seq and cytokine analyses of CSF and blood from COVID-19 patients with neurological symptoms, we find compartmentalized, CNS specific T cell activation and B cell responses. All COVID-19 cases had CSF anti-SARS-CoV-2 antibodies whose target epitopes diverged from serum antibodies. In an animal model, we find that intrathecal SARS-CoV-2 antibodies are found only during brain infection, and are not elicited by pulmonary infection. We produced CSF-derived monoclonal antibodies from a COVID-19 patient, and find that these mAbs target both anti-viral and anti-neural antigens—including one mAb that reacted to both spike protein and neural tissue. Overall, CSF IgG from 5/7 patients contains anti-neural reactivity. This immune survey reveals

evidence of a compartmentalized immune response in the CNS of COVID-19 patients and suggests a role for autoimmunity in neurologic sequelae of COVID-19.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00116-6

A multi-targeting drug design strategy for identifying potent anti-SARS-CoV-2 inhibitors

Abstract

The COVID-19, caused by SARS-CoV-2, is threatening public health, and there is no effective treatment. In this study, we have implemented a multi-targeted anti-viral drug design strategy to discover highly potent SARS-CoV-2 inhibitors, which simultaneously act on the host ribosome, viral RNA as well as RNA-dependent RNA polymerases, and nucleocapsid protein of the virus, to impair viral translation, frameshifting, replication, and assembly. Driven by this strategy, three alkaloids, including lycorine, emetine, and cephaeline, were discovered to inhibit SARS-CoV-2 with EC50 values of low nanomolar levels potently. The findings in this work demonstrate the feasibility of this multi-targeting drug design strategy and provide a rationale for designing more potent anti-virus drugs.

Reference

https://www.nature.com/articles/s41401-021-00668-7

Climate and the spread of COVID-19

Abstract

Visual inspection of world maps shows that coronavirus disease 2019 (COVID-19) is less prevalent in countries closer to the equator, where heat and humidity tend to be higher. Scientists disagree how to interpret this observation because the relationship between COVID-19 and climatic conditions may be confounded by many factors. We regress the logarithm of confirmed COVID-19 cases per million inhabitants in a country against the country's distance from the equator, controlling for key confounding factors: air travel, vehicle concentration, urbanization, COVID-19 testing intensity, cell phone usage, income, old-age dependency ratio, and health expenditure. A one-degree

increase in absolute latitude is associated with a 4.3% increase in cases per million inhabitants as of January 9, 2021 (p value < 0.001). Our results imply that a country, which is located 1000 km closer to the equator, could expect 33% fewer cases per million inhabitants. Since the change in Earth's angle towards the sun between equinox and solstice is about 23.5°, one could expect a difference in cases per million inhabitants of 64% between two hypothetical countries whose climates differ to a similar extent as two adjacent seasons. According to our results, countries are expected to see a decline in new COVID-19 cases during summer and a resurgence during winter. However, our results do not imply that the disease will vanish during summer or will not affect countries close to the equator. Rather, the higher temperatures and more intense UV radiation in summer are likely to support public health measures to contain SARS-CoV-2.

Reference

https://www.nature.com/articles/s41598-021-87692-z

A computational approach to aid clinicians in selecting anti-viral drugs for COVID-19 trials

Abstract

The year 2020 witnessed a heavy death toll due to COVID-19, calling for a global emergency. The continuous ongoing research and clinical trials paved the way for vaccines. But, the vaccine efficacy in the long run is still questionable due to the mutating coronavirus, which makes drug re-positioning a reasonable alternative. COVID-19 has hence fast-paced drug re-positioning for the treatment of COVID-19 and its symptoms. This work builds computational models using matrix completion techniques to predict drug-virus association for drug re-positioning. The aim is to assist clinicians with a tool for selecting prospective antiviral treatments. Since the virus is known to mutate fast, the tool is likely to help clinicians in selecting the right set of antivirals for the mutated isolate. The main contribution of this work is a manually curated database publicly shared, comprising of existing associations between viruses and their corresponding antivirals. The database gathers similarity information using the chemical structure of drugs and the genomic structure of viruses. Along with this database, we make available a set of state-of-the-art computational drug re-positioning tools based on matrix completion. The tools are first analysed on a standard set of

experimental protocols for drug target interactions. The best performing ones are applied for the task of re-positioning antivirals for COVID-19. These tools select six drugs out of which four are currently under various stages of trial, namely Remdesivir (as a cure), Ribavarin (in combination with others for cure), Umifenovir (as a prophylactic and cure) and Sofosbuvir (as a cure). Another unanimous prediction is Tenofovir alafenamide, which is a novel Tenofovir prodrug developed in order to improve renal safety when compared to its original counterpart (older version) Tenofovir disoproxil. Both are under trail, the former as a cure and the latter as a prophylactic. These results establish that the computational methods are in sync with the state-of-practice. We also demonstrate how the drugs to be used against the virus would vary as SARS-Cov-2 mutates over time by predicting the drugs for the mutated strains, suggesting the importance of such a tool in drug prediction. It was believed that this work would open up possibilities for applying machine learning models to clinical research for drug-virus association prediction and other similar biological problems.

Reference

https://www.nature.com/articles/s41598-021-88153-3

An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients

Abstract

Despite several studies designed to evaluate the efficacy of chloroquine and hydroxychloroquine in the treatment of coronavirus disease 2019 (COVID-19), there is still doubt about the effects of these drugs, especially in patients with severe forms of the disease. This randomized, open-label, controlled, phase III trial assessed the efficacy of chloroquine or hydroxychloroquine for five days in combination with standard care compared to standard care alone in patients hospitalized with severe COVID-19. Chloroquine 450 mg BID on day 1 and 450 mg once daily from days 2 to 5 or hydroxychloroquine 400 mg BID on day 1 and 400 mg once daily from days 2 to 5 were administered in the intervention group. Patients were enrolled from April 16 to August 06, 2020, in 6 hospitals in southern Brazil. The primary outcome was the clinical status measured on day 14 after randomization with a 9-point ordinal scale. The main secondary outcomes were all-cause mortality; invasive mechanical ventilation use; the incidence of acute renal dysfunction in 28 days; and the clinical status of patients on

days 5, 7, 10 and 28. All patients with a positive RT-PCR result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were analyzed (modified intention to treat (mITT) population). Arrythmias and cardiovascular complications were assessed as safety outcomes. A total of 105 patients were enrolled and followed for 28 days. The trial was stopped before reaching the planned sample size due to harmful effects. Patients in the intervention group had a worse clinical outcome on the 14th day (odds ratio (OR) 2.45 [1.17 to 4.93], p = 0.016) and on the 28th day (OR 2.47 [1.15 to 5.30], p = 0.020). Moreover, the intervention group had higher incidences of invasive mechanical ventilation use (risk ratio (RR) 2.15 [1.05 to 4.40], p = 0.030) and severe renal dysfunction (KDIGO stage 3) (RR 2.24 [1.01 to 4.99], p = 0.042) until the 28th day of follow-up. No significant arrythmia was noted. In patients with severe COVID-19, the use of chloroquine/hydroxychloroquine added to standard treatment resulted in a significant worsening of clinical status, an increased risk of renal dysfunction and an increased need for invasive mechanical ventilation.

Reference

https://www.nature.com/articles/s41598-021-88509-9

Colorimetric RT-LAMP SARS-CoV-2 diagnostic sensitivity relies on color interpretation and viral load

Abstract

The use of RT-LAMP (reverse transcriptase—loop mediated isothermal amplification) has been considered as a promising point-of-care method to diagnose COVID-19. In this manuscript we show that the RT-LAMP reaction has a sensitivity of only 200 RNA virus copies, with a color change from pink to yellow occurring in 100% of the 62 clinical samples tested positive by RT-qPCR. We also demonstrated that this reaction is 100% specific for SARS-CoV-2 after testing 57 clinical samples infected with dozens of different respiratory viruses and 74 individuals without any viral infection. Although the majority of manuscripts recently published using this technique describe only the presence of two-color states (pink = negative and yellow = positive), we verified by naked-eye and absorbance measurements that there is an evident third color cluster (orange), in general related to positive samples with low viral loads, but which cannot be defined as positive or negative by the naked eye. Orange colors should be repeated or tested by RT-qPCR to avoid a false diagnostic. RT-LAMP is therefore very reliable for

samples with a RT-qPCR Ct < 30 being as sensitive and specific as a RT-qPCR test. All reactions were performed in 30 min at 65 °C. The use of reaction time longer than 30 min is also not recommended since nonspecific amplifications may cause false positives.

Reference

https://www.nature.com/articles/s41598-021-88506-y

The furin cleavage site in the SARS-CoV-2 spike protein is required for transmission in ferrets

Abstract

SARS-CoV-2 entry requires sequential cleavage of the spike glycoprotein at the S1/S2 and the S2' cleavage sites to mediate membrane fusion. SARS-CoV-2 has a polybasic insertion (PRRAR) at the S1/S2 cleavage site that can be cleaved by furin. Using lentiviral pseudotypes and a cell-culture-adapted SARS-CoV-2 virus with an S1/S2 deletion, we show that the polybasic insertion endows SARS-CoV-2 with a selective advantage in lung cells and primary human airway epithelial cells, but impairs replication in Vero E6, a cell line used for passaging SARS-CoV-2. Using engineered spike variants and live virus competition assays and by measuring growth kinetics, we find that the selective advantage in lung and primary human airway epithelial cells depends on the expression of the cell surface protease TMPRSS2, which enables endosome-independent virus entry by a route that avoids antiviral IFITM proteins. SARS-CoV-2 virus lacking the S1/S2 furin cleavage site was shed to lower titres from infected ferrets and was not transmitted to cohoused sentinel animals, unlike wild-type virus. Analysis of 100,000 SARS-CoV-2 sequences derived from patients and 24 human postmortem tissues showed low frequencies of naturally occurring mutants that harbour deletions at the polybasic site. Taken together, our findings reveal that the furin cleavage site is an important determinant of SARS-CoV-2 transmission.

Reference

https://www.nature.com/articles/s41564-021-00908-w

Systematic functional analysis of SARS-CoV-2 proteins uncovers viral innate immune antagonists and remaining vulnerabilities

Abstract

SARS-CoV-2 evades most innate immune responses, but may still be vulnerable to some. Here, the impact of SARS-CoV-2 proteins were systematically analyzed on interferon (IFN) responses and autophagy. It was shown that SARS-CoV-2 proteins synergize to counteract antiviral immune responses. For example, Nsp14 targets the type I IFN receptor for lysosomal degradation, ORF3a prevents fusion of autophagosomes and lysosomes, and ORF7a interferes with autophagosome acidification. Most activities are evolutionarily conserved. However, SARS-CoV-2 Nsp15 antagonizes IFN signaling less efficiently than the orthologues of closely-related RaTG13-CoV and SARS-CoV-1. Overall, SARS-CoV-2 proteins counteract autophagy and type I IFN more efficiently than type II or III IFN signaling and infection experiments confirmed potent inhibition by IFN-γ and -λ1. The results define the repertoire and selected mechanisms of SARS-CoV-2 innate immune antagonists, but also reveal vulnerability to type II and III IFN that may help to develop safe and effective anti-viral approaches.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00465-4

Noncanonical crRNAs derived from host transcripts enable multiplexable RNA detection by Cas9

Abstract

CRISPR-Cas systems recognize foreign genetic material using CRISPR RNAs (crRNAs). In Type II systems, a trans-activating crRNA (tracrRNA) hybridizes to crRNAs to drive their processing and utilization by Cas9. While analyzing Cas9-RNA complexes from Campylobacter jejuni, we discovered tracrRNA hybridizing to cellular RNAs, leading to formation of “noncanonical” crRNAs capable of guiding DNA targeting by Cas9. Our discovery inspired the engineering of reprogrammed tracrRNAs that link the presence of any RNA-of-interest to DNA targeting with different Cas9 orthologs. This capability became the basis for a multiplexable diagnostic platform termed LEOPARD

(Leveraging Engineered tracrRNAs and On-target DNAs for PArallel RNA Detection). LEOPARD allowed simultaneous detection of RNAs from different viruses in one test and distinguished SARS-CoV-2 and its D614G variant with single-base resolution in patient samples.

Reference

https://science.sciencemag.org/content/early/2021/04/26/science.abe7106

Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: A prospective observational study

Abstract

Background: The Pfizer-BioNTech (BNT162b2) and the Oxford-AstraZeneca (ChAdOx1 nCoV-19) COVID-19 vaccines have shown excellent safety and efficacy in phase 3 trials. We aimed to investigate the safety and effectiveness of these vaccines in a UK community setting.

Methods: In this prospective observational study, we examined the proportion and probability of self-reported systemic and local side-effects within 8 days of vaccination in individuals using the COVID Symptom Study app who received one or two doses of the BNT162b2 vaccine or one dose of the ChAdOx1 nCoV-19 vaccine. We also compared infection rates in a subset of vaccinated individuals subsequently tested for SARS-CoV-2 with PCR or lateral flow tests with infection rates in unvaccinated controls. All analyses were adjusted by age (≤55 years vs >55 years), sex, health-care worker status (binary variable), obesity (BMI <30 kg/m2 vs ≥30 kg/m2), and comorbidities (binary variable, with or without comorbidities).

Findings: Between Dec 8, and March 10, 2021, 627 383 individuals reported being vaccinated with 655 590 doses: 282 103 received one dose of BNT162b2, of whom 28 207 received a second dose, and 345 280 received one dose of ChAdOx1 nCoV-19. Systemic side-effects were reported by 13·5% (38 155 of 282 103) of individuals after the first dose of BNT162b2, by 22·0% (6216 of 28 207) after the second dose of BNT162b2, and by 33·7% (116 473 of 345 280) after the first dose of ChAdOx1 nCoV-19. Local side-effects were reported by 71·9% (150 023 of 208 767) of individuals after the first dose of BNT162b2, by 68·5% (9025 of 13 179) after the second dose of

BNT162b2, and by 58·7% (104 282 of 177 655) after the first dose of ChAdOx1 nCoV-19. Systemic side-effects were more common (1·6 times after the first dose of ChAdOx1 nCoV-19 and 2·9 times after the first dose of BNT162b2) among individuals with previous SARS-CoV-2 infection than among those without known past infection. Local effects were similarly higher in individuals previously infected than in those without known past infection (1·4 times after the first dose of ChAdOx1 nCoV-19 and 1·2 times after the first dose of BNT162b2). 3106 of 103 622 vaccinated individuals and 50 340 of 464 356 unvaccinated controls tested positive for SARS-CoV-2 infection. Significant reductions in infection risk were seen starting at 12 days after the first dose, reaching 60% (95% CI 49–68) for ChAdOx1 nCoV-19 and 69% (66–72) for BNT162b2 at 21–44 days and 72% (63–79) for BNT162b2 after 45–59 days.

Interpretation: Systemic and local side-effects after BNT162b2 and ChAdOx1 nCoV-19 vaccination occur at frequencies lower than reported in phase 3 trials. Both vaccines decrease the risk of SARS-CoV-2 infection after 12 days.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00224-3/fulltext

SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy

Abstract

Background: Reinfection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been documented, raising public health concerns. SARS-CoV-2 reinfections were assessed in a cohort of antibody-positive persons in Qatar.

Methods: All SARS-CoV-2 antibody-positive persons from April 16 to December 31, 2020 with a PCR-positive swab ≥14 days after the first-positive antibody test were investigated for evidence of reinfection. Viral genome sequencing was conducted for paired viral specimens to confirm reinfection. Incidence of reinfection was compared to incidence of infection in the complement cohort of those who were antibody-negative.

Findings: Among 43,044 antibody-positive persons who were followed for a median of 16.3 weeks (range: 0–34.6), 314 individuals (0.7%) had at least one PCR positive swab ≥14 days after the first-positive antibody test. Of these individuals, 129 (41.1%) had

supporting epidemiological evidence for reinfection. Reinfection was next investigated using viral genome sequencing. Applying the viral-genome-sequencing confirmation rate, the incidence rate of reinfection was estimated at 0.66 per 10,000 person-weeks (95% CI: 0.56–0.78). Incidence rate of reinfection versus month of follow-up did not show any evidence of waning of immunity for over seven months of follow-up. Meanwhile, in the complement cohort of 149,923 antibody-negative persons followed for a median of 17.0 weeks (range: 0–45.6), incidence rate of infection was estimated at 13.69 per 10,000 person-weeks (95% CI: 13.22–14.14). Efficacy of natural infection against reinfection was estimated at 95.2% (95% CI: 94.1–96.0%). Reinfections were less severe than primary infections. Only one reinfection was severe, two were moderate, and none were critical or fatal. Most reinfections (66.7%) were diagnosed incidentally through random or routine testing, or through contact tracing.

Interpretation: Reinfection is rare in the young and international population of Qatar. Natural infection appears to elicit strong protection against reinfection with an efficacy ~95% for at least seven months.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00141-3/fulltext

Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: Interim analysis of a prospective observational study

Abstract

Background: The efficacy and safety profiles of vaccines against SARS-CoV-2 in patients with cancer is unknown. We aimed to assess the safety and immunogenicity of the BNT162b2 (Pfizer–BioNTech) vaccine in patients with cancer.

Methods: For this prospective observational study, we recruited patients with cancer and healthy controls (mostly health-care workers) from three London hospitals between Dec 8, 2020, and Feb 18, 2021. Participants who were vaccinated between Dec 8 and Dec 29, 2020, received two 30 μg doses of BNT162b2 administered intramuscularly 21 days apart; patients vaccinated after this date received only one 30 μg dose with a planned follow-up boost at 12 weeks. Blood samples were taken before vaccination and

at 3 weeks and 5 weeks after the first vaccination. Where possible, serial nasopharyngeal real-time RT-PCR (rRT-PCR) swab tests were done every 10 days or in cases of symptomatic COVID-19. The coprimary endpoints were seroconversion to SARS-CoV-2 spike (S) protein in patients with cancer following the first vaccination with the BNT162b2 vaccine and the effect of vaccine boosting after 21 days on seroconversion. All participants with available data were included in the safety and immunogenicity analyses. Ongoing follow-up is underway for further blood sampling after the delayed (12-week) vaccine boost. This study is registered with the NHS Health Research Authority and Health and Care Research Wales (REC ID 20/HRA/2031).

Findings: 151 Patients with cancer (95 patients with solid cancer and 56 patients with haematological cancer) and 54 healthy controls were enrolled. For this interim data analysis of the safety and immunogenicity of vaccinated patients with cancer, samples and data obtained up to March 19, 2021, were analysed. After exclusion of 17 patients who had been exposed to SARS-CoV-2 (detected by either antibody seroconversion or a positive rRT-PCR COVID-19 swab test) from the immunogenicity analysis, the proportion of positive anti-S IgG titres at approximately 21 days following a single vaccine inoculum across the three cohorts were 32 (94%; 95% CI 81–98) of 34 healthy controls; 21 (38%; 26–51) of 56 patients with solid cancer, and eight (18%; 10–32) of 44 patients with haematological cancer. 16 healthy controls, 25 patients with solid cancer, and six patients with haematological cancer received a second dose on day 21. Of the patients with available blood samples 2 weeks following a 21-day vaccine boost, and excluding 17 participants with evidence of previous natural SARS-CoV-2 exposure, 18 (95%; 95% CI 75–99) of 19 patients with solid cancer, 12 (100%; 76–100) of 12 healthy controls, and three (60%; 23–88) of five patients with haematological cancers were seropositive, compared with ten (30%; 17–47) of 33, 18 (86%; 65–95) of 21, and four (11%; 4–25) of 36, respectively, who did not receive a boost. The vaccine was well tolerated; no toxicities were reported in 75 (54%) of 140 patients with cancer following the first dose of BNT162b2, and in 22 (71%) of 31 patients with cancer following the second dose. Similarly, no toxicities were reported in 15 (38%) of 40 healthy controls after the first dose and in five (31%) of 16 after the second dose. Injection-site pain within 7 days following the first dose was the most commonly reported local reaction (23 [35%] of 65 patients with cancer; 12 [48%] of 25 healthy controls). No vaccine-related deaths were reported.

Interpretation: In patients with cancer, one dose of the BNT162b2 vaccine yields poor efficacy. Immunogenicity increased significantly in patients with solid cancer within 2 weeks of a vaccine boost at day 21 after the first dose. These data support prioritisation of patients with cancer for an early (day 21) second dose of the BNT162b2 vaccine.

Reference

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00213-8/fulltext

Socioeconomic status determines COVID-19 incidence and related mortality in Santiago, Chile

Abstract

The current COVID-19 pandemic has impacted cities particularly hard. Here, we provide an in-depth characterization of disease incidence and mortality, and their dependence on demographic and socioeconomic strata in Santiago, a highly segregated city and the capital of Chile. Our analyses show a strong association between socioeconomic status and both COVID-19 outcomes and public health capacity. People living in municipalities with low socioeconomic status did not reduce their mobility during lockdowns as much as those in more affluent municipalities. Testing volumes may have been insufficient early in the pandemic in those places, and both test positivity rates and testing delays were much higher. We find a strong association between socioeconomic status and mortality, measured either by COVID-19 attributed deaths or excess deaths. Finally, we show that infection fatality rates in young people are higher in low-income municipalities. Together, these results highlight the critical consequences of socioeconomic inequalities on health outcomes.

Reference

https://science.sciencemag.org/content/early/2021/04/26/science.abg5298

Hepatitis C virus drugs that inhibit the SARS-CoV-2 papain-like protease synergize with remdesivir to suppress viral replication in cell culture

Abstract

Effective control of COVID-19 requires antivirals directed against SARS-CoV-2. We assessed ten hepatitis C virus (HCV) protease-inhibitor drugs as potential SARS-CoV-2 antivirals. There is a striking structural similarity of the substrate binding clefts of SARS-CoV-2 main protease (Mpro) and HCV NS3/4A protease. Virtual docking experiments show that these HCV drugs can potentially bind into the Mpro binding cleft. We show that seven HCV drugs inhibit both SARS-CoV-2 Mpro protease activity and SARS-CoV-2 virus replication in Vero and/or human cells. However, their Mpro inhibiting activities did not correlate with their antiviral activities. This conundrum was resolved by demonstrating that four HCV protease inhibitor drugs, simeprevir, vaniprevir, paritaprevir, and grazoprevir inhibit the SARS CoV-2 papain-like protease (PLpro). HCV drugs that inhibit PLpro synergize with the viral polymerase inhibitor remdesivir to inhibit virus replication, increasing remdesivir's antiviral activity as much as 10-fold, while those that only inhibit Mpro do not synergize with remdesivir.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00472-1

Practical clinical and radiological models to diagnose COVID-19 based on a multicentric teleradiological emergency chest CT cohort

Abstract

The aim was to develop practical models built with simple clinical and radiological features to help diagnosing Coronavirus disease 2019 [COVID-19] in a real-life emergency cohort. To do so, 513 consecutive adult patients suspected of having COVID-19 from 15 emergency departments from 2020-03-13 to 2020-04-14 were included as long as chest CT-scans and real-time polymerase chain reaction (RT-PCR) results were available (244 [47.6%] with a positive RT-PCR). Immediately after their acquisition, the chest CTs were prospectively interpreted by on-call teleradiologists (OCTRs) and systematically reviewed within one week by another senior teleradiologist. Each OCTR reading was concluded using a 5-point scale: normal, non-infectious,

infectious non-COVID-19, indeterminate and highly suspicious of COVID-19. The senior reading reported the lesions' semiology, distribution, extent and differential diagnoses. After pre-filtering clinical and radiological features through univariate Chi-2, Fisher or Student t-tests (as appropriate), multivariate stepwise logistic regression (Step-LR) and classification tree (CART) models to predict a positive RT-PCR were trained on 412 patients, validated on an independent cohort of 101 patients and compared with the OCTR performances (295 and 71 with available clinical data, respectively) through area under the receiver operating characteristics curves (AUC). Regarding models elaborated on radiological variables alone, best performances were reached with the CART model (i.e., AUC = 0.92 [versus 0.88 for OCTR], sensitivity = 0.77, specificity = 0.94) while step-LR provided the highest AUC with clinical-radiological variables (AUC = 0.93 [versus 0.86 for OCTR], sensitivity = 0.82, specificity = 0.91). Hence, these two simple models, depending on the availability of clinical data, provided high performances to diagnose positive RT-PCR and could be used by any radiologist to support, modulate and communicate their conclusion in case of COVID-19 suspicion. Practically, using clinical and radiological variables (GGO, fever, presence of fibrotic bands, presence of diffuse lesions, predominant peripheral distribution) can accurately predict RT-PCR status.

Reference

https://www.nature.com/articles/s41598-021-88053-6

Analysis of IgM, IgA, and IgG isotype antibodies Directed against SARS-CoV-2 spike glycoprotein and ORF8 in the course of COVID-19

Abstract

Immunoassays are a standard diagnostic tool that assesses immunity in severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. However, immunoassays do not provide information about contaminating antigens or cross-reactions and might exhibit inaccurately high sensitivity and low specificity. We aimed to gain insight into the serological immune response of SARS-CoV-2 patients by immunoblot analysis. We analyzed serum immunoglobulins IgM, -A, and -G directed against SARS-CoV-2 proteins by immunoblot analysis from 12 infected patients. We determined IgG isotype antibodies by commercially available ELISA and assessed the clinical parameters of inflammation status and kidney and liver injury. Unexpectedly, we

found no correlation between the presence of antibodies and the future course of the disease. However, attention should be paid to the parameters CRP, IL-6, and LDH. We found evidence of antibody cross-reactivity, which questions the reliability of results for serum samples that tested negative for anti-SARS-CoV-2 antibodies when assessed by immunoassays. Nevertheless, for the detection of IgG anti-SARS-CoV-2 antibodies, our data suggest that the use of the spike glycoprotein in immunoassays should be sufficient to identify positive patients. Using a combination of the spike glycoprotein and the open reading frame 8 protein could prove to be the best way of detecting anti-SARS-CoV-2 IgM antibodies.

Reference

https://www.nature.com/articles/s41598-021-88356-8

SARS-CoV-2 does not have a strong effect on the nasopharyngeal microbial composition

Abstract

The coronavirus disease 2019 (COVID-19) has rapidly spread around the world, impacting the lives of many individuals. Growing evidence suggests that the nasopharyngeal and respiratory tract microbiome are influenced by various health and disease conditions, including the presence and the severity of different viral disease. To evaluate the potential interactions between Severe Acute Respiratory Syndrome Corona 2 (SARS-CoV-2) and the nasopharyngeal microbiome. Microbial composition of nasopharyngeal swab samples submitted to the clinical microbiology lab for suspected SARS-CoV-2 infections was assessed using 16S amplicon sequencing. The study included a total of 55 nasopharyngeal samples from 33 subjects, with longitudinal sampling available for 12 out of the 33 subjects. 21 of the 33 subjects had at least one positive COVID-19 PCR results as determined by the clinical microbiology lab. Inter-personal variation was the strongest factor explaining > 75% of the microbial variation, irrespective of the SARS-CoV-2 status. No significant effect of SARS-CoV-2 on the nasopharyngeal microbial community was observed using multiple analysis methods. These results indicate that unlike some other viruses, for which an effect on the microbial composition was noted, SARS-CoV-2 does not have a strong effect on the nasopharynx microbial habitants.

Reference

https://www.nature.com/articles/s41598-021-88536-6

Analysis and forecasting of global real time RT-PCR primers and probes for SARS-CoV-2

Abstract

Rapid tests for active SARS-CoV-2 infections rely on reverse transcription polymerase chain reaction (RT-PCR). RT-PCR uses reverse transcription of RNA into complementary DNA (cDNA) and amplification of specific DNA (primer and probe) targets using polymerase chain reaction (PCR). The technology makes rapid and specific identification of the virus possible based on sequence homology of nucleic acid sequence and is much faster than tissue culture or animal cell models. However the technique can lose sensitivity over time as the virus evolves and the target sequences diverge from the selective primer sequences. Different primer sequences have been adopted in different geographic regions. As we rely on these existing RT-PCR primers to track and manage the spread of the Coronavirus, it is imperative to understand how SARS-CoV-2 mutations, over time and geographically, diverge from existing primers used today. In this study, we analyze the performance of the SARS-CoV-2 primers in use today by measuring the number of mismatches between primer sequence and genome targets over time and spatially. We find that there is a growing number of mismatches, an increase by 2% per month, as well as a high specificity of virus based on geographic location.

Reference

https://www.nature.com/articles/s41598-021-88532-w

Increased viral variants in children and young adults with impaired humoral immunity and persistent SARS-CoV-2 infection: A consecutive case series

Abstract

Background: There is increasing concern that persistent infection of SARS-CoV-2 within immunocompromised hosts could serve as a reservoir for mutation accumulation and subsequent emergence of novel strains with the potential to evade immune responses.

Methods: Three patients with acute lymphoblastic leukemia were described who were persistently positive for SARS-CoV-2 by real-time polymerase chain reaction. Viral viability from longitudinally-collected specimens was assessed. Whole-genome sequencing and serological studies were performed to measure viral evolution and evidence of immune escape.

Findings: Compelling evidence was found of ongoing replication and infectivity for up to 162 days from initial positive by subgenomic RNA, single-stranded RNA, and viral culture analysis. The results reveal a broad spectrum of infectivity, host immune responses, and accumulation of mutations, some with the potential for immune escape.

Interpretation: The results highlight the potential need to reassess infection control precautions in the management and care of immunocompromised patients. Routine surveillance of mutations and evaluation of their potential impact on viral transmission and immune escape should be considered.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00148-1/fulltext

Publication Date: Apr 25, 2021

An autopsy study of the spectrum of severe COVID-19 in children: From SARS to different phenotypes of MIS-C

Abstract

Background: COVID-19 in children is usually mild or asymptomatic, but severe and fatal paediatric cases have been described. The pathology of COVID-19 in children is not known; the proposed pathogenesis for severe cases includes immune-mediated mechanisms or the direct effect of SARS-CoV-2 on tissues. We describe the autopsy findings in five cases of paediatric COVID-19 and provide mechanistic insight into the mechanisms involved in the pathogenesis of the disease.

Methods: Children and adolescents who died with COVID-19 between March 18 and August 15, 2020 were autopsied with a minimally invasive method. Tissue samples from all vital organs were analysed by histology, electron microscopy (EM), reverse-transcription polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC).

Findings: Five patients were included, one male and four female, aged 7 months to 15 years. Two patients had severe diseases before SARS-CoV-2 infection: adrenal carcinoma and Edwards syndrome. Three patients were previously healthy and had multisystem inflammatory syndrome in children (MIS-C) with distinct clinical presentations: myocarditis, colitis, and acute encephalopathy with status epilepticus. Autopsy findings varied amongst patients and included mild to severe COVID-19 pneumonia, pulmonary microthrombosis, cerebral oedema with reactive gliosis, myocarditis, intestinal inflammation, and haemophagocytosis. SARS-CoV-2 was detected in all patients in lungs, heart and kidneys by at least one method (RT-PCR, IHC or EM), and in endothelial cells from heart and brain in two patients with MIS-C (IHC). In addition, we show for the first time the presence of SARS-CoV-2 in the brain tissue of a child with MIS-C with acute encephalopathy, and in the intestinal tissue of a child with acute colitis. Interpretation: SARS-CoV-2 can infect several cell and tissue types in paediatric patients, and the target organ for the clinical manifestation varies amongst individuals. Two major patterns of severe COVID-19 were observed: a primarily pulmonary disease, with severe acute respiratory disease and diffuse alveolar damage, or a multisystem inflammatory syndrome with the involvement of several organs. The presence of SARS-CoV-2 in several organs, associated with cellular ultrastructural changes, reinforces the hypothesis that a direct effect of SARS-CoV-2 on tissues is involved in the pathogenesis of MIS-C.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00130-9/fulltext

Therapeutic antibodies, targeting the SARS-CoV-2 spike *N*-terminal domain, protect lethally infected K18-hACE2 mice

Abstract

Neutralizing antibodies represent a valuable therapeutic approach to countermeasure the current COVID-19 pandemic. Emergence of SARS-CoV-2 variants emphasizes the notion that antibody treatments need to rely on highly neutralizing monoclonal antibodies (mAbs), targeting several distinct epitopes for circumventing therapy escape-mutants. Previously, we reported efficient human therapeutic mAbs recognizing epitopes on the spike receptor binding domain (RBD) of SARS-CoV-2. Here we report

the isolation, characterization and recombinant production of 12 neutralizing human mAbs, targeting three distinct epitopes on the spike N-terminal domain (NTD) of the virus. Neutralization mechanism of these antibodies involves receptors other than the canonical hACE2 on target cells, relying both on amino-acid and N-glycan epitope-recognition, suggesting alternative viral cellular-portals. Two selected mAbs demonstrated full protection of K18-hACE2 transgenic mice when administered at low doses and late post-exposure, demonstrating the high potential of the mAbs for therapy of SARS-CoV-2 infection.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00447-8

Experimental and natural evidence of SARS-CoV-2 infection-induced activation of type I interferon responses

Abstract

Type I interferons (IFNs) are our first line of defence against virus infection. Recent studies have suggested the ability of SARS-CoV-2 proteins to inhibit IFN responses. Emerging data also suggest that timing and extent of IFN production is associated with manifestation of COVID-19 severity. In spite of progress in understanding how SARS-CoV-2 activates antiviral responses, mechanistic studies into wildtype SARS-CoV-2-mediated induction and inhibition of human type I IFN responses are scarce. Here we demonstrate that SARS-CoV-2 infection induces a type I IFN response in vitro and in moderate cases of COVID-19. In vitro stimulation of type I IFN expression and signaling in human airway epithelial cells is associated with activation of canonical transcriptions factors, and SARS-CoV-2 is unable to inhibit exogenous induction of these responses. Furthermore, we show that physiological levels of IFNα detected in patients with moderate COVID-19 is sufficient to suppress SARS-CoV-2 replication in human airway cells.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00445-4

Analysis of the potential impact of durability, timing, and transmission blocking of COVID-19 vaccine on morbidity and mortality

Abstract

Background: COVID-19 vaccines have been approved and made available. While questions of vaccine allocation strategies have received significant attention, important questions remain regarding the potential impact of the vaccine given uncertainties regarding efficacy against transmission, availability, timing, and durability.

Methods: A susceptible-exposed-infectious-recovered (SEIR) model was adapted to examine the potential impact on hospitalization and mortality assuming increasing rates of vaccine efficacy, coverage, and administration. The uncertainty of the vaccine was also evaluated to prevent infectiousness as well as the impact on outcomes based on the timing of distribution and the potential effects of waning immunity.

Findings: Increased vaccine efficacy against disease reduces hospitalizations and deaths from COVID-19; however, the relative benefit of transmission blocking varied depending on the timing of vaccine distribution. Early in an outbreak, a vaccine that reduces transmission will be relatively more effective than one introduced later in the outbreak. In addition, earlier and accelerated implementation of a less effective vaccine is more impactful than later implementation of a more effective vaccine. These findings are magnified when considering the durability of the vaccine. Vaccination in the spring will be less impactful when immunity is less durable.

Interpretation: Policy choices regarding non-pharmaceutical interventions, such as social distancing and face mask use, will need to remain in place longer if the vaccine is less effective at reducing transmission or distributed slower. In addition, the stage of the local outbreak greatly impacts the overall effectiveness of the vaccine in a region and should be considered when allocating vaccines.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00143-7/fulltext

RNA-induced liquid phase separation of SARS-CoV-2 nucleocapsid protein facilitates NF-κB hyper-activation and inflammation

Abstract

The ongoing 2019 novel coronavirus disease (COVID-19) caused by SARS-CoV-2 has posed a worldwide pandemic and a major global public health threat. The severity and mortality of COVID-19 are associated with virus-induced dysfunctional inflammatory responses and cytokine storms. However, the interplay between host inflammatory responses and SARS-CoV-2 infection remains largely unknown. Here, we demonstrate that SARS-CoV-2 nucleocapsid (N) protein, the major structural protein of the virion, promotes the virus-triggered activation of NF-κB signaling. After binding to viral RNA, N protein robustly undergoes liquid–liquid phase separation (LLPS), which recruits TAK1 and IKK complex, the key kinases of NF-κB signaling, to enhance NF-κB activation. Moreover, 1,6-hexanediol, the inhibitor of LLPS, can attenuate the phase separation of N protein and restrict its regulatory functions in NF-κB activation. These results suggest that LLPS of N protein provides a platform to induce NF-κB hyper-activation, which could be a potential therapeutic target against COVID-19 severe pneumonia.

Reference

https://www.nature.com/articles/s41392-021-00575-7

An integrative drug repositioning framework discovered a potential therapeutic agent targeting COVID-19

Abstract

The global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) requires an urgent need to find effective therapeutics for the treatment of coronavirus disease 2019 (COVID-19). In this study, an integrative drug repositioning framework was developed, which fully takes advantage of machine learning and statistical analysis approaches to systematically integrate and mine large-scale knowledge graph, literature and transcriptome data to discover the potential drug candidates against SARS-CoV-2. Our in silico screening followed by wet-lab validation indicated that a poly-ADP-ribose polymerase 1 (PARP1) inhibitor, CVL218, currently in Phase I clinical trial, may be

repurposed to treat COVID-19. The *in vitro* assays revealed that CVL218 can exhibit effective inhibitory activity against SARS-CoV-2 replication without obvious cytopathic effect. In addition, we showed that CVL218 can interact with the nucleocapsid (N) protein of SARS-CoV-2 and is able to suppress the LPS-induced production of several inflammatory cytokines that are highly relevant to the prevention of immunopathology induced by SARS-CoV-2 infection.

Reference

https://www.nature.com/articles/s41392-021-00568-6

The olfactory route is a potential way for SARS-CoV-2 to invade the central nervous system of rhesus monkeys

Abstract

Neurological manifestations are frequently reported in the COVID-19 patients. Neuromechanism of SARS-CoV-2 remains to be elucidated. In this study, the mechanisms of SARS-CoV-2 neurotropism was explored via the established non-human primate model of COVID-19. In rhesus monkey, SARS-CoV-2 invades the CNS primarily via the olfactory bulb. Thereafter, viruses rapidly spread to functional areas of the central nervous system, such as hippocampus, thalamus, and medulla oblongata. The infection of SARS-CoV-2 induces the inflammation possibly by targeting neurons, microglia, and astrocytes in the CNS. Consistently, SARS-CoV-2 infects neuro-derived SK-N-SH, glial-derived U251, and brain microvascular endothelial cells in vitro. To our knowledge, this is the first experimental evidence of SARS-CoV-2 neuroinvasion in the NHP model, which provides important insights into the CNS-related pathogenesis of SARS-CoV-2.

Reference

https://www.nature.com/articles/s41392-021-00591-7

A comprehensive antigen production and characterisation study for easy-to-implement, specific and quantitative SARS-CoV-2 serotests

Abstract

Background: Antibody tests are essential tools to investigate humoral immunity following SARS-CoV-2 infection or vaccination. While first-generation antibody tests

have primarily provided qualitative results, accurate seroprevalence studies and tracking of antibody levels over time require highly specific, sensitive and quantitative test setups.

Methods: Two quantitative, easy-to-implement SARS-CoV-2 antibody tests were developed, based on the spike receptor binding domain and the nucleocapsid protein. Comprehensive evaluation of antigens from several biotechnological platforms enabled the identification of superior antigen designs for reliable serodiagnostic. Cut-off modelling based on unprecedented large and heterogeneous multicentric validation cohorts allowed us to define optimal thresholds for the tests' broad applications in different aspects of clinical use, such as seroprevalence studies and convalescent plasma donor qualification.

Findings: Both developed serotests individually performed similarly-well as fully-automated CE-marked test systems. The described sensitivity-improved orthogonal test approach assures highest specificity (99.8%); thereby enabling robust serodiagnosis in low-prevalence settings with simple test formats. The inclusion of a calibrator permits accurate quantitative monitoring of antibody concentrations in samples collected at different time points during the acute and convalescent phase of COVID-19 and disclosed antibody level thresholds that correlate well with robust neutralization of authentic SARS-CoV-2 virus.

Interpretation: We demonstrate that antigen source and purity strongly impact serotest performance. Comprehensive biotechnology-assisted selection of antigens and in-depth characterisation of the assays allowed us to overcome limitations of simple ELISA-based antibody test formats based on chromometric reporters, to yield comparable assay performance as fully-automated platforms.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00141-9/fulltext

Accelerated vaccine rollout is imperative to mitigate highly transmissible COVID-19 variants

Abstract

Background: More contagious variants of SARS-CoV-2 have emerged around the world, sparking concerns about impending surge in cases and severe outcomes. Despite the development of effective vaccines, rollout has been slow. We evaluated the impact of accelerated vaccine distribution on curbing the disease burden of novel SARS-CoV-2 variants.

Methods: An agent-based model was used of SARS-CoV-2 transmission and vaccination to simulate the spread of novel variants with S-Gene Target Failure (SGTF) in addition to the original strain. Age-specific risk was incorporated and contact patterns and implemented a two-dose vaccination campaign in accord with CDC-recommended prioritization. As a base case, we projected hospitalizations and deaths at a daily vaccination rate of 1 million doses in the United States (US) and compared with accelerated campaigns in which daily doses were expanded to 1.5, 2, 2.5, or 3 million.

Findings: It was found that at a vaccination rate of 1 million doses per day, an emergent SGTF variant that is 20–70% more transmissible than the original variant would become dominant within 2 to 9 weeks, accounting for as much as 99% of cases at the outbreak peak. The results show that accelerating vaccine delivery would substantially reduce severe health outcomes. For a SGTF with 30% higher transmissibility, increasing vaccine doses from 1 to 3 million per day would avert 152,048 (95% CrI: 134,772–168,696) hospitalizations and 48,448 (95% CrI: 42,042–54,285) deaths over 300 days. Accelerated vaccination would also prevent additional COVID-19 waves that would otherwise be fuelled by waning adherence to non-pharmaceutical interventions (NPIs).

Interpretation: It was found that the current pace of vaccine rollout is insufficient to prevent the exacerbation of the pandemic that will be attributable to the novel, more contagious SARS-CoV-2 variants. Accelerating the vaccination rate should be a public health priority for averting the expected surge in COVID-19 hospitalizations and deaths that would be associated with widespread dissemination of the SGTF variants. Our results underscore the need to bolster the production and distribution of COVID-19 vaccines, to rapidly expand vaccination priority groups and distribution sites.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00145-0/fulltext

Publication Date: Apr 23, 2021

Diverse immunoglobulin gene usage and convergent epitope targeting in neutralizing antibody responses to SARS-CoV-2

Abstract

It is unclear whether individuals with enormous diversity in B cell receptor repertoires are consistently able to mount effective antibody responses against SARS-CoV-2. We analyzed antibody responses in a cohort of 55 convalescent patients and isolated 54 potent neutralizing monoclonal antibodies (mAbs). While most of the mAbs target the angiotensin-converting enzyme 2 (ACE2) binding surface on the receptor binding domain (RBD) of SARS-CoV-2 spike protein, mAb 47D1 binds only to one side of the receptor binding surface on the RBD. Neutralization by 47D1 is achieved independent of interfering RBD-ACE2 binding. A crystal structure of the mAb-RBD complex shows that the IF motif at the tip of 47D1 CDR H2 interacts with a hydrophobic pocket in the RBD. Diverse immunoglobulin gene usage and convergent epitope targeting characterize neutralizing antibody responses to SARS-CoV-2, suggesting that vaccines that effectively present the receptor binding site on the RBD will likely elicit neutralizing antibody responses in a large fraction of the population.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00443-5

COVID-19 pathophysiology may be driven by an imbalance in the renin-angiotensin-aldosterone system

Abstract

SARS-CoV-2 uses ACE2, an inhibitor of the Renin-Angiotensin-Aldosterone System (RAAS), for cellular entry. Studies indicate that RAAS imbalance worsens the prognosis in COVID-19. A consecutive retrospective COVID-19 cohort was presented with findings of frequent pulmonary thromboembolism (17%), high pulmonary artery pressure (60%) and lung MRI perfusion disturbances. It was demonstrated, in swine, that infusing angiotensin II or blocking ACE2 induces increased pulmonary artery pressure, reduces

blood oxygenation, increases coagulation, disturbs lung perfusion, induces diffuse alveolar damage, and acute tubular necrosis compared to control animals. We further demonstrate that this imbalanced state can be ameliorated by infusion of an angiotensin receptor blocker and low-molecular-weight heparin. In this work, we show that a pathophysiological state in swine induced by RAAS imbalance shares several features with the clinical COVID-19 presentation. Therefore, we propose that severe COVID-19 could partially be driven by a RAAS imbalance.

Reference

https://www.nature.com/articles/s41467-021-22713-z

Multiscale statistical physics of the pan-viral interactome unravels the systemic nature of SARS-CoV-2 infections

Abstract

Protein–protein interaction networks have been used to investigate the influence of SARS-CoV-2 viral proteins on the function of human cells, laying out a deeper understanding of COVID–19 and providing ground for applications, such as drug repurposing. Characterizing molecular (dis)similarities between SARS-CoV-2 and other viral agents allows one to exploit existing information about the alteration of key biological processes due to known viruses for predicting the potential effects of this new virus. Here, we compare the novel coronavirus network against 92 known viruses, from the perspective of statistical physics and computational biology. We show that regulatory spreading patterns, physical features and enriched biological pathways in targeted proteins lead, overall, to meaningful clusters of viruses which, across scales, provide complementary perspectives to better characterize SARS-CoV-2 and its effects on humans. Our results indicate that the virus responsible for COVID–19 exhibits expected similarities, such as to Influenza A and Human Respiratory Syncytial viruses, and unexpected ones with different infection types and from distant viral families, like HIV1 and Human Herpes virus. Taken together, our findings indicate that COVID–19 is a systemic disease with potential effects on the function of multiple organs and human body sub-systems.

Reference

https://www.nature.com/articles/s42005-021-00582-8

A small interfering RNA (siRNA) database for SARS-CoV-2

Abstract

Coronavirus disease 2019 (COVID-19) rapidly transformed into a global pandemic, for which a demand for developing antivirals capable of targeting the SARS-CoV-2 RNA genome and blocking the activity of its genes has emerged. In this work, we presented a database of SARS-CoV-2 targets for small interference RNA (siRNA) based approaches, aiming to speed the design process by providing a broad set of possible targets and siRNA sequences. The siRNAs sequences are characterized and evaluated by more than 170 features, including thermodynamic information, base context, target genes and alignment information of sequences against the human genome, and diverse SARS-CoV-2 strains, to assess possible bindings to off-target sequences. This dataset is available as a set of four tables, available in a spreadsheet and CSV (Comma-Separated Values) formats, each one corresponding to sequences of 18, 19, 20, and 21 nucleotides length, aiming to meet the diversity of technology and expertise among laboratories around the world. A metadata table, which describes each feature, is also provided in the aforementioned formats. We hope that this database helps to speed up the development of new target antivirals for SARS-CoV-2, contributing to a possible strategy for a faster and effective response to the COVID-19 pandemic.

Reference

https://www.nature.com/articles/s41598-021-88310-8

Structure and function analysis of a potent human neutralizing antibody CA521FALA against SARS-CoV-2

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing COVID-19 pandemic, which has resulted in more than two million deaths at 2021 February . There is currently no approved therapeutics for treating COVID-19. The SARS-CoV-2 Spike protein is considered a key therapeutic target by many researchers. Here we describe the identification of several monoclonal antibodies that

target SARS-CoV-2 Spike protein. One human antibody, CA521FALA, demonstrated neutralization potential by immunizing human antibody transgenic mice. CA521FALA showed potent SARS-CoV-2-specific neutralization activity against SARS-CoV-2 pseudovirus and authentic SARS-CoV-2 infection in vitro. CA521FALA also demonstrated having a long half-life of 9.5 days in mice and 9.3 days in rhesus monkeys. CA521FALA inhibited SARS-CoV-2 infection in SARS-CoV-2 susceptible mice at a therapeutic setting with virus titer of the lung reduced by 4.5 logs. Structural analysis by cryo-EM revealed that CA521FALA recognizes an epitope overlapping with angiotensin converting enzyme 2 (ACE2)-binding sites in SARS-CoV-2 RBD in the Spike protein. CA521FALA blocks the interaction by binding all three RBDs of one SARS-CoV-2 spike trimer simultaneously. These results demonstrate the importance for antibody-based therapeutic interventions against COVID-19 and identifies CA521FALA a promising antibody that reacts with SARS-CoV-2 Spike protein to strongly neutralize its activity.

Reference

https://www.nature.com/articles/s42003-021-02029-w

Structural insight into SARS-CoV-2 neutralizing antibodies and modulation of syncytia

Abstract

Infection by SARS-CoV-2 is initiated by binding of viral Spike protein to host receptor angiotensin-converting enzyme 2 (ACE2), followed by fusion of viral and host membranes. While antibodies that block this interaction are in emergency use as early COVID-19 therapies, precise determinants of neutralization potency remain unknown. We discovered a series of antibodies that all potently block ACE2 binding, yet exhibit divergent neutralization efficacy against live virus. Strikingly, these neutralizing antibodies can either inhibit or enhance Spike-mediated membrane fusion and formation of syncytia, which are associated with chronic tissue damage in COVID-19 patients. Multiple cryogenic electron microscopy structures of Spike-antibody complexes reveal distinct binding modes that not only block ACE2 binding, but also alter the Spike protein conformational cycle triggered by ACE2 binding. We show that stabilization of different Spike conformations leads to modulation of Spike-mediated membrane fusion, with profound implications in COVID-19 pathology and immunity.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00536-5

B cell genomics behind cross-neutralization of SARS-CoV-2 variants and SARS-CoV

Abstract

Monoclonal antibodies (mAbs) are a focus in vaccine and therapeutic design to counteract SARS-CoV-2 and its variants. Here, we combined B cell sorting with single-cell VDJ and RNA-seq and mAb structures to characterize B cell responses against SARS-CoV-2. We show that the SARS-CoV-2-specific B cell repertoire consists of transcriptionally distinct B cell populations with cells producing potently neutralizing antibodies (nAbs) localized in two clusters that resemble memory and activated B cells. Cryo-electron microscopy structures of selected nAbs from these two clusters complexed with SARS-CoV-2 spike trimers show recognition of various receptor-binding domain (RBD) epitopes. One of these mAbs, BG10-19, locks the spike trimer in a closed conformation to potently neutralize SARS-CoV-2, the recently arising mutants B.1.1.7 and B.1.351, and SARS-CoV and cross-reacts with heterologous RBDs. Together, our results characterize transcriptional differences among SARS-CoV-2-specific B cells and uncover cross-neutralizing Ab targets that will inform immunogen and therapeutic design against coronaviruses.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00535-3

Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: A national prospective cohort study

Abstract

Background: The BNT162b2 mRNA (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (Oxford–AstraZeneca) COVID-19 vaccines have shown high efficacy against disease in phase 3 clinical trials and are now being used in national vaccination programmes in the UK and several other countries. Studying the real-world effects of these vaccines is an urgent requirement. The aim of our study was to investigate the association between

the mass roll-out of the first doses of these COVID-19 vaccines and hospital admissions for COVID-19.

Methods: A prospective cohort study was done using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19—EAVE II—database comprising linked vaccination, primary care, real-time reverse transcription-PCR testing, and hospital admission patient records for 5·4 million people in Scotland (about 99% of the population) registered at 940 general practices. Individuals who had previously tested positive were excluded from the analysis. A time-dependent Cox model and Poisson regression models with inverse propensity weights were fitted to estimate effectiveness against COVID-19 hospital admission (defined as 1–adjusted rate ratio) following the first dose of vaccine.

Findings: Between Dec 8, 2020, and Feb 22, 2021, a total of 1 331 993 people were vaccinated over the study period. The mean age of those vaccinated was 65·0 years (SD 16·2). The first dose of the BNT162b2 mRNA vaccine was associated with a vaccine effect of 91% (95% CI 85–94) for reduced COVID-19 hospital admission at 28–34 days post-vaccination. Vaccine effect at the same time interval for the ChAdOx1 vaccine was 88% (95% CI 75–94). Results of combined vaccine effects against hospital admission due to COVID-19 were similar when restricting the analysis to those aged 80 years and older (83%, 95% CI 72–89 at 28–34 days post-vaccination).

Interpretation: Mass roll-out of the first doses of the BNT162b2 mRNA and ChAdOx1 vaccines was associated with substantial reductions in the risk of hospital admission due to COVID-19 in Scotland. There remains the possibility that some of the observed effects might have been due to residual confounding.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00677-2/fulltext

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

Abstract

Background: BNT162b2 mRNA and ChAdOx1 nCOV-19 adenoviral vector vaccines have been rapidly rolled out in the UK from December, 2020. It was aimed to determine the factors associated with vaccine coverage for both vaccines and documented the vaccine effectiveness of the BNT162b2 mRNA vaccine in a cohort of health-care workers undergoing regular asymptomatic testing.

Methods: The SIREN study is a prospective cohort study among staff (aged ≥18 years) working in publicly-funded hospitals in the UK. Participants were assigned into either the positive cohort (antibody positive or history of infection [indicated by previous positivity of antibody or PCR tests]) or the negative cohort (antibody negative with no previous positive test) at the beginning of the follow-up period. Baseline risk factors were collected at enrolment, symptom status was collected every 2 weeks, and vaccination status was collected through linkage to the National Immunisations Management System and questionnaires. Participants had fortnightly asymptomatic SARS-CoV-2 PCR testing and monthly antibody testing, and all tests (including symptomatic testing) outside SIREN were captured. Data cutoff for this analysis was Feb 5, 2021. The follow-up period was Dec 7, 2020, to Feb 5, 2021. The primary outcomes were vaccinated participants (binary ever vacinated variable; indicated by at least one vaccine dose recorded by at least one of the two vaccination data sources) for the vaccine coverage analysis and SARS-CoV-2 infection confirmed by a PCR test for the vaccine effectiveness analysis. A mixed-effect logistic regression analysis was done to identify factors associated with vaccine coverage. We used a piecewise exponential hazard mixed-effects model (shared frailty-type model) using a Poisson distribution to calculate hazard ratios to compare time-to-infection in unvaccinated and vaccinated participants and estimate the impact of the BNT162b2 vaccine on all PCR-positive infections (asymptomatic and symptomatic). This study is registered with ISRCTN, number ISRCTN11041050, and is ongoing.

Findings: 23 324 Participants from 104 sites (all in England) met the inclusion criteria for this analysis and were enrolled. Included participants had a median age of 46·1 years

(IQR 36·0–54·1) and 19 692 (84%) were female; 8203 (35%) were assigned to the positive cohort at the start of the analysis period, and 15 121 (65%) assigned to the negative cohort. Total follow-up time was 2 calendar months and 1 106 905 person-days (396 318 vaccinated and 710 587 unvaccinated). Vaccine coverage was 89% on Feb 5, 2021, 94% of whom had BNT162b2 vaccine. Significantly lower coverage was associated with previous infection, gender, age, ethnicity, job role, and Index of Multiple Deprivation score. During follow-up, there were 977 new infections in the unvaccinated cohort, an incidence density of 14 infections per 10 000 person-days; the vaccinated cohort had 71 new infections 21 days or more after their first dose (incidence density of eight infections per 10 000 person-days) and nine infections 7 days after the second dose (incidence density four infections per 10 000 person-days). In the unvaccinated cohort, 543 (56%) participants had typical COVID-19 symptoms and 140 (14%) were asymptomatic on or 14 days before their PCR positive test date, compared with 29 (36%) with typical COVID-19 symptoms and 15 (19%) asymptomatic in the vaccinated cohort. A single dose of BNT162b2 vaccine showed vaccine effectiveness of 70% (95% CI 55–85) 21 days after first dose and 85% (74–96) 7 days after two doses in the study population.

Interpretation: The findings show that the BNT162b2 vaccine can prevent both symptomatic and asymptomatic infection in working-age adults. This cohort was vaccinated when the dominant variant in circulation was B1.1.7 and shows effectiveness against this variant.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00790-X/fulltext

Publication Date: Apr 22, 2021

METTL3 regulates viral m6A RNA modification and host cell innate immune responses during SARS-CoV-2 infection

Abstract

It is urgent and important to understand the relationship of the widespread severe acute respiratory syndrome coronavirus clade 2 (SARS-CoV-2) with host immune response and study the underlining molecular mechanism. N^6-methylation of adenosine (m6A) in

RNA regulates many physiological and disease processes. Here, we investigate m6A modification of SARS-CoV-2 gene in regulating host cell innate immune response. Our data show that SARS-CoV-2 virus has m6A modifications which are enriched in the 3'-end of the viral genome. We find that host cell m6A methyltransferase METTL3 depletion decreases m6A levels in SARS-CoV-2 and host genes, and m6A reduction in viral RNA increases RIG-I binding and subsequently enhances downstream innate immune signaling pathway and inflammatory gene expression. METTL3 expression is reduced and inflammatory genes are induced in severe COVID-19 patients. These findings will aid to understand the COVID-19 pathogenesis and help in designing future studies of regulating innate immunity for COVID-19 treatment.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00425-3

Immunogenicity of a new gorilla adenovirus vaccine candidate for COVID-19

Abstract

The COVID-19 pandemic caused by the emergent SARS-CoV-2 coronavirus threatens global public health and there is an urgent need to develop safe and effective vaccines. Here we report the generation and the preclinical evaluation of a novel replication-defective gorilla adenovirus-vectored vaccine encoding the pre-fusion stabilized Spike (S) protein of SARS-CoV2. We show that our vaccine candidate, GRAd-COV2, is highly immunogenic both in mice and macaques, eliciting both functional antibodies which neutralize SARS-CoV-2 infection and block Spike protein binding to the ACE2 receptor, and a robust, Th1-dominated cellular response. We show here that the pre-fusion stabilized Spike antigen is superior to the wild type in inducing ACE2-interfering, SARS-CoV2 neutralizing antibodies. To face the unprecedented need for vaccine manufacturing at massive scale, different GRAd genome deletions were compared to select the vector backbone showing the highest productivity in stirred tank bioreactors. This preliminary dataset identified GRAd-COV2 as a potential COVID-19 vaccine candidate, supporting the translation of GRAd-COV2 vaccine in a currently ongoing Phase I clinical trial (NCT04528641).

Reference

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(21)00210-0

Maternal respiratory SARS-CoV-2 infection in pregnancy is associated with a robust inflammatory response at the maternal-fetal interface

Abstract

Background: Pregnant women are at increased risk for severe outcomes from coronavirus disease 2019 (COVID-19), but the pathophysiology underlying this increased morbidity and its potential effect on the developing fetus is not well understood.

Methods: Placental histology, ACE2 expression, and viral and immune dynamics were assessed at the term placenta in pregnant women with and without respiratory severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Findings: The majority (13 of 15) of placentas analyzed had no detectable viral RNA. ACE2 was detected by immunohistochemistry in syncytiotrophoblast cells of the normal placenta during early pregnancy but was rarely seen in healthy placentas at full term, suggesting that low ACE2 expression may protect the term placenta from viral infection. Using immortalized cell lines and primary isolated placental cells, it was found that cytotrophoblasts, the trophoblast stem cells and precursors to syncytiotrophoblasts, rather than syncytiotrophoblasts or Hofbauer cells, are most vulnerable to SARS-CoV-2 infection *in vitro*. To better understand potential immune mechanisms shielding placental cells from infection in vivo, we performed bulk and single-cell transcriptomics analyses and found that the maternal-fetal interface of SARS-CoV-2-infected women exhibited robust immune responses, including increased activation of natural killer (NK) and T cells, increased expression of interferon-related genes, as well as markers associated with pregnancy complications such as preeclampsia.

Conclusions: SARS-CoV-2 infection in late pregnancy is associated with immune activation at the maternal-fetal interface even in the absence of detectable local viral invasion.

Reference

https://www.cell.com/med/fulltext/S2666-6340(21)00165-3

Transcriptional and epi-transcriptional dynamics of SARS-CoV-2 during cellular infection

Abstract

SARS-CoV-2 uses subgenomic (sg)RNA to produce viral proteins for replication and immune evasion. We applied long-read RNA and cDNA sequencing to in vitro human and primate infection models to study transcriptional dynamics. Transcription-regulating sequence (TRS)-dependent sgRNA was upregulated earlier in infection than TRS-independent sgRNA. An abundant class of TRS-independent sgRNA consisting of a portion of ORF1ab containing nsp1 joined to ORF10 and 3'UTR was upregulated at 48 hours post infection in human cell lines. We identified double-junction sgRNA containing both TRS-dependent and independent junctions. We found multiple sites at which the SARS-CoV-2 genome is consistently more modified than sgRNA, and that sgRNA modifications are stable across transcript clusters, host cells and time since infection. The work highlights the dynamic nature of the SARS-CoV-2 transcriptome during its replication cycle.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00442-3

Psychiatric disorders among hospitalized patients deceased with COVID-19 in Italy

Abstract

Background: There is concern about the increased risk for SARS-CoV-2 infection, COVID-19 severe outcomes and disparity of care among patients with a psychiatric disorder (PD). Based on the Italian COVID-19 death surveillance, which collects data from all the hospitals throughout the country, we aimed to describe clinical features and care pathway of patients dying with COVID-19 and a preceding diagnosis of a PD.

Methods: In this cross-sectional study, the characteristics of a representative sample of patients, who have died with COVID-19 in Italian hospitals between February 21st and

August 3rd 2020, were drawn from medical charts, described and analysed by multinomial logistic regression according to the recorded psychiatric diagnosis: no PD, severe PD (SPD) (i.e. schizophrenia and other psychotic disorders, bipolar and related disorders), common mental disorder (CMD) (i.e. depression without psychotic features, anxiety disorders).

Findings: The 4020 COVID-19 deaths included in the study took place in 365 hospitals across Italy. Out of the 4020 deceased patients, 84 (2•1%) had a previous SPD, 177 (4.4%) a CMD. The mean age at death was 78.0 (95%CI 77.6–78.3) years among patients without a PD, 71.8 (95%CI 69.3–72.0) among those with an SPD, 79.5 (95%CI 78.0–81.1) in individuals with a CMD. 2253 (61.2%) patients without a PD, 62 (73.8%) with an SPD, and 136 (78.2%) with a CMD were diagnosed with three or more non-psychiatric comorbidities. When it was adjusted for clinically relevant variables, including hospital of death, we found that SPD patients died at a younger age than those without a PD (adjusted OR per 1 year increment 0.96; 95% CI 0.94–0.98). Women were significantly more represented among CMD patients compared to patients without previous psychiatric history (aOR 1.56; 95% CI 1.05–2.32). Hospital admission from long-term care facilities (LTCFs) was strongly associated with having an SPD (aOR 9.02; 95% CI 4.99–16.3) or a CMD (aOR 2.09; 95% CI 1.19–3.66). Comorbidity burden, fever, admission to intensive care and time from symptoms' onset to nasopharyngeal swab did not result significantly associated with an SPD or with a CMD in comparison to those without any PD.

Interpretation: Even where equal treatment is in place, the vulnerability of patients with a PD may reduce their chance of recovering from COVID-19. The promotion of personalised therapeutic projects aimed at including people with PD in the community rather than in non-psychiatric LTCFs should be prioritised.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00134-6/fulltext

Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial

Abstract

Background: The trans-membrane protease serine 2 (TMPRSS2) is essential for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry and infection. Efficacy and safety of TMPRSS2 inhibitors in patients with coronavirus disease 2019 (Covid-19) have not been evaluated in randomized trials.

Methods: An investigator-initiated, double-blind, randomized, placebo-controlled multicenter trial was conducted in patients hospitalized with confirmed SARS-CoV-2 infection from April 4, to December 31, 2020. Within 48 h of admission, participants were randomly assigned in a 2:1 ratio to receive the TMPRSS2 inhibitor camostat mesilate 200 mg three times daily for 5 days or placebo. The primary outcome was time to discharge or clinical improvement measured as ≥2 points improvement on a 7-point ordinal scale. Other outcomes included 30-day mortality, safety and change in oropharyngeal viral load. ClinicalTrials.gov Identifier: NCT04321096. EudraCT Number: 2020–001,200–42.

Findings: 137 patients were assigned to receive camostat mesilate and 68 to placebo. Median time to clinical improvement was 5 days (interquartile range [IQR], 3 to 7) in the camostat group and 5 days (IQR, 2 to 10) in the placebo group (P = 0·31). The hazard ratio for 30-day mortality in the camostat compared with the placebo group was 0·82 (95% confidence interval [CI], 0·24 to 2·79; P = 0·75). The frequency of adverse events was similar in the two groups. Median change in viral load from baseline to day 5 in the camostat group was -0·22 log10 copies/mL (p <0·05) and -0·82 log10 in the placebo group (P <0·05).

Interpretation: Under this protocol, camostat mesilate treatment was not associated with increased adverse events during hospitalization for Covid-19 and did not affect time to clinical improvement, progression to ICU admission or mortality.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00129-2/fulltext

CpG-adjuvanted stable prefusion SARS-CoV-2 spike protein protected hamsters from SARS-CoV-2 challenge

Abstract

The COVID-19 pandemic presents an unprecedented challenge to global public health. Rapid development and deployment of safe and effective vaccines are imperative to control the pandemic. In the current study, we applied our adjuvanted stable prefusion SARS-CoV-2 spike (S-2P)-based vaccine, MVC-COV1901, to hamster models to demonstrate immunogenicity and protection from virus challenge. Golden Syrian hamsters immunized intramuscularly with two injections of 1 μg or 5 μg of S-2P adjuvanted with CpG 1018 and aluminum hydroxide (alum) were challenged intranasally with SARS-CoV-2. Prior to virus challenge, the vaccine induced high levels of neutralizing antibodies with 10,000-fold higher IgG level and an average of 50-fold higher pseudovirus neutralizing titers in either dose groups than vehicle or adjuvant control groups. Six days after infection, vaccinated hamsters did not display any weight loss associated with infection and had significantly reduced lung pathology and most importantly, lung viral load levels were reduced to lower than detection limit compared to unvaccinated animals. Vaccination with either 1 μg or 5 μg of adjuvanted S-2P produced comparable immunogenicity and protection from infection. This study builds upon our previous results to support the clinical development of MVC-COV1901 as a safe, highly immunogenic, and protective COVID-19 vaccine.

Reference

https://www.nature.com/articles/s41598-021-88283-8

Quantification of SARS-CoV-2 neutralizing antibody by wild-type plaque reduction neutralization, microneutralization and pseudotyped virus neutralization assays

Abstract

Virus neutralization assays measure neutralizing antibodies in serum and plasma, and the plaque reduction neutralization test (PRNT) is considered the gold standard for measuring levels of these antibodies for many viral diseases. We have developed procedures for the standard PRNT, microneutralization assay (MNA) and pseudotyped virus neutralization assay (PNA) for severe acute respiratory syndrome coronavirus 2. The MNA offers advantages over the PRNT by reducing assay time, allowing increased

throughput and reducing operator workload while remaining dependent upon the use of wild-type virus. This ensures that all severe acute respiratory syndrome coronavirus 2 antigens are present, but Biosafety Level 3 facilities are required. In addition to the advantages of MNA, PNA can be performed with lower biocontainment (Biosafety Level 2 facilities) and allows for further increases in throughput. For each new vaccine, it is critical to ensure good correlation of the neutralizing activity measured using PNA against the PRNT or MNA. These assays have been used in the development and licensure of the ChAdOx1 nCoV-19 (AstraZeneca; Oxford University) and Ad26.COV2.S (Janssen) coronavirus disease 2019 vaccines and are critical for demonstrating bioequivalence of future vaccines.

Reference

https://www.nature.com/articles/s41596-021-00536-y

***Trans*-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity**

Abstract

COVID-19 presents with a wide range of severity, from asymptomatic in some individuals to fatal in others. Based on a study of 1,051,032 23andMe research participants, we report genetic and nongenetic associations with testing positive for SARS-CoV-2, respiratory symptoms and hospitalization. Using trans-ancestry genome-wide association studies, we identified a strong association between blood type and COVID-19 diagnosis, as well as a gene-rich locus on chromosome 3p21.31 that is more strongly associated with outcome severity. Hospitalization risk factors include advancing age, male sex, obesity, lower socioeconomic status, non-European ancestry and preexisting cardiometabolic conditions. While non-European ancestry was a significant risk factor for hospitalization after adjusting for sociodemographics and preexisting health conditions, we did not find evidence that these two primary genetic associations explain risk differences between populations for severe COVID-19 outcomes.

Reference

https://www.nature.com/articles/s41588-021-00854-7

Ambient temperature and subsequent COVID-19 mortality in the OECD countries and individual United States

Abstract

Epidemiological studies have yielded conflicting results regarding climate and incident SARS-CoV-2 infection, and seasonality of infection rates is debated. Moreover, few studies have focused on COVD-19 deaths. We studied the association of average ambient temperature with subsequent COVID-19 mortality in the OECD countries and the individual United States (US), while accounting for other important meteorological and non-meteorological co-variates. The exposure of interest was average temperature and other weather conditions, measured at 25 days prior and 25 days after the first reported COVID-19 death was collected in the OECD countries and US states. The outcome of interest was cumulative COVID-19 mortality, assessed for each region at 25, 30, 35, and 40 days after the first reported death. Analyses were performed with negative binomial regression and adjusted for other weather conditions, particulate matter, sociodemographic factors, smoking, obesity, ICU beds, and social distancing. A 1 °C increase in ambient temperature was associated with 6% lower COVID-19 mortality at 30 days following the first reported death (multivariate-adjusted mortality rate ratio: 0.94, 95% CI 0.90, 0.99, $p = 0.016$). The results were robust for COVID-19 mortality at 25, 35 and 40 days after the first death, as well as other sensitivity analyses. The results provide consistent evidence across various models of an inverse association between higher average temperatures and subsequent COVID-19 mortality rates after accounting for other meteorological variables and predictors of SARS-CoV-2 infection or death. This suggests potentially decreased viral transmission in warmer regions and during the summer season.

Reference

https://www.nature.com/articles/s41598-021-87803-w

Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: A randomized, placebo-controlled, double-blind phase 1 study

Abstract

An effective vaccine is needed to end the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Here, we assess the preliminary safety, tolerability and immunogenicity data from an ongoing single-center (in Jiangsu province, China), parallel-group, double-blind phase 1 trial of the vaccine candidate BNT162b1 in 144 healthy SARS-CoV-2-naive Chinese participants. These participants are randomized 1:1:1 to receive prime and boost vaccinations of 10 μg or 30 μg BNT162b1 or placebo, given 21 d apart, with equal allocation of younger (aged 18–55 years) and older adults (aged 65–85 years) to each treatment group (ChiCTR2000034825). BNT162b1 encodes the SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) and is one of several messenger RNA-based vaccine candidates under clinical investigation. Local reactions and systemic events were generally dose dependent, transient and mild to moderate. Fever was the only grade 3 adverse event. BNT162b1 induced robust interferon-γ T cell responses to a peptide pool including the RBD in both younger and older Chinese adults, and geometric mean neutralizing titers reached 2.1-fold (for younger participants) and 1.3-fold (for the older participants) that of a panel of COVID-19 convalescent human sera obtained at least 14 d after positive SARS-CoV-2 polymerase chain reaction test. In summary, BNT162b1 has an acceptable safety profile and produces high levels of humoral and T cell responses in an Asian population.

Reference

https://www.nature.com/articles/s41591-021-01330-9

Nanoparticle composite TPNT1 is effective against SARS-CoV-2 and influenza viruses

Abstract

A metal nanoparticle composite, namely TPNT1, which contains Au-NP (1 ppm), Ag-NP (5 ppm), ZnO-NP (60 ppm) and ClO2 (42.5 ppm) in aqueous solution was prepared and characterized by spectroscopy, transmission electron microscopy, dynamic light scattering analysis and potentiometric titration. Based on the in vitro cell-based assay,

TPNT1 inhibited six major clades of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with effective concentration within the range to be used as food additives. TPNT1 was shown to block viral entry by inhibiting the binding of SARS-CoV-2 spike proteins to the angiotensin-converting enzyme 2 (ACE2) receptor and to interfere with the syncytium formation. In addition, TPNT1 also effectively reduced the cytopathic effects induced by human (H1N1) and avian (H5N1) influenza viruses, including the wild-type and oseltamivir-resistant virus isolates. Together with previously demonstrated efficacy as antimicrobials, TPNT1 can block viral entry and inhibit or prevent viral infection to provide prophylactic effects against both SARS-CoV-2 and opportunistic infections.

Reference

https://www.nature.com/articles/s41598-021-87254-3

REPORT

Publication Date: Apr 23, 2021

Resurgence of SARS-CoV-2: Detection by community viral surveillance

Abstract

Surveillance of the SARS-CoV-2 epidemic has mainly relied on case reporting which is biased by health service performance, test availability and test-seeking behaviors. We report a community-wide national representative surveillance program in England involving self-administered swab results from 594,000 individuals tested for SARS-CoV-2, regardless of symptoms, from May to beginning of September 2020. The epidemic declined between May and July 2020 but then increased gradually from mid-August, accelerating into early September 2020 at the start of the second wave. When compared to cases detected through routine surveillance, we report here a longer period of decline and a younger age distribution. Representative community sampling for SARS-CoV-2 can substantially improve situational awareness and feed into the public health response even at low prevalence.

Reference

https://science.sciencemag.org/content/early/2021/04/22/science.abf0874

COMMENTARY

Publication Date: Apr 26, 2021

ROS-Driven selection pressure on COVID-19 patients with cardiovascular comorbidities

Coronavirus disease 2019 (COVID-19) has imposed a global health threat which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Currently available data point out that ACE2, the receptor of SARS-CoV-2 in host cells, does not predispose the risk or severity of COVID-19, but rather elevated levels of reactive oxygen species (ROS) impose abnormal selection pressure on patients having cardiovascular comorbidities. As clinical and preventative practice, ROS scavengers are thus recommended for effective therapeutic control of COVID-19 and cardiovascular diseases.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758(21)00032-1

Publication Date: Apr 22, 2021

Higher fatality from COVID-19 in patients with cancer in the UK than in Europe

Echoing concerns expressed by oncologists early in the COVID-19 pandemic, a study led by researchers from Imperial College London (London, UK) has reported that the survival of patients with cancer after infection with SARS-CoV-2 seems to be disparate between the UK and countries in continental Europe, with apparently more detrimental outcomes for patients in the UK compared with their European counterparts. In the retrospective study, David Pinato (Imperial College London) and colleagues analysed the risk of death from all causes at 30 days and 6 months following a diagnosis of COVID-19, in 468 patients with cancer from the UK and 924 patients with cancer from Italy, Spain, France, Belgium, and Germany. The data were obtained from the OnCovid study database, a European registry of patients with cancer consecutively diagnosed with COVID-19 in 27 centres between Feb 27 and Sept 10, 2020. Notably, compared with the continental Europe cohort, the UK cohort had a lower proportion of patients with breast cancer (12·39% vs 23·70%) and a higher proportion of patients with gynaecological or genito-urinary cancers (31·20% vs 14·29%). Even after adjusting for key clinicopathological factors, including age, comorbidities, and tumour stage and status (although the authors noted that their analyses could be affected by unmeasured bias, such as of SARS-CoV-2 viral load), patients in the UK had a significantly higher case-fatality rate at 30 days after a COVID-19 diagnosis than did those in Europe (40·38% vs 26·5%; p<0·0001). This difference in case-fatality rate persisted at 6 months after a COVID-19 diagnosis (47·64% in the UK vs 33·33% in Europe; p<0·0001). Similarly, the risk of death at 30 days after a COVID-19 diagnosis was 1·52-times higher for UK patients than for their European counterparts; at 6 months, this risk of death remained elevated at 1·41-times higher in the UK versus Europe. The authors also reported that UK patients diagnosed with COVID-19 were less likely to be receiving either COVID-19-specific therapies (eg, corticosteroids or antiviral drugs) or to have received active anti-cancer treatment within the previous 4 weeks, compared with those in Europe. In multivariable analyses, exposure to any COVID-19 treatment was associated with a reduced risk of death at both 30 days and at 6 months, whereas

receipt of anticancer therapy exerted a protective effect on the risk of death at the 6 month timepoint only. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00248-5/fulltext

RESOURCE

Publication Date: Apr 12, 2021

The SARS-CoV-2 RNA interactome

Abstract

SARS-CoV-2 is an RNA virus whose success as a pathogen relies on its abilities to repurpose host RNA-binding proteins (RBPs) and to evade antiviral RBPs. To uncover the SARS-CoV-2 RNA interactome, we here develop a robust ribonucleoprotein (RNP) capture protocol and identify 109 host factors that directly bind to SARS-CoV-2 RNAs. Applying RNP capture on another coronavirus HCoV-OC43 revealed evolutionarily conserved interactions between coronaviral RNAs and host proteins. Transcriptome analyses and knockdown experiments delineated 17 antiviral RBPs including ZC3HAV1, TRIM25, PARP12, and SHFL and 8 proviral RBPs such as EIF3D and CSDE1 which are responsible for co-opting multiple steps of the mRNA life cycle. This also led to the identification of LARP1, a downstream target of the mTOR signaling pathway, as an antiviral host factor that interacts with the SARS-CoV-2 RNAs. Overall, this study provides a comprehensive list of RBPs regulating coronaviral replication and opens new avenues for therapeutic interventions.

Reference

https://www.cell.com/molecular-cell/fulltext/S1097-2765(21)00327-0

PERSPECTIVE

Publication Date: Apr 23, 2021

Addressing racial inequities in medicine

COVID-19 inequitably affects marginalized racial and ethnic populations across the world. A review of more than 17 million adult patients in the United Kingdom revealed a nearly twofold risk of death from COVID-19 among Black and Asian populations compared with white populations. Black people comprise 12.5% of the US population, yet they account for more than 18% of COVID-19 associated deaths. Although Black and Latinx populations in the US experience higher rates of infection, hospitalization, and deaths compared with white populations, they have similar case fatality rates, suggesting that there is no innate vulnerability or susceptibility to COVID-19. Persistent COVID-19 racial and ethnic inequities are likely caused by structural racism that results in an increased risk of exposure and inadequate health care access in communities of color. Structural racism, or the discriminatory policies, practices, and systems that reinforce an unequal distribution of power and resources in social institutions, is a considerable driver of health inequities. The COVID-19 pandemic has exacerbated the socioeconomic disadvantages that have led to an overrepresentation of marginalized groups in service-industry jobs and excessive financial insecurities that affect how people live and their ability to access health care. Communities of color are more likely to reside in shared and congregate housing, use public transportation for commuting, and support themselves and their families with low-income jobs. These factors increase COVID-19 exposure, because of the likelihood for more person-to-person contact, and limit the ability to self-isolate. Additionally, these social conditions increase a person's risk for chronic conditions, including hypertension, diabetes, cardiovascular disease, and obesity, that are associated with more severe COVID-19 outcomes. A broad, multisector community-engaged response is required to address the social determinants of health and achieve health equity with COVID-19 and other diseases. The medical and scientific community must be a willing partner in dismantling structural racism in society, which includes an emphasis on addressing the socioeconomic, environmental, and behavioral factors that influence most health outcomes. Although these efforts are critical, there is also an urgent need and opportunity to dismantle

structural racism within the traditional functions of the medical and scientific community (see the figure). This necessitates several actions in clinical practice, medical education, and research: acknowledging that race (group categorizations based on physical traits such as skin color) and ethnicity (groups defined by shared language, history, religion, and culture) are social and political constructs and are a poor proxy for ancestry (inherited genetic variations traced to geographical origins of a person's ancestors); uprooting the racism that is deeply embedded in perspectives, policies, and practices in health systems; and co-creating a new system that incorporates the voices of marginalized populations who are unjustly suffering with unmet social needs and adverse health outcomes related to COVID-19 and other diseases.

Reference

https://science.sciencemag.org/content/372/6540/348