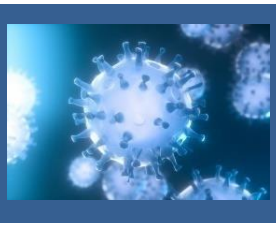
COVID-19

Apr 08-14, 2021



RESEARCH PUBLICATIONS

Publication Date: Apr 14, 2021

Safety, tolerability, and immunogenicity of the respiratory syncytial virus prefusion F subunit vaccine DS-Cav1: A phase 1, randomised, open-label, dose-escalation clinical trial

Abstract

Background: Multiple active vaccination approaches have proven ineffective in reducing the substantial morbidity and mortality caused by respiratory syncytial virus (RSV) in infants and older adults (aged ≥65 years). A vaccine conferring a substantial and sustainable boost in neutralising activity is required to protect against severe RSV disease. To that end, the safety and immunogenicity of DS-Cav1, a prefusion F subunit vaccine, was evaluated.

Methods: In this randomised, open-label, phase 1 clinical trial, the stabilised prefusion F vaccine DS-Cav1 was evaluated for dose, safety, tolerability, and immunogenicity in healthy adults aged 18–50 years at a single US site. Participants were assigned to receive escalating doses of either 50 μg, 150 μg, or 500 μg DS-Cav1 at weeks 0 and 12, and were randomly allocated in a 1:1 ratio within each dose group to receive the vaccine with or without aluminium hydroxide (AlOH) adjuvant. After 71 participants had been randomised, the protocol was amended to allow some participants to receive a single vaccination at week 0. The primary objectives evaluated the safety and tolerability at every dose within 28 days following each injection. Neutralising activity and RSV F-binding antibodies were evaluated from week 0 to week 44 as secondary and exploratory objectives. Safety was assessed in all participants who received at least one vaccine dose; secondary and exploratory immunogenicity analysis included all

participants with available data at a given visit. The trial is registered with ClinicalTrials.gov, NCT03049488, and is complete and no longer recruiting.

Findings: Between Feb 21, 2017, and Nov 29, 2018, 244 participants were screened for eligibility and 95 were enrolled to receive DS-Cav1 at the 50 μg (n=30, of which n=15 with AlOH), 150 μg (n=35, of which n=15 with AlOH), or 500 μg (n=30, of which n=15 with AlOH) doses. DS-Cav1 was safe and well tolerated and no serious vaccine-associated adverse events deemed related to the vaccine were identified. DS-Cav1 vaccination elicited robust neutralising activity and binding antibodies by 4 weeks after a single vaccination (p<0·0001 for F-binding and neutralising antibodies). In analyses of exploratory endpoints at week 44, pre-F-binding IgG and neutralising activity were significantly increased compared with baseline in all groups. At week 44, RSV A neutralising activity was 3·1 fold above baseline in the 50 μg group, 3·8 fold in the 150 μg group, and 4·5 fold in the 500 μg group (p<0·0001). RSV B neutralising activity was 2·8 fold above baseline in the 50 μg group, 3·4 fold in the 150 μg group, and 3·7 fold in the 500 μg group (p<0·0001). Pre-F-binding IgG remained significantly 3·2 fold above baseline in the 50 μg group, 3·4 fold in the 150 μg group, and 4·0 fold in the 500 μg group (p<0·0001). Pre-F-binding serum IgA remained 4·1 fold above baseline in the 50 μg group, 4·3 fold in the 150 μg group, and 4·8 fold in the 500 μg group (p<0·0001). Although a higher vaccine dose or second immunisation elicited a transient advantage compared with lower doses or a single immunisation, neither significantly impacted long-term neutralisation. There was no long-term effect of dose, number of vaccinations, or adjuvant on neutralising activity.

Interpretation: In this phase 1 study, DS-Cav1 vaccination was safe and well tolerated. DS-Cav1 vaccination elicited a robust boost in RSV F-specific antibodies and neutralising activity that was sustained above baseline for at least 44 weeks. A single low-dose of pre-F immunisation of antigen-experienced individuals might confer protection that extends throughout an entire RSV season.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00098-9/fulltext

Data suggest COVID-19 affected numbers greatly exceeded detected numbers, in four European countries, as per a delayed SEIQR model

Abstract

People in many countries are now infected with COVID-19. By now, it is clear that the number of people infected is much greater than the number of reported cases. To estimate the infected but undetected/unreported cases using a mathematical model, we can use a parameter called the probability of quarantining an infected individual. This parameter exists in the time-delayed SEIQR model (Scientific Reports, article number: 3505). Here, two limiting cases of a network of such models are used to estimate the undetected population. The first limit corresponds to the network collapsing onto a single node and is referred to as the mean-\beta model. In the second case, the number of nodes in the network is infinite and results in a continuum model wherein the infectivity is statistically distributed. We use a generalized Pareto distribution to model the infectivity. This distribution has a fat tail and models the presence of super-spreaders that contribute to the disease progression. While both models capture the detected numbers well, the predictions of affected numbers from the continuum model are more realistic. Our results suggest that affected people outnumber detected people by one to two orders of magnitude in Spain, the UK, Italy, and Germany. Our results are consistent with corresponding trends obtained from published serological studies in Spain, the UK and Italy. The match with limited studies in Germany is poor, possibly because Germany's partial lockdown approach requires different modeling.

Reference

https://www.nature.com/articles/s41598-021-87630-z

A compartmental model that predicts the effect of social distancing and vaccination on controlling COVID-19

Abstract

The understanding of the interaction between disease dynamics and human behavior is an important and essential point to control infectious. Disease outbreak can be influenced by social distancing and vaccination. In this study, we introduce two compartmental models to derive the epidemic curve and analyze the individual's

behavior in spreading and controlling the COVID-19 epidemic. The first model includes Susceptible, Exposed, Infectious, Hospitalized, Recovered and Death compartments and in the second model, we added a new compartment namely, semi-susceptible individuals that are assumed to be more immune than the susceptible. A comparison of the two models shows that the second model provides a better fit to the daily infected cases from Egypt, Belgium, Japan, Nigeria, Italy, and Germany released by WHO. Finally, we added a vaccinated term to the model to predict how vaccination could control the epidemic. The model was applied on the record data from WHO.

Reference

https://www.nature.com/articles/s41598-021-86873-0

Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil

Abstract

Cases of SARS-CoV-2 infection in Manaus, Brazil, resurged in late 2020, despite previously high levels of infection. Genome sequencing of viruses sampled in Manaus between November 2020 and January 2021 revealed the emergence and circulation of a novel SARS-CoV-2 variant of concern. Lineage P.1, acquired 17 mutations, including a trio in the spike protein (K417T, E484K and N501Y) associated with increased binding to the human ACE2 receptor. Molecular clock analysis shows that P.1 emergence occurred around mid-November 2020 and was preceded by a period of faster molecular evolution. Using a two-category dynamical model that integrates genomic and mortality data, we estimate that P.1 may be 1.7–2.4-fold more transmissible, and that previous (non-P.1) infection provides 54–79% of the protection against infection with P.1 that it provides against non-P.1 lineages. Enhanced global genomic surveillance of variants of concern, which may exhibit increased transmissibility and/or immune evasion, is critical to accelerate pandemic responsiveness.

Reference

https://science.sciencemag.org/content/early/2021/04/13/science.abh2644

Exploration of prognostic factors for critical COVID-19 patients using a nomogram model

Abstract

The study aimed to explore the influencing factors on critical coronavirus disease 2019 (COVID-19) patients' prognosis and to construct a nomogram model to predict the mortality risk. It was retrospectively analyzed the demographic data and corresponding laboratory biomarkers of 102 critical COVID-19 patients with a residence time ≥ 24 h and divided patients into survival and death groups according to their prognosis. Multiple logistic regression analysis was performed to assess risk factors for critical COVID-19 patients and a nomogram was constructed based on the screened risk factors. Logistic regression analysis showed that advanced age, high peripheral white blood cell count (WBC), low lymphocyte count (L), low platelet count (PLT), and high-sensitivity C-reactive protein (hs-CRP) were associated with critical COVID-19 patients mortality risk ($p < 0.05$) and these were integrated into the nomogram model. Nomogram analysis showed that the total factor score ranged from 179 to 270 while the corresponding mortality risk ranged from 0.05 to 0.95. Findings from this study suggest advanced age, high WBC, high hs-CRP, low L, and low PLT are risk factors for death in critical COVID-19 patients. The Nomogram model is helpful for timely intervention to reduce mortality in critical COVID-19 patients.

Reference

https://www.nature.com/articles/s41598-021-87373-x#Sec1

Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: A systematic review and meta-analysis stroke

Abstract

Background: The comparative performance of different clinical sampling methods for diagnosis of SARS-CoV-2 infection by RT-PCR among populations with suspected infection remains unclear. This meta-analysis aims to systematically compare the diagnostic performance of different clinical specimen collection methods.

Methods: In this systematic review and meta-analysis, PubMed, Embase, MEDLINE, Web of Science, medRxiv, bioRxiv, SSRN, and Research Square were systematically

searched from Jan 1, 2000, to Nov 16, 2020. Original clinical studies were included that examined the performance of nasopharyngeal swabs and any additional respiratory specimens for the diagnosis of SARS-CoV-2 infection among individuals presenting in ambulatory care. Studies without data on paired samples, or those that only examined different samples from confirmed SARS-CoV-2 cases were not useful for examining diagnostic performance of a test and were excluded. Diagnostic performance, including sensitivity, specificity, positive predictive value, and negative predictive value, was examined using random effects models and double arcsine transformation.

Findings: Of the 5577 studies identified in our search, 23 studies including 7973 participants with 16 762 respiratory samples were included. Respiratory specimens examined in these studies included 7973 nasopharyngeal swabs, 1622 nasal swabs, 6110 saliva samples, 338 throat swabs, and 719 pooled nasal and throat swabs. Using nasopharyngeal swabs as the gold standard, pooled nasal and throat swabs gave the highest sensitivity of 97% (95% CI 93–100), whereas lower sensitivities were achieved by saliva (85%, 75–93) and nasal swabs (86%, 77–93) and a much lower sensitivity by throat swabs (68%, 35–94). A comparably high positive predictive value was obtained by pooled nasal and throat (97%, 90–100) and nasal swabs (96%, 87–100) and a slightly lower positive predictive value by saliva (93%, 88–97). Throat swabs have the lowest positive predictive value of 75% (95% CI 45–96). Comparably high specificities (range 97–99%) and negative predictive value (range 95–99%) were observed among different clinical specimens. Comparison between health-care-worker collection and self-collection for pooled nasal and throat swabs and nasal swabs showed comparable diagnostic performance. No significant heterogeneity was observed in the analysis of pooled nasal and throat swabs and throat swabs, whereas moderate to substantial heterogeneity ($I^2 \geq 30\%$) was observed in studies on saliva and nasal swabs.

Interpretation: This review suggests that, compared with the gold standard of nasopharyngeal swabs, pooled nasal and throat swabs offered the best diagnostic performance of the alternative sampling approaches for diagnosis of SARS-CoV-2 infection in ambulatory care. Saliva and nasal swabs gave comparable and very good diagnostic performance and are clinically acceptable alternative specimen collection methods. Throat swabs gave a much lower sensitivity and positive predictive value and should not be recommended. Self-collection for pooled nasal and throat swabs and

nasal swabs was not associated with any significant impairment of diagnostic accuracy. Our results also provide a useful reference framework for the proper interpretation of SARS-CoV-2 testing results using different clinical specimens.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00146-8/fulltext

Publication Date: Apr 13, 2021

Dynamic changes of acquired maternal SARS-CoV-2 IgG in infants

Abstract

At present, there are still ambiguous reports about the perinatal infection of infants born to mothers infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The dynamic characteristics of infantile serum antibodies born to mother with SARS-CoV-2 has not been well described. In this study, we analyzed the seroconversion of 27 newborns born to 26 pregnant women infected with SARS-CoV-2. The SARS-CoV-2 IgG positive rate of parturient was 80.8%, and half of their infants obtained maternal IgG. IgG transfer rates were 18.8% and 81.8% in those infants whose mother infected less and more than 2 weeks before delivery. In the first two months of life, the IgG level of infants dropped sharply to one tenth of that at birth. These results suggest that maternal SARS-CoV-2 IgG provides limited protection for infants.

Reference

https://www.nature.com/articles/s41598-021-87535-x

Distinct uptake, amplification, and release of SARS-CoV-2 by M1 and M2 alveolar macrophages

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invades the alveoli, where abundant alveolar macrophages (AMs) reside. How AMs respond to SARS-CoV-2 invasion remains elusive. Here, it was shown that classically activated M1 AMs facilitate viral spread; however, alternatively activated M2 AMs limit the spread. M1 AMs utilize cellular softness to efficiently take up SARS-CoV-2. Subsequently, the invaded

viruses take over the endo-lysosomal system to escape. M1 AMs have a lower endosomal pH, favoring membrane fusion and allowing the entry of viral RNA from the endosomes into the cytoplasm, where the virus achieves replication and is packaged to be released. In contrast, M2 AMs have a higher endosomal pH but a lower lysosomal pH, thus delivering the virus to lysosomes for degradation. In hACE2 transgenic mouse model, M1 AMs are found to facilitate SARS-CoV-2 infection of the lungs. These findings provide insights into the complex roles of AMs during SARS-CoV-2 infection, along with potential therapeutic targets.

Reference

https://www.nature.com/articles/s41421-021-00258-1

Gut mycobiota alterations in patients with COVID-19 and H1N1 infections and their associations with clinical features

Abstract

The relationship between gut microbes and COVID-19 or H1N1 infections is not fully understood. Here, we compared the gut mycobiota of 67 COVID-19 patients, 35 H1N1-infected patients and 48 healthy controls (HCs) using internal transcribed spacer (ITS) 3-ITS4 sequencing and analysed their associations with clinical features and the bacterial microbiota. Compared to HCs, the fungal burden was higher. Fungal mycobiota dysbiosis in both COVID-19 and H1N1-infected patients was mainly characterized by the depletion of fungi such as Aspergillus and Penicillium, but several fungi, including Candida glabrata, were enriched in H1N1-infected patients. The gut mycobiota profiles in COVID-19 patients with mild and severe symptoms were similar. Hospitalization had no apparent additional effects. In COVID-19 patients, Mucoromycota was positively correlated with Fusicatenibacter, Aspergillus niger was positively correlated with diarrhoea, and Penicillium citrinum was negatively correlated with C-reactive protein (CRP). In H1N1-infected patients, Aspergillus penicilloides was positively correlated with Lachnospiraceae members, Aspergillus was positively correlated with CRP, and Mucoromycota was negatively correlated with procalcitonin. Therefore, gut mycobiota dysbiosis occurs in both COVID-19 patients and H1N1-infected patients and does not improve until the patients are discharged and no longer require medical attention.

Reference

https://www.nature.com/articles/s42003-021-02036-x

Cell type resolved quantitative proteomics map of interferon response against SARS-CoV-2

Abstract

The commonly used laboratory cell lines are the first line of experimental models to study the pathogenicity and performing antiviral assays for emerging viruses. Here, we assessed the tropism and cytopathogenicity of the first Swedish isolate of SARS-CoV-2 in six different human cell lines, compared their growth characteristics and performed quantitative proteomics for the susceptible cell lines. Overall, Calu-3, Caco2, Huh7, and 293FT cell lines showed a high to moderate level of susceptibility to SARS-CoV-2. In Caco2 cells the virus can achieve high titers in the absence of any prominent cytopathic effect. The protein abundance profile during SARS-CoV-2 infection revealed cell-type-specific regulation of cellular pathways. Type-I interferon signaling was identified as the common dysregulated cellular response in Caco2, Calu-3 and Huh7 cells. Together, our data shows cell-type specific variability for cytopathogenicity, susceptibility and cellular response to SARS-CoV-2 and provide important clues to guide future studies.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00146-8/fulltext

Characterization of respiratory microbial dysbiosis in hospitalized COVID-19 patients

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic of Coronavirus disease 2019 (COVID-19). However, the microbial composition of the respiratory tract and other infected tissues as well as their possible pathogenic contributions to varying degrees of disease severity in COVID-19 patients remain unclear. Between 27 January and 26 February 2020, serial clinical specimens (sputum, nasal and throat swab, anal swab and feces) were collected from a cohort of hospitalized COVID-19 patients, including 8 mildly and 15 severely ill patients in Guangdong province, China. Total RNA was extracted and ultra-deep

metatranscriptomic sequencing was performed in combination with laboratory diagnostic assays. It was identified distinct signatures of microbial dysbiosis among severely ill COVID-19 patients on broad spectrum antimicrobial therapy. Co-detection of other human respiratory viruses (including human alphaherpesvirus 1, rhinovirus B, and human orthopneumovirus) was demonstrated in 30.8% (4/13) of the severely ill patients, but not in any of the mildly affected patients. Notably, the predominant respiratory microbial taxa of severely ill patients were *Burkholderia cepacia* complex (BCC), *Staphylococcus epidermidis*, or *Mycoplasma* spp. (including M. hominis and M. orale). The presence of the former two bacterial taxa was also confirmed by clinical cultures of respiratory specimens (expectorated sputum or nasal secretions) in 23.1% (3/13) of the severe cases. Finally, a time-dependent, secondary infection of *B. cenocepacia* with expressions of multiple virulence genes was demonstrated in one severely ill patient, which might accelerate his disease deterioration and death occurring one month after ICU admission. These findings point to SARS-CoV-2-related microbial dysbiosis and various antibiotic-resistant respiratory microbes/pathogens in hospitalized COVID-19 patients in relation to disease severity. Detection and tracking strategies are needed to prevent the spread of antimicrobial resistance, improve the treatment regimen and clinical outcomes of hospitalized, severely ill COVID-19 patients.

Reference

https://www.nature.com/articles/s41421-021-00257-2

Role of interferon therapy in severe COVID-19: The COVIFERON randomized controlled trial

Abstract

Type 1 Interferons (IFNs) have been associated with positive effects on Coronaviruses. Previous studies point towards the superior potency of IFNβ compared to IFNα against viral infections. We conducted a three-armed, individually-randomized, open-label, controlled trial of IFNβ1a and IFNβ1b, comparing them against each other and a control group. Patients were randomly assigned in a 1:1:1 ratio to IFNβ1a (subcutaneous injections of 12,000 IU on days 1, 3, 6), IFNβ1b (subcutaneous injections of 8,000,000 IU on days 1, 3, 6), or the control group. All three arms orally received Lopinavir/Ritonavir (400 mg/100 mg twice a day for ten days) and a single dose of

Hydroxychloroquine 400 mg on the first day. This utilized primary outcome measure was Time To Clinical Improvement (TTCI) defined as the time from enrollment to discharge or a decline of two steps on the clinical seven-step ordinal scale, which so ever came first. A total of 60 severely ill patients with positive RT-PCR and Chest CT scans underwent randomization (20 patients to each arm). In the Intention-To-Treat population, IFNβ1a was associated with a significant difference against the control group, in the TTCI; (HR; 2.36, 95% CI 1.10–5.17, P-value = 0.031) while the IFNβ1b indicated no significant difference compared with the control; HR; 1.42, (95% CI 0.63–3.16, P-value = 0.395). The median TTCI for both of the intervention groups was five days vs. seven days for the control group. The mortality was numerically lower in both of the intervention groups (20% in the IFNβ1a group and 30% in the IFNβ1b group vs. 45% in the control group). There were no significant differences between the three arms regarding the adverse events. In patients with laboratory-confirmed SARS-CoV-2 infection, as compared with the base therapeutic regiment, the benefit of a significant reduction in TTCI was observed in the IFNβ1a arm. This finding needs further confirmation in larger studies.

Reference

https://www.nature.com/articles/s41598-021-86859-y

Pattern of inflammatory immune response determines the clinical course and outcome of COVID-19: Unbiased clustering analysis

Abstract

The objective of the study was to identify distinct patterns in inflammatory immune responses of COVID-19 patients and to investigate their association with clinical course and outcome. Data from hospitalized COVID-19 patients were retrieved from electronic medical record. Supervised k-means clustering of serial C-reactive protein levels (CRP), absolute neutrophil counts (ANC), and absolute lymphocyte counts (ALC) was used to assign immune responses to one of three groups. Then, relationships between patterns of inflammatory responses and clinical course and outcome of COVID-19 were assessed in a discovery and validation cohort. Unbiased clustering analysis grouped 105 patients of a discovery cohort into three distinct clusters. Cluster 1 (hyper-inflammatory immune response) was characterized by high CRP levels, high ANC, and

low ALC, whereas Cluster 3 (hypo-inflammatory immune response) was associated with low CRP levels and normal ANC and ALC. Cluster 2 showed an intermediate pattern. All patients in Cluster 1 required oxygen support whilst 61% patients in Cluster 2 and no patient in Cluster 3 required supplementary oxygen. Two (13.3%) patients in Cluster 1 died, whereas no patient in Clusters 2 and 3 died. The results were confirmed in an independent validation cohort of 116 patients. Three different patterns of inflammatory immune response to COVID-19 were identified. Hyper-inflammatory immune responses with elevated CRP, neutrophilia, and lymphopenia are associated with a severe disease and a worse outcome. Therefore, targeting the hyper-inflammatory response might improve the clinical outcome of COVID-19.

Reference

https://www.nature.com/articles/s41598-021-87668-z

A comprehensive evaluation of early potential risk factors for disease aggravation in patients with COVID-19

Abstract

The 2019 Coronavirus Disease (COVID-19) has become an unprecedented public crisis. We retrospectively investigated the clinical data of 197 COVID-19 patients and identified 88 patients as disease aggravation cases. Compared with patients without disease aggravation, the aggravation cases had more comorbidities, including hypertension (25.9%) and diabetes (20.8%), and presented with dyspnoea (23.4%), neutrophilia (31.5%), and lymphocytopenia (46.7%). These patients were more prone to develop organ damage in liver, kidney, and heart ($P < 0.05$). A multivariable regression analysis showed that advanced age, comorbidities, dyspnea, lymphopenia, and elevated levels of Fbg, CTnI, IL-6, and serum ferritin were significant predictors of disease aggravation. Further, we performed a Kaplan–Meier analysis to evaluate the prognosis of COVID-19 patients, which suggested that 64.9% of the patients had not experienced ICU transfers and survival from the hospital.

Reference

https://www.nature.com/articles/s41598-021-87413-6

Human pluripotent stem cell-derived intestinal organoids model SARS-CoV-2 infection revealing a common epithelial inflammatory response

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to coronavirus disease 2019 (COVID-19) usually results in respiratory disease, but extrapulmonary manifestations are of major clinical interest. Intestinal symptoms of COVID-19 are present in a significant number of patients, and include nausea, diarrhea, and viral RNA shedding in feces. Human induced pluripotent stem cell-derived intestinal organoids (HIOs) represent an inexhaustible cellular resource that could serve as a valuable tool to study SARS-CoV-2 as well as other enteric viruses that infect the intestinal epithelium. Here, it was reported that SARS-CoV-2 productively infects both proximally and distally patterned HIOs, leading to the release of infectious viral particles while stimulating a robust transcriptomic response, including a significant upregulation of interferon-related genes that appeared to be conserved across multiple epithelial cell types. These findings illuminate a potential inflammatory epithelial-specific signature that may contribute to both the multisystemic nature of COVID-19 as well as its highly variable clinical presentation.

Reference

https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(21)00099-0

Functional landscape of SARS-CoV-2 cellular restriction

Abstract

A deficient interferon response to SARS-CoV-2 infection has been implicated as a determinant of severe COVID-19. To identify the molecular effectors that govern interferon control of SARS-CoV-2 infection, a large-scale gain-of-function analysis was conducted that evaluated the impact of human interferon stimulated genes (ISGs) on viral replication. A limited subset of ISGs were found to control viral infection, including endosomal factors inhibiting viral entry, RNA binding proteins suppressing viral RNA synthesis, and a highly enriched cluster of ER-Golgi-resident ISGs inhibiting viral assembly-egress. These included broad-acting antiviral ISGs, and eight ISGs that specifically inhibited SARS-CoV-2 and -1 replication. Amongst the broad-acting ISGs

was BST2/tetherin, which impeded viral release, and is antagonized by SARS-CoV-2 Orf7a protein. Overall, these data illuminate a set of ISGs that underlie innate immune control of SARS-CoV-2/-1 infection, which will facilitate the understanding of host determinants that impact disease severity and offer potential therapeutic strategies for COVID-19.

Reference

https://www.cell.com/molecular-cell/fulltext/S1097-2765(21)00313-0

CD8+ T cells specific for an immunodominant SARS-CoV-2 nucleocapsid epitope cross-react with selective seasonal coronaviruses

Abstract

Efforts are being made worldwide to understand the immune response to SARS-CoV-2, the virus responsible for the COVID-19 pandemic, including the impact of T cell immunity and cross-recognition with seasonal coronaviruses. Screening SARS-CoV-2 peptide pools revealed that the nucleocapsid (N) protein induced an immunodominant response in HLA-B7+ COVID-19-recovered individuals that was also detectable in unexposed donors. A single N-encoded epitope that was highly conserved across circulating coronaviruses drove this immunodominant response. *In vitro* peptide stimulation and crystal structure analyses revealed T cell-mediated cross-reactivity towards circulating OC43 and HKU-1 beta coronaviruses, but not 229E or NL63 alpha coronaviruses, due to different peptide conformations. TCR sequencing indicated cross-reactivity was driven by private T cell receptor repertoires with a bias for TRBV27 and a long CDR3β loop. Together, our findings demonstrate the basis of selective T cell cross-reactivity towards an immunodominant SARS-CoV-2 epitope and its homologues from seasonal coronaviruses, suggesting long-lived protective immunity.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00168-0

Immune dysregulation and auto-reactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children

Abstract

Multisystem inflammatory syndrome in children (MIS-C) is a life-threatening post-infectious complication occurring unpredictably weeks after mild or asymptomatic SARS-CoV-2 infection. We profiled MIS-C, adult COVID-19, and healthy pediatric and adult individuals using single-cell RNA sequencing, flow cytometry, antigen receptor repertoire analysis, and unbiased serum proteomics, which collectively identified a signature in MIS-C patients that correlated with disease severity. Despite no evidence of active infection, MIS-C patients had elevated S100A-family alarmins and decreased antigen presentation signatures, indicative of myeloid dysfunction. MIS-C patients showed elevated expression of cytotoxicity genes in NK and CD8+ T cells and expansion of specific IgG-expressing plasmablasts. Clinically severe MIS-C patients displayed skewed memory T cell TCR repertoires and autoimmunity characterized by endothelium-reactive IgG. The alarmin, cytotoxicity, TCR repertoire, and plasmablast signatures we defined have potential for application in the clinic to better diagnose and potentially predict disease severity early in the course of MIS-C.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00165-5

SARS-CoV-2 infection of primary human lung epithelium for COVID-19 modeling and drug discovery

Abstract

Coronavirus disease 2019 (COVID-19) is the latest respiratory pandemic caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). While infection initiates in the proximal airways, severe and sometimes fatal symptoms of the disease are caused by infection of the alveolar type 2 (AT2) cells of the distal lung and associated inflammation. In this study we develop primary human lung epithelial infection models to understand initial responses of proximal and distal lung epithelium to SARS-CoV-2 infection. Differentiated air-liquid interface (ALI) cultures of proximal airway epithelium and alveosphere cultures of distal lung AT2 cells are readily infected

by SARS-CoV-2, leading to an epithelial cell-autonomous proinflammatory response with increased expression of interferon signaling genes. Studies to validate the efficacy of selected candidate COVID-19 drugs confirm that Remdesivir strongly suppresses viral infection/replication. A relevant platform was provided for study of COVID-19 pathobiology and for rapid drug screening against SARS-CoV-2 and emergent respiratory pathogens.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00371-5

Publication Date: Apr 12, 2021

Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: An ecological study

Abstract

Background: The SARS-CoV-2 variant B.1.1.7 was first identified in December, 2020, in England. It was aimed to investigate whether increases in the proportion of infections with this variant are associated with differences in symptoms or disease course, reinfection rates, or transmissibility.

Methods: An ecological study was done to examine the association between the regional proportion of infections with the SARS-CoV-2 B.1.1.7 variant and reported symptoms, disease course, rates of reinfection, and transmissibility. Data on types and duration of symptoms were obtained from longitudinal reports from users of the COVID Symptom Study app who reported a positive test for COVID-19 between Sept 28 and Dec 27, 2020 (during which the prevalence of B.1.1.7 increased most notably in parts of the UK). From this dataset, it was also estimated the frequency of possible reinfection, defined as the presence of two reported positive tests separated by more than 90 days with a period of reporting no symptoms for more than 7 days before the second positive test. The proportion of SARS-CoV-2 infections with the B.1.1.7 variant across the UK was estimated with use of genomic data from the COVID-19 Genomics UK Consortium and data from Public Health England on spike-gene target failure (a non-specific indicator of the B.1.1.7 variant) in community cases in England. We used linear regression to examine the association between reported symptoms and proportion of

B.1.1.7. The Spearman correlation was assessed between the proportion of B.1.1.7 cases and number of reinfections over time, and between the number of positive tests and reinfections. Incidence was estimated for B.1.1.7 and previous variants, and compared the effective reproduction number, Rt, for the two incidence estimates.

Findings: From Sept 28 to Dec 27, 2020, positive COVID-19 tests were reported by 36 920 COVID Symptom Study app users whose region was known and who reported as healthy on app sign-up. No changes were found in reported symptoms or disease duration associated with B.1.1.7. For the same period, possible reinfections were identified in 249 (0·7% [95% CI 0·6–0·8]) of 36 509 app users who reported a positive swab test before Oct 1, 2020, but there was no evidence that the frequency of reinfections was higher for the B.1.1.7 variant than for pre-existing variants. Reinfection occurrences were more positively correlated with the overall regional rise in cases (Spearman correlation 0·56–0·69 for South East, London, and East of England) than with the regional increase in the proportion of infections with the B.1.1.7 variant (Spearman correlation 0·38–0·56 in the same regions), suggesting B.1.1.7 does not substantially alter the risk of reinfection. A multiplicative increase was found in the Rt of B.1.1.7 by a factor of 1·35 (95% CI 1·02–1·69) relative to pre-existing variants. However, Rt fell below 1 during regional and national lockdowns, even in regions with high proportions of infections with the B.1.1.7 variant.

Interpretation: The lack of change in symptoms identified in this study indicates that existing testing and surveillance infrastructure do not need to change specifically for the B.1.1.7 variant. In addition, given that there was no apparent increase in the reinfection rate, vaccines are likely to remain effective against the B.1.1.7 variant.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(21)00055-4/fulltext

COVID-19 information retrieval with deep-learning based semantic search, question answering, and abstractive summarization

Abstract

The COVID-19 global pandemic has resulted in international efforts to understand, track, and mitigate the disease, yielding a significant corpus of COVID-19 and SARS-

CoV-2-related publications across scientific disciplines. Throughout 2020, over 400,000 coronavirus-related publications have been collected through the COVID-19 Open Research Dataset. Here, CO-Search was presented, which was a semantic, multi-stage, search engine designed to handle complex queries over the COVID-19 literature, potentially aiding overburdened health workers in finding scientific answers and avoiding misinformation during a time of crisis. CO-Search is built from two sequential parts: a hybrid semantic-keyword retriever, which takes an input query and returns a sorted list of the 1000 most relevant documents, and a re-ranker, which further orders them by relevance. The retriever is composed of a deep learning model (Siamese-BERT) that encodes query-level meaning, along with two keyword-based models (BM25, TF-IDF) that emphasize the most important words of a query. The re-ranker assigns a relevance score to each document, computed from the outputs of (1) a question–answering module which gauges how much each document answers the query, and (2) an abstractive summarization module which determines how well a query matches a generated summary of the document. To account for the relatively limited dataset, we develop a text augmentation technique which splits the documents into pairs of paragraphs and the citations contained in them, creating millions of (citation title, paragraph) tuples for training the retriever. We evaluate our system (http://einstein.ai/covid) on the data of the TREC-COVID information retrieval challenge, obtaining strong performance across multiple key information retrieval metrics.

Reference

https://www.nature.com/articles/s41746-021-00437-0

Cardiometabolic risks of SARS-CoV-2 hospitalization using Mendelian Randomization

Abstract

Many cardiometabolic conditions have demonstrated associative evidence with COVID-19 hospitalization risk. However, the observational designs of the studies in which these associations are observed preclude causal inferences of hospitalization risk. Mendelian Randomization (MR) is an alternative risk estimation method more robust to these limitations that allows for causal inferences. Four MR methods (MRMix, IMRP, IVW, MREgger) were applied to publicly available GWAS summary statistics from European

(COVID-19 GWAS n = 2956) and multi-ethnic populations (COVID-19 GWAS n = 10,908) to better understand extant causal associations between Type II Diabetes (GWAS n = 659,316), BMI (n = 681,275), diastolic and systolic blood pressure, and pulse pressure (n = 757,601 for each) and COVID-19 hospitalization risk across populations. Although no significant causal effect evidence was observed, our data suggested a trend of increasing hospitalization risk for Type II diabetes (IMRP OR, 95% CI 1.67, 0.96–2.92) and pulse pressure (OR, 95% CI 1.27, 0.97–1.66) in the multi-ethnic sample. Type II diabetes and Pulse pressure demonstrates a potential causal association with COVID-19 hospitalization risk, the proper treatment of which may work to reduce the risk of a severe COVID-19 illness requiring hospitalization. However, GWAS of COVID-19 with large sample size is warranted to confirm the causality.

Reference

https://www.nature.com/articles/s41598-021-86757-3

Complement C3 identified as a unique risk factor for disease severity among young COVID-19 patients in Wuhan, China

Abstract

Given that a substantial proportion of the subgroup of COVID-19 patients that face a severe disease course are younger than 60 years, it is critical to understand the disease-specific characteristics of young COVID-19 patients. Risk factors for a severe disease course for young COVID-19 patients and possible non-linear influences remain unknown. Data were analyzed from COVID-19 patients with clinical outcome in a single hospital in Wuhan, China, collected retrospectively from Jan 24th to Mar 27th. Clinical, demographic, treatment and laboratory data were collected from patients' medical records. Uni- and multivariable analysis using logistic regression and random forest, with the latter allowing the study of non-linear influences, were performed to investigate the clinical characteristics of a severe disease course. A total of 762 young patients (median age 47 years, interquartile range [IQR] 38–55, range 18–60; 55.9% female) were included, as well as 714 elderly patients as a comparison group. Among the young patients, 362 (47.5%) had a severe/critical disease course and the mean age was statistically significantly higher in the severe subgroup than in the mild subgroup (59.3 vs. 56.0, Student's t-test: $p < 0.001$). The uni- and multivariable analysis suggested that

several covariates such as elevated levels of serum amyloid A (SAA), C-reactive protein (CRP) and lactate dehydrogenase (LDH), and decreased lymphocyte counts influence disease severity independently of age. Elevated levels of complement C3 (odds ratio [OR] 15.6, 95% CI 2.41–122.3; p = 0.039) are particularly associated with the risk of developing severe COVID-19 specifically in young patients, whereas no such influence seems to exist for elderly patients. Additional analysis suggests that the influence of complement C3 in young patients is independent of age, gender, and comorbidities. Variable importance values and partial dependence plots obtained using random forests delivered additional insights, in particular indicating non-linear influences of risk factors on disease severity. This study identified increased levels of complement C3 as a unique risk factor for adverse outcomes specific to young COVID-19 patients.

Reference

https://www.nature.com/articles/s41598-021-82810-3

Multilevel proteomics reveals host perturbations by SARS-CoV-2 and SARS-CoV

Abstract

The global emergence of SARS-CoV-2 urgently requires an in-depth understanding of molecular functions of viral proteins and their interactions with the host proteome. Several individual omics studies have extended the knowledge of COVID-19 pathophysiology. Integration of such datasets to obtain a holistic view of virus-host interactions and to define the pathogenic properties of SARS-CoV-2 is limited by the heterogeneity of the experimental systems. A concurrent multi-omics study of SARS-CoV-2 and SARS-CoV was therefore conducted. Using state-of-the-art proteomics, we profiled the interactome of both viruses, as well as their influence on transcriptome, proteome, ubiquitinome and phosphoproteome in a lung-derived human cell line. Projecting these data onto the global network of cellular interactions revealed crosstalk between the perturbations taking place upon SARS-CoV-2 and SARS-CoV infections at different layers and identified unique and common molecular mechanisms of these closely related coronaviruses. The TGF-β pathway, known for its involvement in tissue fibrosis, was specifically dysregulated by SARS-CoV-2 ORF8 and autophagy by SARS-CoV-2 ORF3. The extensive dataset (available at https://covinet.innatelab.org) highlights many hotspots that can be targeted by existing drugs and it can guide rational

design of virus- and host-directed therapies, which we exemplify by identifying kinase and MMPs inhibitors with potent antiviral effects against SARS-CoV-2.

Reference

https://www.nature.com/articles/s41586-021-03493-4

Genetic evidence for the association between COVID-19 epidemic severity and timing of non-pharmaceutical interventions

Abstract

Unprecedented public health interventions including travel restrictions and national lockdowns have been implemented to stem the COVID-19 epidemic, but the effectiveness of non-pharmaceutical interventions is still debated. A phylogenetic analysis of more than 29,000 publicly available whole genome SARS-CoV-2 sequences from 57 locations were carried out to estimate the time that the epidemic originated in different places. These estimates were examined in relation to the dates of the most stringent interventions in each location as well as to the number of cumulative COVID-19 deaths and phylodynamic estimates of epidemic size. Here we report that the time elapsed between epidemic origin and maximum intervention is associated with different measures of epidemic severity and explains 11% of the variance in reported deaths one month after the most stringent intervention. Locations where strong non-pharmaceutical interventions were implemented earlier experienced much less severe COVID-19 morbidity and mortality during the period of study.

Reference

https://www.nature.com/articles/s41467-021-22366-y

A reporting and analysis framework for structured evaluation of COVID-19 clinical and imaging data

Abstract

The COVID-19 pandemic has worldwide individual and socioeconomic consequences. Chest computed tomography has been found to support diagnostics and disease monitoring. A standardized approach to generate, collect, analyze, and share clinical and imaging information in the highest quality possible is urgently needed. We

developed systematic, computer-assisted and context-guided electronic data capture on the FDA-approved mint LesionTM software platform to enable cloud-based data collection and real-time analysis. The acquisition and annotation include radiological findings and radiomics performed directly on primary imaging data together with information from the patient history and clinical data. As proof of concept, anonymized data of 283 patients with either suspected or confirmed SARS-CoV-2 infection from eight European medical centers were aggregated in data analysis dashboards. Aggregated data were compared to key findings of landmark research literature. This concept has been chosen for use in the national COVID-19 response of the radiological departments of all university hospitals in Germany.

Reference

https://www.nature.com/articles/s41746-021-00439-y

A study of differential circRNA and lncRNA expressions in COVID-19-infected peripheral blood

Abstract

To conquer the worldwide outbreak of COVID-19 virus, a large number of studies have been carried out on COVID-19 infection, transmission and treatment. However, few studies have been conducted from the perspectives of circRNA and lncRNA, which are known to be involved in regulating many life activities, such as immune tolerance and immune escapes, and hence may provide invaluable information in the emerging COVID-19 infection and recurrence. Moreover, exosomes has been reported to play an important role in COVID-19 recurrence, and thus may interact with the expression of circRNA and lncRNA. In this work, we sequenced circRNA, lncRNA and mRNA from recurrent COVID-19 patients and healthy people, and compared the differences. GO and KEGG enrichment analysis show that differentially expressed circRNA and lncRNA are mainly involved in the regulation of host cell cycle, apoptosis, immune inflammation, signaling pathway and other processes. The comparison to exosomes related databases shows that there are 114 differentially expressed circRNA, and 10 differentially expressed lncRNA related to exosomes. These studies provide reference for exploring circRNA and lncRNA to study the infection mechanism of COVID-19, their

diagnostic and therapeutic values, as well as the possibility to employ them as biomarkers.

Reference

https://www.nature.com/articles/s41598-021-86134-0

Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: A whole-genome sequencing and hospital-based cohort study

Abstract

Background: Emergence of variants with specific mutations in key epitopes in the spike protein of SARS-CoV-2 raises concerns pertinent to mass vaccination campaigns and use of monoclonal antibodies. We aimed to describe the emergence of the B.1.1.7 variant of concern (VOC), including virological characteristics and clinical severity in contemporaneous patients with and without the variant.

Methods: In this cohort study, samples positive for SARS-CoV-2 on PCR that were collected from Nov 9, 2020, for patients acutely admitted to one of two hospitals on or before Dec 20, 2020, in London, UK, were sequenced and analysed for the presence of VOC-defining mutations. Poisson regression models were fitted to investigate the association between B.1.1.7 infection and severe disease (defined as point 6 or higher on the WHO ordinal scale within 14 days of symptoms or positive test) and death within 28 days of a positive test and did supplementary genomic analyses in a cohort of chronically shedding patients and in a cohort of remdesivir-treated patients. Viral load was compared by proxy, using PCR cycle threshold values and sequencing read depths.

Findings: Of 496 patients with samples positive for SARS-CoV-2 on PCR and who met inclusion criteria, 341 had samples that could be sequenced. 198 (58%) of 341 had B.1.1.7 infection and 143 (42%) had non-B.1.1.7 infection. We found no evidence of an association between severe disease and death and lineage (B.1.1.7 vs non-B.1.1.7) in unadjusted analyses (prevalence ratio [PR] 0·97 [95% CI 0·72–1·31]), or in analyses adjusted for hospital, sex, age, comorbidities, and ethnicity (adjusted PR 1·02 [0·76–1·38]). We detected no B.1.1.7 VOC-defining mutations in 123 chronically shedding

immunocompromised patients or in 32 remdesivir-treated patients. Viral load by proxy was higher in B.1.1.7 samples than in non-B.1.1.7 samples, as measured by cycle threshold value (mean 28·8 [SD 4·7] vs 32·0 [4·8]; p=0·0085) and genomic read depth (1280 [1004] vs 831 [682]; p=0·0011).

Interpretation: Emerging evidence exists of increased transmissibility of B.1.1.7, and we found increased virus load by proxy for B.1.1.7 in our data. An association of the variant with severe disease was did not identify in this hospitalised cohort.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00170-5/fulltext

Publication Date: Apr 11, 2021

RBD-specific polyclonal F(ab´)2 fragments of equine antibodies in patients with moderate to severe COVID-19 disease: A randomized, multicenter, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial

Abstract

Background: Passive immunotherapy is a therapeutic alternative for patients with COVID-19. Equine polyclonal antibodies (EpAbs) could represent a source of scalable neutralizing antibodies against SARS-CoV-2.

Methods: A double-blind, randomized, placebo-controlled trial was conducted to assess efficacy and safety of EpAbs (INM005) in hospitalized adult patients with moderate and severe COVID-19 pneumonia in 19 hospitals of Argentina. Primary endpoint was improvement in at least two categories in WHO ordinal clinical scale at day 28 or hospital discharge (ClinicalTrials.gov number NCT04494984).

Findings: Between August 1st and October 26th, 2020, a total of 245 patients were enrolled. Enrolled patients were assigned to receive two blinded doses of INM005 (n = 118) or placebo (n = 123). Median age was 54 years old, 65•1% were male and 61% had moderate disease at baseline. Median time from symptoms onset to study treatment was 6 days (interquartile range 5 to 8). No statistically significant difference was noted between study groups on primary endpoint (risk difference [95% IC]: 5•28% [-3•95; 14•50]; p = 0•15). Rate of improvement in at least two categories was statistically

significantly higher for INM005 at days 14 and 21 of follow-up. Time to improvement in two ordinal categories or hospital discharge was 14•2 (± 0•7) days in the INM005 group and 16•3 (± 0•7) days in the placebo group, hazard ratio 1•31 (95% CI 1•0 to 1•74). Subgroup analyses showed a beneficial effect of INM005 over severe patients and in those with negative baseline antibodies. Overall mortality was 6•9% the INM005 group and 11•4% in the placebo group (risk difference [95% IC]: 0•57 [0•24 to 1•37]). Adverse events of special interest were mild or moderate; no anaphylaxis was reported.

Interpretation: Albeit not having reached the primary endpoint, we found clinical improvement of hospitalized patients with SARS-CoV-2 pneumonia, particularly those with severe disease.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00170-5/fulltext

Publication Date: Apr 09, 2021

SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: A large, multicentre, prospective cohort study (SIREN)

Abstract

Background: Increased understanding of whether individuals who have recovered from COVID-19 are protected from future SARS-CoV-2 infection is an urgent requirement. We aimed to investigate whether antibodies against SARS-CoV-2 were associated with a decreased risk of symptomatic and asymptomatic reinfection.

Methods: A large, multicentre, prospective cohort study was done, with participants recruited from publicly funded hospitals in all regions of England. All health-care workers, support staff, and administrative staff working at hospitals who could remain engaged in follow-up for 12 months were eligible to join The SARS-CoV-2 Immunity and Reinfection Evaluation study. Participants were excluded if they had no PCR tests after enrolment, enrolled after Dec 31, 2020, or had insufficient PCR and antibody data for cohort assignment. Participants attended regular SARS-CoV-2 PCR and antibody testing (every 2–4 weeks) and completed questionnaires every 2 weeks on symptoms and exposures. At enrolment, participants were assigned to either the positive cohort

(antibody positive, or previous positive PCR or antibody test) or negative cohort (antibody negative, no previous positive PCR or antibody test). The primary outcome was a reinfection in the positive cohort or a primary infection in the negative cohort, determined by PCR tests. Potential reinfections were clinically reviewed and classified according to case definitions (confirmed, probable, or possible) and symptom-status, depending on the hierarchy of evidence. Primary infections in the negative cohort were defined as a first positive PCR test and seroconversions were excluded when not associated with a positive PCR test. A proportional hazards frailty model using a Poisson distribution was used to estimate incidence rate ratios (IRR) to compare infection rates in the two cohorts.

Findings: From June 18, 2020, to Dec 31, 2020, 30 625 participants were enrolled into the study. 51 participants withdrew from the study, 4913 were excluded, and 25 661 participants (with linked data on antibody and PCR testing) were included in the analysis. Data were extracted from all sources on Feb 5, 2021, and include data up to and including Jan 11, 2021. 155 infections were detected in the baseline positive cohort of 8278 participants, collectively contributing 2 047 113 person-days of follow-up. This compares with 1704 new PCR positive infections in the negative cohort of 17 383 participants, contributing 2 971 436 person-days of follow-up. The incidence density was 7·6 reinfections per 100 000 person-days in the positive cohort, compared with 57·3 primary infections per 100 000 person-days in the negative cohort, between June, 2020, and January, 2021. The adjusted IRR was 0·159 for all reinfections (95% CI 0·13–0·19) compared with PCR-confirmed primary infections. The median interval between primary infection and reinfection was more than 200 days.

Interpretation: A previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. This time period is the minimum probable effect because seroconversions were not included. This study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00675-9/fulltext

Seroprevalence and correlates of SARS-CoV-2 neutralizing antibodies from a population-based study in Bonn, Germany

Abstract

To estimate the seroprevalence and temporal course of SARS-CoV-2 neutralizing antibodies, we embedded a multi-tiered seroprevalence survey within an ongoing community-based cohort study in Bonn, Germany. Anti-SARS-CoV-2 immunoglobulin G levels was first assessed with an immunoassay, followed by confirmatory testing of borderline and positive test results with a recombinant spike-based immunofluorescence assay and a plaque reduction neutralization test (PRNT). Those with a borderline or positive immunoassay result were retested after 4 to 5 months. At baseline, 4771 persons participated (88% response rate). Between April 24th and June 30th, 2020, seroprevalence was 0.97% (95% CI: 0.72−1.30) by immunoassay and 0.36% (95% CI: 0.21−0.61) when considering only those with two additional positive confirmatory tests. Importantly, about 20% of PRNT+ individuals lost their neutralizing antibodies within five months. Here, it was shown that neutralizing antibodies are detectable in only one third of those with a positive immunoassay result, and wane relatively quickly.

Reference

https://www.nature.com/articles/s41467-021-22351-5

GCG inhibits SARS-CoV-2 replication by disrupting the liquid phase condensation of its nucleocapsid protein

Abstract

Lack of detailed knowledge of SARS-CoV-2 infection has been hampering the development of treatments for coronavirus disease 2019 (COVID-19). Here, we report that RNA triggers the liquid–liquid phase separation (LLPS) of the SARS-CoV-2 nucleocapsid protein, N. By analyzing all 29 proteins of SARS-CoV-2, we find that only N is predicted as an LLPS protein. We further confirm the LLPS of N during SARS-CoV-2 infection. Among the 100,849 genome variants of SARS-CoV-2 in the GISAID database, we identify that ~37% (36,941) of the genomes contain a specific trio-nucleotide polymorphism (GGG-to-AAC) in the coding sequence of N, which leads to

the amino acid substitutions, R203K/G204R. Interestingly, NR203K/G204R exhibits a higher propensity to undergo LLPS and a greater effect on IFN inhibition. By screening the chemicals known to interfere with N-RNA binding in other viruses, we find that (-)-gallocatechin gallate (GCG), a polyphenol from green tea, disrupts the LLPS of N and inhibits SARS-CoV-2 replication. Thus, this study reveals that targeting N-RNA condensation with GCG could be a potential treatment for COVID-19.

Reference

https://www.nature.com/articles/s41467-021-22297-8

Actionable druggable genome-wide Mendelian randomization identifies repurposing opportunities for COVID-19

Abstract

Drug repurposing provides a rapid approach to meet the urgent need for therapeutics to address COVID-19. To identify therapeutic targets relevant to COVID-19, Mendelian randomization analyses was conducted, deriving genetic instruments based on transcriptomic and proteomic data for 1,263 actionable proteins that are targeted by approved drugs or in clinical phase of drug development. Using summary statistics from the Host Genetics Initiative and the Million Veteran Program, we studied 7,554 patients hospitalized with COVID-19 and >1 million controls. We found significant Mendelian randomization results for three proteins (ACE2, $P = 1.6 \times 10^{-6}$; IFNAR2, $P = 9.8 \times 10^{-11}$ and IL-10RB, $P = 2.3 \times 10^{-14}$) using *cis*-expression quantitative trait loci genetic instruments that also had strong evidence for colocalization with COVID-19 hospitalization. To disentangle the shared expression quantitative trait loci signal for IL10RB and IFNAR2, phenome-wide association scans and pathway enrichment analysis was conducted, which suggested that IFNAR2 is more likely to play a role in COVID-19 hospitalization. The findings prioritize trials of drugs targeting IFNAR2 and ACE2 for early management of COVID-19.

Reference

https://www.nature.com/articles/s41591-021-01310-z

IL-33 expression in response to SARS-CoV-2 correlates with seropositivity in COVID-19 convalescent individuals

Abstract

The understanding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still developing. An observational study was performed to investigate seroprevalence and immune responses in subjects professionally exposed to SARS-CoV-2 and their family members (155 individuals; ages 5–79 years). Seropositivity for SARS-CoV-2 Spike glycoprotein aligns with PCR results that confirm the previous infection. Anti-Spike IgG/IgM titers remain high 60 days post-infection and do not strongly associate with symptoms, except for fever. We analyze PBMCs from a subset of seropositive and seronegative adults. TLR7 agonist-activation reveals an increased population of IL-6+TNF-IL-1β+ monocytes, while SARS-CoV-2 peptide stimulation elicits IL-33, IL-6, IFNa2, and IL-23 expression in seropositive individuals. IL-33 correlates with CD4+ T cell activation in PBMCs from convalescent subjects and is likely due to T cell-mediated effects on IL-33-producing cells. IL-33 is associated with pulmonary infection and chronic diseases like asthma and COPD, but its role in COVID-19 is unknown. Analysis of published scRNAseq data of bronchoalveolar lavage fluid (BALF) from patients with mild to severe COVID-19 reveals a population of IL-33-producing cells that increases with the disease. Together these findings show that IL-33 production is linked to SARS-CoV-2 infection and warrant further investigation of IL-33 in COVID-19 pathogenesis and immunity.

Reference

https://www.nature.com/articles/s41467-021-22449-w

Inhaled budesonide in the treatment of early COVID-19 (STOIC): A phase 2, open-label, randomised controlled trial

Abstract

Background: Multiple early reports of patients admitted to hospital with COVID-19 showed that patients with chronic respiratory disease were significantly under-represented in these cohorts. It was hypothesised that the widespread use of inhaled

glucocorticoids among these patients was responsible for this finding, and tested if inhaled glucocorticoids would be an effective treatment for early COVID-19.

Methods: An open-label, parallel-group, phase 2, randomised controlled trial (Steroids in COVID-19; STOIC) of inhaled budesonide was performed, compared with usual care, in adults within 7 days of the onset of mild COVID-19 symptoms. The trial was done in the community in Oxfordshire, UK. Participants were randomly assigned to inhaled budsonide or usual care stratified for age (≤40 years or >40 years), sex (male or female), and number of comorbidities (≤1 and ≥2). Randomisation was done using random sequence generation in block randomisation in a 1:1 ratio. Budesonide dry powder was delivered using a turbohaler at a dose of 400 µg per actuation. Participants were asked to take two inhalations twice a day until symptom resolution. The primary endpoint was COVID-19-related urgent care visit, including emergency department assessment or hospitalisation, analysed for both the per-protocol and intention-to-treat (ITT) populations. The secondary outcomes were self-reported clinical recovery (symptom resolution), viral symptoms measured using the Common Cold Questionnare (CCQ) and the InFLUenza Patient Reported Outcome Questionnaire (FLUPro), body temperature, blood oxygen saturations, and SARS-CoV-2 viral load. The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment. This trial is registered with ClinicalTrials.gov, NCT04416399.

Findings: From July 16 to Dec 9, 2020, 167 participants were recruited and assessed for eligibility. 21 did not meet eligibility criteria and were excluded. 146 participants were randomly assigned—73 to usual care and 73 to budesonide. For the per-protocol population (n=139), the primary outcome occurred in ten (14%) of 70 participants in the usual care group and one (1%) of 69 participants in the budesonide group (difference in proportions 0·131, 95% CI 0·043 to 0·218; p=0·004). For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportions 0·123, 95% CI 0·033 to 0·213; p=0·009). The number needed to treat with inhaled budesonide to reduce COVID-19 deterioration was eight. Clinical recovery was 1 day shorter in the budesonide group compared with the usual care group (median 7 days [95% CI 6 to 9] in the budesonide group vs 8 days [7 to 11] in the usual care group; log-rank test

p=0·007). The mean proportion of days with a fever in the first 14 days was lower in the budesonide group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0·051) and the proportion of participants with at least 1 day of fever was lower in the budesonide group when compared with the usual care group. As-needed antipyretic medication was required for fewer proportion of days in the budesonide group compared with the usual care group (27% [IQR 0–50] vs 50% [15–71]; p=0·025) Fewer participants randomly assigned to budesonide had persistent symptoms at days 14 and 28 compared with participants receiving usual care (difference in proportions 0·204, 95% CI 0·075 to 0·334; p=0·003). The mean total score change in the CCQ and FLUPro over 14 days was significantly better in the budesonide group compared with the usual care group (CCQ mean difference −0·12, 95% CI −0·21 to −0·02 [p=0·016]; FLUPro mean difference −0·10, 95% CI −0·21 to −0·00 [p=0·044]). Blood oxygen saturations and SARS-CoV-2 load, measured by cycle threshold, were not different between the groups. Budesonide was safe, with only five (7%) participants reporting self-limiting adverse events.

Interpretation: Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00160-0/fulltext

Publication Date: Apr 08, 2021

Monitoring the proportion of the population infected by SARS-CoV-2 using age-stratified hospitalisation and serological data: A modelling study

Abstract

Background: Regional monitoring of the proportion of the population who have been infected by SARS-CoV-2 is important to guide local management of the epidemic, but is difficult in the absence of regular nationwide serosurveys. It was aimed to estimate in near real time the proportion of adults who have been infected by SARS-CoV-2.

Methods: In this modelling study, a method was developed to reconstruct the proportion of adults who have been infected by SARS-CoV-2 and the proportion of infections being detected, using the joint analysis of age-stratified seroprevalence, hospitalisation, and

case data, with deconvolution methods. This method was developed on a dataset consisting of seroprevalence estimates from 9782 participants (aged ≥20 years) in the two worst affected regions of France in May, 2020, and applied our approach to the 13 French metropolitan regions over the period March, 2020, to January, 2021. Our method was validated externally using data from a national seroprevalence study done between May and June, 2020.

Findings: It was estimated that 5·7% (95% CI 5·1–6·4) of adults in metropolitan France had been infected with SARS-CoV-2 by May 11, 2020. This proportion remained stable until August, 2020, and increased to 14·9% (13·2–16·9) by Jan 15, 2021. With 26·5% (23·4–29·8) of adult residents having been infected in Île-de-France (Paris region) compared with 5·1% (4·5–5·8) in Brittany by January, 2021, regional variations remained large (coefficient of variation [CV] 0·50) although less so than in May, 2020 (CV 0·74). The proportion infected was twice as high (20·4%, 15·6–26·3) in 20–49-year-olds than in individuals aged 50 years or older (9·7%, 6·9–14·1). 40·2% (34·3–46·3) of infections in adults were detected in June to August, 2020, compared with 49·3% (42·9–55·9) in November, 2020, to January, 2021. Our regional estimates of seroprevalence were strongly correlated with the external validation dataset (coefficient of correlation 0·89).

Interpretation: The simple approach to estimate the proportion of adults that have been infected with SARS-CoV-2 can help to characterise the burden of SARS-CoV-2 infection, epidemic dynamics, and the performance of surveillance in different regions.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(21)00064-5/fulltext

Self-sampling of capillary blood for SARS-CoV-2 serology

Abstract

Serological testing is emerging as a powerful tool to progress our understanding of COVID-19 exposure, transmission and immune response. Large-scale testing is limited by the need for in-person blood collection by staff trained in venepuncture, and the limited sensitivity of lateral flow tests. Capillary blood self-sampling and postage to laboratories for analysis could provide a reliable alternative. Two-hundred and nine

matched venous and capillary blood samples were obtained from thirty nine participants and analysed using a COVID-19 IgG ELISA to detect antibodies against SARS-CoV-2. Thirty eight out of thirty nine participants were able to self-collect an adequate sample of capillary blood (≥ 50 µl). Using plasma from venous blood collected in lithium heparin as the reference standard, matched capillary blood samples, collected in lithium heparin-treated tubes and on filter paper as dried blood spots, achieved a Cohen's kappa coefficient of > 0.88 (near-perfect agreement, 95% CI 0.738–1.000). Storage of capillary blood at room temperature for up to 7 days post sampling did not affect concordance. The results indicate that capillary blood self-sampling is a reliable and feasible alternative to venepuncture for serological assessment in COVID-19.

Reference

https://www.nature.com/articles/s41598-021-86008-5

Are psychiatric disorders risk factors for COVID-19 susceptibility and severity? A two-sample, bidirectional, univariable, and multivariable Mendelian Randomization study

Abstract

Observational studies have suggested bidirectional associations between psychiatric disorders and COVID-19 phenotypes, but results of such studies are inconsistent. Mendelian Randomization (MR) may overcome the limitations of observational studies, e.g., unmeasured confounding and uncertainties about cause and effect. It was aimed to elucidate associations between neuropsychiatric disorders and COVID-19 susceptibility and severity. To that end, a two-sample, bidirectional, univariable, and multivariable MR design was applied to genetic data from genome-wide association studies (GWASs) of neuropsychiatric disorders and COVID-19 phenotypes (released in January 2021). In single-variable Generalized Summary MR analysis, the most significant and only Bonferroni-corrected significant result was found for genetic liability to BIP-SCZ (a combined GWAS of bipolar disorder and schizophrenia as cases vs. controls) increasing risk of COVID-19 (OR = 1.17, 95% CI, 1.06–1.28). However, we found a significant, positive genetic correlation between BIP-SCZ and COVID-19 of 0.295 and could not confirm causal or horizontally pleiotropic effects using another method. No genetic liabilities to COVID-19 phenotypes increased the risk of

(neuro)psychiatric disorders. In multivariable MR using both neuropsychiatric and a range of other phenotypes, only genetic instruments of BMI remained causally associated with COVID-19. All sensitivity analyses confirmed the results. In conclusion, while genetic liability to bipolar disorder and schizophrenia combined slightly increased COVID-19 susceptibility in one univariable analysis, other MR and multivariable analyses could only confirm genetic underpinnings of BMI to be causally implicated in COVID-19 susceptibility. Thus, using MR we found no consistent proof of genetic liabilities to (neuro)psychiatric disorders contributing to COVID-19 liability or vice versa, which is in line with at least two observational studies. Previously reported positive associations between psychiatric disorders and COVID-19 by others may have resulted from statistical models incompletely capturing BMI as a continuous covariate.

Reference

https://www.nature.com/articles/s41398-021-01325-7

The role of chest CT quantitative pulmonary inflammatory index in the evaluation of the course and treatment outcome of COVID-19 pneumonia

Abstract

To explore the clinical application value of chest CT quantitative pulmonary inflammation index (PII) in the evaluation of the course and treatment outcome of COVID-19 pneumonia. One hundred and eighteen patients with COVID-19 pneumonia diagnosed by RT-PCR were analyzed retrospectively. The correlation between chest CT PII, clinical symptoms and laboratory examinations during the entire hospitalization period was compared. The average age of the patients was 46.0 ± 15 (range: 1–74) years. Of the 118 patients, 62 are male (52.5%) and 56 are female (47.5%). Among them, 116 patients recovered and were discharged, 2 patients died, and the median length of hospital stay was 22 (range: 9–41) days. On admission, 76.3% of the patients presented with fever, and the laboratory studies showed a decrease in lymphocyte (LYM) count and an increase in lactate dehydrogenase (LDH) levels, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR). Within the studies' chest CTs, the median number of involved lung lobes was 4 (range: 0–5) and the median number of involved lung segments was 9 (range 0–20). The left lower lobe and the right lower lobe were the most likely areas to be involved (89.0% and 83.9%), and 84.7% of the

patients had inflammatory changes in both lungs. The main manifestations on chest CT were ground glass opacities (31.4%), ground glass opacities and consolidation (20.3%), ground glass opacities and reticular patterns (32.2%), mixed type (13.6%), and white lungs (1.7%); common accompanying signs included linear opacities (55.9%), air bronchograms (46.6%), thick small vessel shadows (36.4%), and pleural hypertrophy (13.6%). The chest CT at discharge showed complete absorption of lesions in 19 cases (16.1%), but not in the remaining 99 cases. Lesions remained in a median of 3 lung lobes (range: 0–5). Residual lesions remained in a median of 5 lung segments (range: 0–20). The residual lesions mainly presented as ground glass opacities (61.0%), and the main accompanying sign was linear opacities (59.3%). Based on chest CT, the median maximum PII of lungs was 30.0% (range: 0–97.5%), and the median PII after discharge in the patients excluding the two deaths was 12.5% (range: 0–53.0%). PII was significantly negatively correlated with the LYM count and significantly positively correlated with body temperature, LDH, CRP, and ESR. There was no significant correlation between the PII and the white blood cell count, but the grade of PII correlated well with the clinical classification. PII can be used to monitor the severity and the treatment outcome of COVID-19 pneumonia, provide help for clinical classification, assist in treatment plan adjustments and aid assessments for discharge.

Reference

https://www.nature.com/articles/s41598-021-87430-5

Heterogeneous interventions reduce the spread of COVID-19 in simulations on real mobility data

Abstract

Major interventions have been introduced worldwide to slow down the spread of the SARS-CoV-2 virus. Large scale lockdown of human movements are effective in reducing the spread, but they come at a cost of significantly limited societal functions. We show that natural human movements are statistically diverse, and the spread of the disease is significantly influenced by a small group of active individuals and gathering venues. We find that interventions focused on these most mobile individuals and popular venues reduce both the peak infection rate and the total infected population while retaining high social activity levels. These trends are seen consistently in

simulations with real human mobility data of different scales, resolutions, and modalities from multiple cities across the world. The observation implies that compared to broad sweeping interventions, more heterogeneous strategies that are targeted based on the network effects in human mobility provide a better balance between pandemic control and regular social activities.

Reference

https://www.nature.com/articles/s41598-021-87034-z

Prognostic value of thrombin generation parameters in hospitalized COVID-19 patients

Abstract

SARS-CoV-2 infection increases the risk of thrombosis by different mechanisms not fully characterized. Although still debated, an increase in D-dimer has been proposed as a first-line hemostasis test associated with thromboembolic risk and unfavorable prognosis. We aim to systematically and comprehensively evaluate the association between thrombin generation parameters and the inflammatory and hypercoagulable state, as well as their prognostic value in COVID-19 patients. A total of 127 hospitalized patients with confirmed COVID-19, 24 hospitalized patients with SARS-CoV-2-negative pneumonia and 12 healthy subjects were included. Clinical characteristics, thrombin generation triggered by tissue factor with and without soluble thrombomodulin, and also by silica, as well as other biochemical parameters were assessed. Despite the frequent use of heparin, COVID-19 patients had similar thrombin generation to healthy controls. In COVID-19 patients, the thrombin generation lag-time positively correlated with markers of cell lysis (LDH), inflammation (CRP, IL-6) and coagulation (D-dimer), while the endogenous thrombin potential (ETP) inversely correlated with D-dimer and LDH, and positively correlated with fibrinogen levels. Patients with more prolonged lag-time and decreased ETP had higher peak ISTH-DIC scores, and had more severe disease (vascular events and death). The ROC curve and Kaplan Meier estimate indicated that the D-dimer/ETP ratio was associated with in-hospital mortality (HR 2.5; $p = 0.006$), and with the occurrence of major adverse events (composite end-point of vascular events and death) (HR 2.38; $p = 0.004$). The thrombin generation ETP and lag-time variables

correlate with thromboinflammatory markers, and the D-dimer/ETP ratio can predict major adverse events in COVID-19.

Reference

https://www.nature.com/articles/s41598-021-85906-y

CORRESPONDANCE

Publication Date: Apr 14, 2021

Lowering SARS-CoV-2 viral load might affect transmission but not disease severity in secondary cases

Personal View by Matthew A Spinelli and colleagues was read by the authors and were agreed with the authors on the evident advantage provided by non-pharmaceutical interventions (facial masking, social distancing, and improved ventilation) in lowering SARS-CoV-2 inoculum, thereby reducing viral transmission. Nevertheless, we call for caution before asserting that such measures could make a substantial difference in reducing COVID-19 severity.

Animal models examining a potential dose–response relationship reported conflicting results, and experimental inoculation might inaccurately mimic real-life infection dynamics, including inoculum doses. Two studies are cited to support Spinelli and colleagues' hypothesis. Bielecki and colleagues observed no symptomatic SARS-CoV-2 infections in a military company where protective measures were rigorously implemented, whereas 47% of all infections were symptomatic in an identical company where such measures were less strict. This finding is hardly applicable to the general population as the study was in young (median age 20 years), healthy individuals. Bias due to sampling and testing based on self-reported symptoms could not be ruled out, non-airborne routes of transmission could have prevailed, and the primary study aim was not to assess the potential relationship of viral inoculum with disease severity.

The second study cited by Spinelli and colleagues investigated the relationship of viral load with several characteristics of index and secondary cases, as well as with transmission risk in outpatient clusters. The study did not observe any dose–response relationship between index viral load and the probability of symptomatic infections in contacts, nor did it identify any correlation between the index cases' viral amount and COVID-19 incubation length or first viral load in incident secondary cases, by contrast with what was stated by Spinelli and colleagues.

It was recently observed no difference in occurrence of symptomatic infections, hospitalisation, and death in household secondary cases when stratified by viral load of

their linked index source cases. As previously detailed, it seems that host permissiveness (eg, age, sex, receptor density, genetic and epigenetic factors, host immunological features, comorbidities, comedications) is the key factor in allowing subsequent viral replication and triggering of inflammatory and immune-pathological processes rather than viral amount at exposure. While reducing the amount of virus circulating in and between individuals might be a key strategy to limit SARS-CoV-2 spread, on the basis of the existing evident, it seems unlikely that the inoculum size has any major role in determining disease severity of secondary cases.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00205-X/fulltext

Were pregnant women more affected by COVID-19 in the second wave of the pandemic?

At the emergence of the COVID-19 pandemic in 2020, there was justified concern that this disease might have similar effects on pregnant women as influenza or other coronavirus infections. During the 2009 H1N1 influenza pandemic, influenza mortality in pregnant women in the USA was 4·3%. In global analyses, maternal deaths from severe acute respiratory syndrome or Middle East respiratory syndrome have been reported in 13% (n=24) and 40% (n=10) of published case reports, respectively. Reassuringly, US data from the first wave of the COVID-19 pandemic (from January to June, 2020) show that death from COVID-19 during pregnancy was low (0·19%) and consistent with that of non-pregnant women of childbearing age (0·25%). However, by September, 2020, findings from a systematic review and meta-analysis of global data suggested that pregnancy is a significant risk factor for hospitalisation and more severe illness, with a critical care admission odds ratio for pregnant women with COVID-19 compared with infected women of childbearing age of 2·13 (95% CI 1·53–2·95) and an invasive ventilation odds ratio of 2·59 (2·28–2·94).

Since September, 2020, a second wave in the UK appears to have had a more marked impact on pregant women. At the Royal Brompton Hospital in London, one of five commissioned centres in England for severe acute respiratory failure that offer extracorporeal membrane oxygenation (ECMO), we have treated pregnant and peripartum women with severe COVID-19 disease since March, 2020. The numbers of

pregnant and peripartum women with severe COVID-19 disease increased during the second wave, and it appears that more of these individuals are requiring admission to intensive care and are being considered for ECMO. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00716-9/fulltext

Publication Date: Apr 13, 2021

Serum sample neutralisation of BBIBP-CorV and ZF2001 vaccines to SARS-CoV-2 501Y.V2

Reports BBIBP-CorV and ZF2001 are two COVID-19 vaccines developed in China. BBIBP-CorV is an inactivated virus vaccine approved for conditional marketing authorisation and ZF2001 is a recombinant dimeric receptor-binding domain (RBD) protein vaccine currently in phase 3 clinical trials and approved for emergency use in China and Uzbekistan. Both vaccines showed good immunogenicity in phase 1 and 2 trials. In the past few months, several SARS-CoV-2 variants of concern have been reported, especially the 501Y.V2, which was first isolated in South Africa, raising serious concern about the efficacy of the vaccines under development. This variant was first isolated in China on Jan 25, 2021, which contains ten amino acid mutation sites in spike (S) protein with five (Asp80Ala, Leu242del, Ala243del, Leu244del, and Arg246Ile) located at N-terminal domain, three (Lys417Asn, Glu484Lys, and Asn501Tyr) in RBD, and two in C-terminal domain 2 (CTD2) and S1/S2-S2' region.

Neutralisation activity were assessed in 24 serum samples from participants in two clinical trials, 12 who had been vaccinated with BBIBP-CorV and 12 who had been vaccinated with ZF2001, who were randomly selected to cover a range of different neutralising titres (appendix p 3). The neutralising activity were measured in these serum samples against live SARS-CoV-2 strains GDPCC (501Y.V2)5. SARS-CoV-2 strains HB02 (wild type) and BJ01 (D614G) were tested as the control.

All 24 serum samples from either recipients of BBIBP-CorV or ZF2001 largely preserved neutralisation of the 501Y.V2 variant, with slightly reduced geometric mean titres (GMTs) compared with their titres against the wild type or D614G strains (appendix p 2).

For BBIBP-CorV, the GMT decreased from 110·9 (95% CI 76·7–160·2) to 71·5 (51·1–100·1). For ZF2001, this the GMT decreased from 106·1 (95% CI 75·0–150·1) to 66·6 (51·0–86·9). The findings suggest that the 501Y.V2 variant does not escape the immunity induced by vaccines targeting the whole virus (BBIBP-CorV) or S protein dimeric RBD (ZF2001). The potential 1·5 to 1·6 times reduction in neutralising GMTs should be taken into account for their effect on the clinical efficacy of these vaccines. For both vaccines, immune serum samples neutralise both variant 501Y.V2 and D614G, the variant currently circulating globally, non-significantly. For ZF2001, a some significance (p=0·04) between variant 501Y.V2 and the wild type might be due to the sample selection and size. The neutralisation-reduction discrepancy between our protein-based vaccine against authentic virus and mRNA vaccine against pseudotyped virus needs further investigation in the future.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00082-3/fulltext

COMMENT

Publication Date: Apr 14, 2021

COVID-19 may become nanomedicine's finest hour yet

The nanotechnology-enabled mRNA-based vaccine platform recently approved against COVID-19 bears hope for improved vaccine development and trialling capacities in low- and middle-income countries as part of a broader global public health agenda. For more details, read the given link below.

Reference

https://www.nature.com/articles/s41577-021-00553-8

Publication Date: Apr 13, 2021

Is IL-6 a key cytokine target for therapy in COVID-19?

The identification of elevated IL-6 levels in patients with severe COVID-19 led to the rapid development of clinical trials targeting this cytokine. Overall, these trials do not support the widespread use of IL-6 antagonists in hospitalized patients with mild-to-moderate disease, but IL-6 antagonists may be beneficial when rapidly deployed in patients with severe COVID-19. For more details, read the given link below.

Reference

https://www.nature.com/articles/s41577-021-00553-8

Publication Date: Apr 12, 2021

Monitoring differences between the SARS-CoV-2 B.1.1.7 variant and other lineages

As focus in the SARS-CoV-2 pandemic shifts to the emergence of new variants of concern (VOC), characterising the differences between new variants and non-VOC lineages will become increasingly important for surveillance and maintaining the effectiveness of both public health and vaccination programmes. In The *Lancet Public Health*, Mark Graham and colleagues report on ecological associations between the

prevalence of SARS-CoV-2 variant B.1.1.7 and changes in the presentation of the virus, including differences in symptomatology, disease course, reinfection rate, and transmissibility of B.1.1.7. The study used data from the COVID Symptom Study app in the UK on SARS-CoV-2 test results, proportions of the population with self-reported individual symptoms, and self-reported hospitalisation, in combination with genomic data from the COVID-19 UK Genetics Consortium. The results indicated no association between B.1.1.7 prevalence and the type or frequency of symptoms reported by users (after controlling for age, sex, and seasonal variables), the proportion of asymptomatic cases, possible reinfections, long disease duration, or admission to hospital relative to other lineages. Similar to earlier studies, B.1.1.7 was estimated to be more infectious than non-VOC lineages, increasing the effective reproduction number, Rt, by a factor of 1·35 (95% CI 1·02–1·69). For more details, read the given link below.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(21)00073-6/fulltext

Lack of detail in population-level data impedes analysis of SARS-CoV-2 variants of concern and clinical outcomes

The SARS-CoV-2 lineage B.1.1.7 is characterised by a suite of defining mutations in the immunodominant spike protein, including a signature Asp501Tyr substitution in the receptor-binding domain.1 First reported in December 2020, in the UK, the variant's discovery coincided with a substantial surge in case numbers and fatalities in the UK, raising concerns that this variant was both more infectious and virulent than previous variants. Epidemiological and modelling studies have yielded good evidence that B.1.1.7 is more transmissible than other variants. However, conclusions as to the effects of B.1.1.7 on disease severity are less certain. Confounding factors including health-care resource use, demographic changes, and socio-behavioural trends affect clinical outcomes, including mortality, and are difficult to adjust for without detailed, robust, patient-level data.

In *The Lancet Infectious Diseases*, Dan Frampton and colleagues report their findings from such a study. Analysing a cohort of 341 patients, including 198 (58%) with B.1.1.7 infections, the authors correlated outcomes with granular clinical data. Their observation that B.1.1.7 infections were associated with increased viral loads corroborates findings

from two other studies and provides a mechanistic hypothesis that increased transmissibility is via increased respiratory shedding. Yet, disease severity and clinical outcomes between patients with B.1.1.7 and non-B.1.1.7 infections were similar after adjusting for differences in age, sex, ethnicity, and comorbidities. Importantly, this study was done from Nov 9, to Dec 20, 2020, before the late-December peak in UK COVID-19 infections, avoiding any confounding effect of the availability of health-care resources on mortality. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00201-2/fulltext

Publication Date: Apr 09, 2021

COVID-19 severity and obesity: Are MAIT cells a factor?

People with obesity have an increased risk of severe COVID-19: A meta-analysis by Popkin and colleagues found that the odds ratio of people with obesity being hospitalised with COVID-19 was 2·13 when compared with those without obesity, and mortality was 48% higher in patients with obesity than in those without. This increased risk of severe disease is linked to higher rates of metabolic and cardiovascular complications. Another major contributing factor is the presence of substantial immune dysregulation and chronic systemic inflammation. Obesity is associated with increased levels of numerous inflammatory mediators, including interleukin (IL)-1, IL-6, IL-17, and tumour necrosis factor α. These cytokines are also implicated in the pathogenesis of COVID-19. In addition to inflammation, obesity is associated with important defects in immune cells tasked with host protection, including natural killer cells and mucosal associated invariant T (MAIT) cells.

Several publications have highlighted MAIT cells as potentially having a crucial role in the host response to SARS-CoV-2. In each of these studies, reduced peripheral serum MAIT-cell frequencies were observed in a COVID-19 severity-dependent manner (ie, with lower frequency associated with more severe COVID-19). Conversely, increased numbers of MAIT cells were noted in the lungs of patients with COVID-19 together with higher expression of MAIT-cell chemoattractants, and increased levels of activated MAIT cells producing granzyme B were noted in patients with COVID-19. Furthermore,

importantly, after co-culturing MAIT cells with SARS-CoV-2-infected macrophages, increased activity of the MAIT cells producing granzyme B was observed, suggesting a possible ability of MAIT cells to respond to or directly kill infected cells. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00140-5/fulltext

REPORT

Publication Date: Apr 12, 2021

Shared B cell memory to coronaviruses and other pathogens varies in human age groups and tissues

Abstract

Vaccination and infection promote the formation, tissue distribution, and clonal evolution of B cells, which encode humoral immune memory. convergent antigen-specific antibody genes of similar sequences shared between individuals in pediatric and adult blood, and deceased organ donor tissues, were evaluated. B cell memory varied for different pathogens. Polysaccharide antigen-specific clones were not exclusive to the spleen. Adults had higher clone frequencies and greater class-switching in lymphoid tissues than blood, while pediatric blood had abundant class-switched convergent clones. Consistent with reported serology, pre-pandemic children had class-switched convergent clones to SARS-CoV-2 with weak cross-reactivity to other coronaviruses, while adult blood or tissues showed few such clones. The results highlight the prominence of early childhood B cell clonal expansions and cross-reactivity for future responses to novel pathogens.

Reference

https://science.sciencemag.org/content/early/2021/04/09/science.abf6648

PERSPECTIVE

Publication Date: Apr 13, 2021

Considerations for bioanalytical characterization and batch release of COVID-19 vaccines

The COVID-19 pandemic has prompted hundreds of laboratories around the world to employ traditional as well as novel technologies to develop vaccines against SARS-CoV-2. The hallmarks of a successful vaccine are safety and efficacy. Analytical evaluation methods, that can ensure the high quality of the products and that can be executed speedily, must be in place as an integral component of Chemistry, Manufacturing, and Control (CMC). These methods or assays are developed to quantitatively test for critical quality attributes (CQAs) of a vaccine product. While clinical (human) efficacy of a vaccine can never be predicted from pre-clinical evaluation of CQA, precise and accurate measurements of antigen content and a relevant biological activity (termed “potency”) elicited by the antigen allow selection of potentially safe and immunogenic doses for entry into clinical trials. All available vaccine technology platforms, novel and traditional, are being utilized by different developers to produce vaccines against SARS-CoV-2. It took less than a year from the publication of SARS-CoV-2 gene sequence to Emergency Use Authorization (EUA) of the first vaccine, setting a record for speed in the history of vaccine development. The largest ever global demand for vaccines has prompted some vaccine developers to enter multiple manufacturing partnerships in different countries in addition to implementing unprecedented scale-up plans. Quantitative, robust, and rapid analytical testing for CQA of a product is essential in ensuring smooth technology transfer between partners and allowing analytical bridging between vaccine batches used in different clinical phases leading up to regulatory approvals and commercialization. Here opportunities were discussed to improve the speed and quality of the critical batch release and characterization assays.

Reference

https://www.nature.com/articles/s41541-021-00317-4

Publication Date: Apr 14, 2021

Sputnik V, a host of coronavirus mutations and a rocket stack

Sputnik V vaccine is no match for a fast-spreading variant:

A variant of the virus SARS-CoV-2 detected in South Africa can evade antibodies elicited by the Sputnik V vaccine against COVID-19. Many vaccines — including Sputnik V, developed in Russia — trigger the production of antibodies targeting the SARS-CoV-2 protein called spike, which the virus uses to infect host cells. Scientists worry that the vaccines might be ineffective against SARS-CoV-2 variants with mutations in the spike-encoding gene.

Benhur Lee at the Icahn School of Medicine at Mount Sinai in New York City and his colleagues obtained samples of antibody-laden blood serum from 12 people vaccinated with Sputnik V (S. Ikegame et al. Preprint at medRxiv https://doi.org/f5h9; 2021). The authors tested the serum against benign viruses engineered to make the versions of spike found in certain SARS-CoV-2 variants. Eight of the 12 samples did not inhibit viruses equipped with spike from B.1.351, the variant identified in South Africa. But the samples effectively overcame viruses with spike from the B.1.1.7 variant, which was detected in Britain. The emergence of variants might require a new generation of vaccines, the authors say. The findings have not yet been peer reviewed.

Air traveller yields a new variant bristling with mutations

A coronavirus variant identified in Angola carries more mutations than any strain previously identified. A team led by Tulio de Oliveira, at the University of KwaZulu-Natal in Durban, South Africa, and Silvia Lutucuta, at the Angola Ministry of Health in Luanda, identified the variant after sequencing samples from three people who flew to Angola from Tanzania in February 2021 (T. de Oliveira et al. Preprint at medRxiv https://doi.org/f48g; 2021). The variant, named A.VOI.V2, carries 34 mutations, including 14 in the spike protein, which the virus uses to infect cells. The variant deserves further study, the authors say, because it carries mutations that might help it

to escape some people's immune responses. The finding has not yet been peer reviewed.

Reference

https://www.nature.com/articles/d41586-021-00962-8

Publication Date: Apr 13, 2021

Daily briefing: *J&J* COVID vaccine pause recommended

Authorities in the United States have recommended a pause in the use of Johnson & Johnson's COVID-19 vaccine "out of an abundance of caution", after six blood-clotting cases were reported in people who received the vaccine. The rare clotting problem is similar to the one linked to the Oxford–AstraZeneca vaccine. In a statement, Johnson & Johnson said it is working closely with medical experts to investigate the issue. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-021-00990-4

Publication Date: Apr 09, 2021

How could a COVID vaccine cause blood clots? Scientists race to investigate

The very rare occurrence of a mysterious blood-clotting disorder among some recipients of the Oxford–AstraZeneca COVID-19 vaccine has got researchers scrambling to uncover whether, and if so, how the inoculation could trigger such an unusual reaction. Even so, the clotting disorder — described today in two reports in *The New England Journal of Medicine* — is so uncommon that the benefits of the vaccine still outweigh its risks, EMA executive director Emer Cooke told reporters. Researchers are searching for possible links between unusual clotting and the Oxford–AstraZeneca coronavirus vaccine. But the finding leaves researchers wrestling with a medical mystery: why would a vaccine trigger such an unusual condition? "Of course, there are hypotheses: maybe it's something with the vector, maybe it's an additive in the vaccine, maybe it's something in the production process…For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-021-00940-0

PERSONAL VIEW

Publication Date: Apr 12, 2021

Confronting COVID-19-associated cough and the post-COVID syndrome: Role of viral neurotropism, neuroinflammation, and neuroimmune responses

Cough is one of the most common presenting symptoms of COVID-19, along with fever and loss of taste and smell. Cough can persist for weeks or months after SARS-CoV-2 infection, often accompanied by chronic fatigue, cognitive impairment, dyspnoea, or pain—a collection of long-term effects referred to as the post-COVID syndrome or long COVID. The pathways of neurotropism, neuroinflammation, and neuroimmunomodulation through the vagal sensory nerves were hypothesized, which are implicated in SARS-CoV-2 infection, lead to a cough hypersensitivity state. The post-COVID syndrome might also result from neuroinflammatory events in the brain. Gaps were highlighted in understanding of the mechanisms of acute and chronic COVID-19-associated cough and post-COVID syndrome, consider potential ways to reduce the effect of COVID-19 by controlling cough, and suggest future directions for research and clinical practice. Although neuromodulators such as gabapentin or opioids might be considered for acute and chronic COVID-19 cough, the possible mechanisms of COVID-19-associated cough and the promise of new anti-inflammatories or neuromodulators were discussed that might successfully target both the cough of COVID-19 and the post-COVID syndrome.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00125-9/fulltext