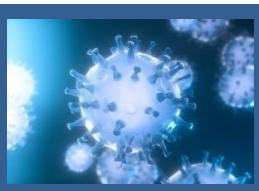
COVID-19

Mar 04-10, 2021



RESEARCH PUBLICATIONS

Publication Date: Mar 10, 2021

Antibody isotype diversity against SARS-CoV-2 is associated with differential serum neutralization capacities

Abstract

Understanding antibody responses to SARS-CoV-2 is indispensable for the development of containment measures to overcome the current COVID-19 pandemic. Recent studies showed that serum from convalescent patients can display variable neutralization capacities. Still, it remains unclear whether there are specific signatures that can be used to predict neutralization. Here, we performed a detailed analysis of sera from a cohort of 101 recovered healthcare workers and we addressed their SARS-CoV-2 antibody response by ELISA against SARS-CoV-2 Spike receptor binding domain and nucleoprotein. Both ELISA methods detected sustained levels of serum IgG against both antigens. Yet, the majority of individuals from our cohort generated antibodies with low neutralization capacity and only 6% showed high neutralizing titers against both authentic SARS-CoV-2 virus and the Spike pseudotyped virus. Interestingly, higher neutralizing sera correlate with detection of -IgG, IgM and IgA antibodies against both antigens, while individuals with positive IgG alone showed poor neutralization response. These results suggest that having a broader repertoire of antibodies may contribute to more potent SARS-CoV-2 neutralization. Altogether, our work provides a cross sectional snapshot of the SARS-CoV-2 neutralizing antibody response in recovered healthcare workers and provides preliminary evidence that possessing multiple antibody isotypes can play an important role in predicting SARS-CoV-2 neutralization.

Reference

https://www.nature.com/articles/s41598-021-84913-3

Neutralization of SARS-CoV-2 with IgG from COVID-19-convalescent plasma

Abstract

While there are various attempts to administer COVID-19-convalescent plasmas to SARS-CoV-2-infected patients, neither appropriate approach nor clinical utility has been established. We examined the presence and temporal changes of the neutralizing activity of IgG fractions from 43 COVID-19-convalescent plasmas using cell-based assays with multiple endpoints. IgG fractions from 27 cases (62.8%) had significant neutralizing activity and moderately to potently inhibited SARS-CoV-2 infection in cell-based assays; however, no detectable neutralizing activity was found in 16 cases (37.2%). Approximately half of the patients (~ 41%), who had significant neutralizing activity, lost the neutralization activity within ~ 1 month. Despite the rapid decline of neutralizing activity in plasmas, good amounts of SARS-CoV-2-S1-binding antibodies were persistently seen. The longer exposure of COVID-19 patients to greater amounts of SARS-CoV-2 elicits potent immune response to SARS-CoV-2, producing greater neutralization activity and SARS-CoV-2-S1-binding antibody amounts. The dilution of highly-neutralizing plasmas with poorly-neutralizing plasmas relatively readily reduced neutralizing activity. The presence of good amounts of SARS-CoV-2-S1-binding antibodies does not serve as a surrogate ensuring the presence of good neutralizing activity. In selecting good COVID-19-convalescent plasmas, quantification of neutralizing activity in each plasma sample before collection and use is required.

Reference

https://www.nature.com/articles/s41598-021-84733-5

Drug design and repurposing with DockThor-VS web server focusing on SARS-CoV-2 therapeutic targets and their non-synonym variants

Abstract

The COVID-19 caused by the SARS-CoV-2 virus was declared a pandemic disease in March 2020 by the World Health Organization (WHO). Structure-Based Drug Design strategies based on docking methodologies have been widely used for both new drug

development and drug repurposing to find effective treatments against this disease. In this work, we present the developments implemented in the DockThor-VS web server to provide a virtual screening (VS) platform with curated structures of potential therapeutic targets from SARS-CoV-2 incorporating genetic information regarding relevant non-synonymous variations. The web server facilitates repurposing VS experiments providing curated libraries of currently available drugs on the market. At present, DockThor-VS provides ready-for-docking 3D structures for wild type and selected mutations for Nsp3 (papain-like, PLpro domain), Nsp5 (Mpro, 3CLpro), Nsp12 (RdRp), Nsp15 (NendoU), N protein, and Spike. We performed VS experiments of FDA-approved drugs considering the therapeutic targets available at the web server to assess the impact of considering different structures and mutations to identify possible new treatments of SARS-CoV-2 infections.

Reference

https://www.nature.com/articles/s41598-021-84700-0

Blockade of SARS-CoV-2 spike protein-mediated cell–cell fusion using COVID-19 convalescent plasma

Abstract

The recent COVID-19 pandemic poses a serious threat to global public health, thus there is an urgent need to define the molecular mechanisms involved in SARS-CoV-2 spike (S) protein-mediated virus entry that is essential for preventing and/or treating this emerging infectious disease. In this study, the blocking activity of human COVID-19 convalescent plasma was examined by cell–cell fusion assays using SARS-CoV-2-S-transfected 293 T as effector cells and ACE2-expressing 293 T as target cells. We demonstrate that the SARS-CoV-2 S protein exhibits a very high capacity for membrane fusion and is efficient in mediating virus fusion and entry into target cells. Importantly, we find that COVID-19 convalescent plasma with high titers of IgG neutralizing antibodies can block cell–cell fusion and virus entry by interfering with the SARS-CoV-2-S/ACE2 or SARS-CoV-S/ACE2 interactions. These findings suggest that COVID-19 convalescent plasma may not only inhibit SARS-CoV-2-S but also cross-neutralize SARS-CoV-S-mediated membrane fusion and virus entry, supporting its potential as a

preventive and/or therapeutic agent against SARS-CoV-2 as well as other SARS-CoV infections.

Reference

https://www.nature.com/articles/s41598-021-84840-3

Overexpression of angiotensin-converting enzyme 2 by renin-angiotensin system inhibitors. Truth or myth? A systematic review of animal studies

Abstract

Angiotensin-converting enzyme 2 (ACE2) protects against organ damage in hypertension and cardiovascular diseases by counter regulating the renin-angiotensin system (RAS). ACE2 is also the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Based on the claim that RAS inhibitors (RASIs) cause ACE2 overexpression in some animal experiments, concerns have arisen that RASIs may aggravate SARS-CoV-2 infection and coronavirus disease-2019 severity in RASI-treated patients. To achieve a comprehensive review, a systematic search of MEDLINE/PubMed was conducted regarding the effects of RASIs on tissue ACE2 mRNA/protein expression in healthy animals and animal models of human diseases. We identified 88 eligible articles involving 168 experiments in the heart, kidneys, lungs, and other organs. Three of 38 experiments involving healthy animals showed ACE2 expression greater than twice that of the control (overexpression). Among 102 disease models (130 experiments), baseline ACE2 was overexpressed in 16 models (18 experiments) and less than half the control level (repression) in 28 models (40 experiments). In 72 experiments, RASIs did not change ACE2 levels from the baseline levels of disease models. RASIs caused ACE2 overexpression compared to control levels in seven experiments, some of which were unsupported by other experiments under similar conditions. In 36 experiments, RASIs reversed or prevented disease-induced ACE2 repression, yielding no or marginal changes. Therefore, ACE2 overexpression appears to be a rare rather than common consequence of RASI treatment in healthy animals and disease models. Future studies should clarify the pathophysiological significance of RASI-induced reversal or prevention of ACE2 repression in disease models.

Reference

https://www.nature.com/articles/s41440-021-00641-1

***In vitro* characterization of engineered red blood cells as viral traps against HIV-1 and SARS-CoV-2**

Abstract

Engineered red blood cells (RBCs) expressing viral receptors could be used therapeutically as viral traps as RBCs lack nuclei and other organelles required for viral replication. However, expression of viral receptors on RBCs is difficult to achieve since mature erythrocytes lack the cellular machinery to synthesize proteins. Here it was shown that the combination of a powerful erythroid-specific expression system and transgene codon optimization yields high expression levels of the HIV-1 receptors CD4 and CCR5, as well as a CD4-glycophorin A (CD4-GpA) fusion protein in erythroid progenitor cells, which efficiently differentiated into enucleated RBCs. HIV-1 efficiently entered RBCs that co-expressed CD4 and CCR5, but viral entry was not required for neutralization as CD4 or CD4-GpA expression in the absence of CCR5 was sufficient to potently neutralize HIV-1 and prevent infection of CD4+ T-cells *in vitro* due to the formation of high-avidity interactions with trimeric HIV-1 Env spikes on virions. To facilitate continuous large-scale production of RBC viral traps, we generated erythroblast cell lines stably expressing CD4-GpA or ACE2-GpA fusion proteins, which produced potent RBC viral traps against HIV-1 and SARS-CoV-2. The *in vitro* results suggest that this approach warrants further investigation as a potential treatment against acute and chronic viral infections.

Reference

https://www.cell.com/molecular-therapy-family/methods/fulltext/S2329-0501(21)00043-7

COVID-19 and liver disease: Mechanistic and clinical perspectives

Abstract

The understanding of the hepatic consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its resultant coronavirus disease 2019 (COVID-19) has evolved rapidly since the onset of the pandemic. In this Review, the hepatotropism of SARS-CoV-2 was discussed, including the differential expression of

viral receptors on liver cell types, and we describe the liver histology features present in patients with COVID-19. An overview of the pattern and relevance of abnormal liver biochemistry was provided during COVID-19 and present the possible underlying direct and indirect mechanisms for liver injury. Furthermore, large international cohorts have been able to characterize the disease course of COVID-19 in patients with pre-existing chronic liver disease. Patients with cirrhosis have particularly high rates of hepatic decompensation and death following SARS-CoV-2 infection and we outline hypotheses to explain these findings, including the possible role of cirrhosis-associated immune dysfunction. This finding contrasts with outcome data in pharmacologically immunosuppressed patients after liver transplantation who seem to have comparatively better outcomes from COVID-19 than those with advanced liver disease. Finally, we discuss the approach to SARS-CoV-2 vaccination in patients with cirrhosis and after liver transplantation and predict how changes in social behaviours and clinical care pathways during the pandemic might lead to increased liver disease incidence and severity.

Reference

https://www.nature.com/articles/s41575-021-00426-4

Virus vaccines: Proteins prefer pralines

Abstract

Most viral vaccines are based on inducing neutralizing antibodies (NAbs) against the virus envelope or spike glycoproteins. Many viral surface proteins exist as trimers that transition from a pre-fusion state when key NAb epitopes are exposed to a post-fusion form in which the potential for virus-cell fusion no longer exists. For optimal vaccine performance, these viral proteins are often engineered to enhance stability and presentation of these NAb epitopes. The method involves the structure-guided introduction of proline residues at key positions that maintain the trimer in the pre-fusion configuration. We review how this technique emerged during HIV-1 Env vaccine development and its subsequent wider application to other viral vaccines including SARS-CoV-2.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00048-2

Publication Date: Mar 09, 2021

Broad-spectrum anti-coronavirus vaccines and therapeutics to combat the current COVID-19 pandemic and future coronavirus disease outbreaks

Abstract

While the COVID-19 pandemic caused by SARS-CoV-2 is continuing, it may become worse in the coming winter months with a high potential for the emergence and spread of escape variants of SARS-CoV-2. SARS-related CoVs (SARSr-CoVs) from bats may also cause outbreaks of emerging coronavirus diseases in the future. These predictions call for the development of broad-spectrum anti-coronavirus vaccines and therapeutics to combat the current COVID-19 pandemic and future emerging coronavirus disease epidemics. In this review, we describe advances and challenges in the development of broad-spectrum vaccines and neutralizing antibodies against lineage B betacoronaviruses (β-CoV-Bs), including SARS-CoV-2, SARS-CoV, and SARSr-CoVs, as well as peptide-based pan-CoV fusion inhibitors and their potential in the prevention and treatment of COVID-19 and other human coronavirus infections.

Reference

https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(20)30505-1

Field-deployable, rapid diagnostic testing of saliva for SARS-CoV-2

Abstract

To safely re-open economies and prevent future outbreaks, rapid, frequent, point-of-need, SARS-CoV-2 diagnostic testing is necessary. However, existing field-deployable COVID-19 testing methods require the use of uncomfortable swabs and trained providers in PPE, while saliva-based methods must be transported to high complexity laboratories for testing. Here, the development and clinical validation of High-Performance Loop-mediated isothermal Amplification (HP-LAMP), a rapid, saliva-based, SARS-CoV-2 test was reported with a limit of detection of 1.4 copies of virus per µl of saliva and a sensitivity and specificity with clinical samples of > 96%, on par with

traditional RT-PCR based methods using swabs, but can deliver results using only a single fluid transfer step and simple heat block. Testing of 120 patient samples in 40 pools comprised of 5 patient samples each with either all negative or a single positive patient sample was 100% accurate. Thus, HP-LAMP may enable rapid and accurate results in the field using saliva, without need of a high-complexity laboratory.

Reference

https://www.nature.com/articles/s41598-021-84792-8

Predictive values, uncertainty, and interpretation of serology tests for the novel coronavirus

Abstract

Antibodies testing in the coronavirus era is frequently promoted, but the underlying statistics behind their validation has come under more scrutiny in recent weeks. We provide calculations, interpretations, and plots of positive and negative predictive values under a variety of scenarios. Prevalence, sensitivity, and specificity are estimated within ranges of values from researchers and antibodies manufacturers. Implications are discussed for society overall and across diverse locations with different levels of disease burden. Specifically, the proportion of positive serology tests that are false can differ drastically from up to 3%–88% for people from different places with different proportions of infected people in the populations while the false negative rate is typically under 10%.

Reference

https://www.nature.com/articles/s41598-021-84173-1

Cross-linking peptide and repurposed drugs inhibit both entry pathways of SARS-CoV-2

Abstract

Up to date, effective antivirals have not been widely available for treating COVID-19. In this study, we identify a dual-functional cross-linking peptide 8P9R which can inhibit the two entry pathways (endocytic pathway and TMPRSS2-mediated surface pathway) of SARS-CoV-2 in cells. The endosomal acidification inhibitors (8P9R and chloroquine)

can synergistically enhance the activity of arbidol, a spike-ACE2 fusion inhibitor, against SARS-CoV-2 and SARS-CoV in cells. In vivo studies indicate that 8P9R or the combination of repurposed drugs (umifenovir also known as arbidol, chloroquine and camostat which is a TMPRSS2 inhibitor), simultaneously interfering with the two entry pathways of coronaviruses, can significantly suppress SARS-CoV-2 replication in hamsters and SARS-CoV in mice. Here, drug combination (arbidol, chloroquine, and camostat) and a dual-functional 8P9R was used to demonstrate that blocking the two entry pathways of coronavirus can be a promising and achievable approach for inhibiting SARS-CoV-2 replication *in vivo*. Cocktail therapy of these drug combinations should be considered in treatment trials for COVID-19.

Reference

https://www.nature.com/articles/s41467-021-21825-w

Infectivity, susceptibility, and risk factors associated with SARS-CoV-2 transmission under intensive contact tracing in Hunan, China

Abstract

Several mechanisms driving SARS-CoV-2 transmission remain unclear. Based on individual records of 1178 potential SARS-CoV-2 infectors and their 15,648 contacts in Hunan, China, we estimated key transmission parameters. The mean generation time was estimated to be 5.7 (median: 5.5, IQR: 4.5, 6.8) days, with infectiousness peaking 1.8 days before symptom onset, with 95% of transmission events occurring between 8.8 days before and 9.5 days after symptom onset. Most transmission events occurred during the pre-symptomatic phase (59.2%). SARS-CoV-2 susceptibility to infection increases with age, while transmissibility is not significantly different between age groups and between symptomatic and asymptomatic individuals. Contacts in households and exposure to first-generation cases are associated with higher odds of transmission. Our findings support the hypothesis that children can effectively transmit SARS-CoV-2 and highlight how pre-symptomatic and asymptomatic transmission can hinder control efforts.

Reference

https://www.nature.com/articles/s41467-021-21710-6

The Organoid platform: Promises and challenges as tools in the fight against COVID-19

Abstract

Many pathogenic viruses that affect man display species specificity, limiting the use of animal models. Studying viral biology and identifying potential treatments therefore benefits from the development of *in vitro* cell systems that closely mimic human physiology. In the current COVID-19 pandemic, rapid scientific insights are of the utmost importance to limit its impact on public health and society. Organoids are emerging as versatile tools to progress the understanding of SARS-CoV-2 biology and to aid in the quest for novel treatments.

Reference

https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(20)30457-4

ORF8 contributes to cytokine storm during SARS-CoV-2 infection by activating IL-17 pathway

Abstract

Recently, COVID-19 caused by the novel coronavirus SARS-CoV-2 has brought great challenges to the world. More and more studies have shown that severe patients may suffer from cytokine storm syndrome; however, there are few studies on its pathogenesis. Here we demonstrated that SARS-CoV-2 coding protein open reading frame 8 (ORF8) acted as a contributing factor to cytokine storm during COVID-19 infection. ORF8 could activate IL-17 signaling pathway and promote the expression of pro-inflammatory factors. Moreover, treatment of IL17RA antibody protected mice from ORF8-induced inflammation was demonstrated. The findings are helpful to understand the pathogenesis of cytokine storm caused by SARS-CoV-2, and provide a potential target for the development of COVID-19 therapeutic drugs.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00261-3

Th1 Skewed immune response of Whole Virion Inactivated SARS CoV 2 Vaccine and its safety evaluation

Abstract

The development and evaluation of safety and immunogenicity of a whole virion inactivated (WVI) SARS-CoV-2 vaccine (BBV152), adjuvanted with aluminium hydroxide gel (Algel), or TLR7/8 agonist chemisorbed Algel was reported. A well-characterized SARS-CoV-2 strain was used and an established Vero cell platform to produce large-scale GMP grade highly purified inactivated antigen. Product development and manufacturing process were carried out in a BSL-3 facility. Immunogenicity and safety was determined at two antigen concentrations (3µg and 6µg), with two different adjuvants, in mice, rats and rabbits. The results showed that BBV152 vaccine formulations generated significantly high antigen-binding and neutralizing antibody titers (NAb), at both concentrations, in all three species with excellent safety profiles. The inactivated vaccine formulation containing TLR7/8 agonist adjuvant-induced Th1 biased antibody responses with elevated IgG2a/IgG1 ratio and increased levels of SARS-CoV-2 specific IFN-γ+ CD4+ T lymphocyte response. The results support further development for Phase I/II clinical trials in humans.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00266-2

SARS-CoV-2 within-host diversity and transmission

Abstract

Extensive global sampling and sequencing of the pandemic virus SARS-CoV-2 have enabled researchers to monitor its spread, and to identify concerning new variants. Two important determinants of variant spread are how frequently they arise within individuals, and how likely they are to be transmitted. To characterize within-host diversity and transmission we deep-sequenced 1313 clinical samples from the UK. SARS-CoV-2 infections are characterized by low levels of within-host diversity when viral loads are high, and a narrow bottleneck at transmission. Most variants are either lost, or occasionally fixed, at the point of transmission, with minimal persistence of shared diversity - patterns which are readily observable on the phylogenetic tree. The

results suggest that transmission-enhancing and/or immune-escape variants are likely to arise infrequently, but could spread rapidly if successfully transmitted.

Reference

https://science.sciencemag.org/content/early/2021/03/09/science.abg0821

Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes

Abstract

In the face of vaccine dose shortages and logistical challenges, various deployment strategies are being proposed to increase population immunity levels to SARS-CoV-2. Two critical issues arise: how will the timing of delivery of the second dose affect both infection dynamics and prospects for the evolution of viral immune escape via a build-up of partially immune individuals. Both hinge on the robustness of the immune response elicited by a single dose, compared to natural and two-dose immunity. Building on an existing immuno-epidemiological model, we find that in the short-term, focusing on one dose generally decreases infections, but longer-term outcomes depend on this relative immune robustness. Three scenarios of selection were then explored and find that a one-dose policy may increase the potential for antigenic evolution under certain conditions of partial population immunity. The critical need to test viral loads and quantify immune responses after one vaccine dose was also highlighted, and to ramp up vaccination efforts throughout the world.

Reference

https://science.sciencemag.org/content/early/2021/03/08/science.abg8663

Enoxaparin is associated with lower rates of mortality than unfractionated Heparin in hospitalized COVID-19 patients

Abstract

Background: Coagulopathies are a major class among COVID-19 associated complications. Although anticoagulants such as unfractionated Heparin and Enoxaparin are both being used for therapeutic mitigation of COVID associated coagulopathy (CAC), differences in their clinical outcomes remain to be investigated.

Methods: Records of 1,113 patients were analyzed in the Mayo Clinic Electronic Health Record (EHR) database who were admitted to the hospital for COVID-19 between April 4, 2020 and August 31, 2020, including 19 different Mayo Clinic sites in Arizona, Florida, Minnesota, and Wisconsin. Among this patient population, we compared cohorts of patients who received different types of anticoagulants, including 441 patients who received unfractionated Heparin and 166 patients who received Enoxaparin. Clinical outcomes at 28 days were compared, and propensity score matching was used to control for potential confounding variables including: demographics, comorbidities, ICU status, chronic kidney disease stage, and oxygenation status. Patients with a history of acute kidney injury and patients who received multiple types of anticoagulants were excluded from the study.

Findings: It was found that COVID-19 patients administered unfractionated Heparin but not Enoxaparin have higher rates of 28-day mortality (risk ratio: 4.3; 95% Confidence Interval [C.I.].: [1.8, 10.2]; p-value: 8.5e−4, Benjamini Hochberg [BH] adjusted p-value: 2.1e−3), after controlling for potential confounding factors.

Interpretation: This study emphasizes the need for mechanistically investigating differential modulation of the COVID-associated coagulation cascades by Enoxaparin versus unfractionated Heparin.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00054-7/fulltext

Publication Date: Mar 08, 2021

MRC5 cells engineered to express ACE2 serve as a model system for the discovery of antivirals targeting SARS-CoV-2

Abstract

Although the spread of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has resulted in a worldwide pandemic, there are currently no virus-specific drugs that are fully effective against SARS-CoV-2. Only a limited number of human-derived cells are capable of supporting SARS-CoV-2 replication and the infectivity of SARS-CoV-2 in these cells remains poor. In contrast, monkey-derived Vero cells are highly susceptibility to infection with SARS-CoV-2, although they are not suitable for the

study of antiviral effects by small molecules due to their limited capacity to metabolize drugs compared to human-derived cells. In this study, the goal was to generate a virus-susceptible human cell line that would be useful for the identification and testing of candidate drugs. Towards this end, we stably transfected human lung-derived MRC5 cells with a lentiviral vector encoding angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV-2. The results revealed that SARS-CoV-2 replicates efficiently in MRC5/ACE2 cells. Furthermore, viral RNA replication and progeny virus production were significantly reduced in response to administration of the replication inhibitor, remdesivir, in MRC5/ACE2 cells compared with Vero cells. It was concluded that the MRC5/ACE2 cells will be important in developing specific anti-viral therapeutics and will assist in vaccine development to combat SARS-CoV-2 infections.

Reference

https://www.nature.com/articles/s41598-021-84882-7

Genome-wide CRISPR screening identifies TMEM106B as a proviral host factor for SARS-CoV-2

Abstract

The ongoing COVID-19 pandemic has caused a global economic and health crisis. To identify host factors essential for coronavirus infection, we performed genome-wide functional genetic screens with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human coronavirus 229E. These screens uncovered virus-specific as well as shared host factors, including TMEM41B and PI3K type 3. We discovered that SARS-CoV-2 requires the lysosomal protein TMEM106B to infect human cell lines and primary lung cells. TMEM106B overexpression enhanced SARS-CoV-2 infection as well as pseudovirus infection, suggesting a role in viral entry. Furthermore, single-cell RNA-sequencing of airway cells from patients with COVID-19 demonstrated that TMEM106B expression correlates with SARS-CoV-2 infection. The present study uncovered a collection of coronavirus host factors that may be exploited to develop drugs against SARS-CoV-2 infection or future zoonotic coronavirus outbreaks.

Reference

https://www.nature.com/articles/s41588-021-00805-2

Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7

Abstract

The COVID-19 pandemic has ravaged the globe, and its causative agent, SARS-CoV-2, continues to rage. The prospects of ending this pandemic rest on the development of effective interventions. Single and combination monoclonal antibody (mAb) therapeutics have received emergency use authorization, with more in the pipeline. Furthermore, multiple vaccine constructs have shown promise, including two with ~95% protective efficacy against COVID-19. However, these interventions were directed toward the initial SARS-CoV-2 that emerged in 2019. The recent emergence of new SARS-CoV-2 variants B.1.1.7 in the UK and B.1.351 in South Africa is of concern because of their purported ease of transmission and extensive mutations in the spike protein. We now report that B.1.1.7 is refractory to neutralization by most mAbs to the N-terminal domain (NTD) of the spike and relatively resistant to a few mAbs to the receptor-binding domain (RBD). It is not more resistant to convalescent plasma or vaccinee sera. Findings on B.1.351 are more worrisome in that this variant is not only refractory to neutralization by most NTD mAbs but also by multiple individual mAbs to the receptor-binding motif on RBD, largely owing to an E484K mutation. Moreover, B.1.351 is markedly more resistant to neutralization by convalescent plasma (9.4 fold) and vaccinee sera (10.3-12.4 fold). B.1.351 and emergent variants with similar spike mutations present new challenges for mAb therapy and threaten the protective efficacy of current vaccines.

Reference

https://www.nature.com/articles/s41586-021-03398-2

The *in-vitro* effect of famotidine on SARS-COV-2 proteases and virus replication

Abstract

The lack of coronavirus-specific antiviral drugs has instigated multiple drug repurposing studies to redirect previously approved medicines for the treatment of SARS-CoV-2, the coronavirus behind the ongoing COVID-19 pandemic. A recent, large-scale, retrospective clinical study showed that famotidine, when administered at a high dose to hospitalized COVID-19 patients, reduced the rates of intubation and mortality. A separate, patient-reported study associated famotidine use with improvements in mild to

moderate symptoms such as cough and shortness of breath. While a prospective, multi-center clinical study is ongoing, two parallel *in silico* studies have proposed one of the two SARS-CoV-2 proteases, 3CLpro or PLpro, as potential molecular targets of famotidine activity; however, this remains to be experimentally validated. In this report, we systematically analyzed the effect of famotidine on viral proteases and virus replication. Leveraging a series of biophysical and enzymatic assays, we show that famotidine neither binds with nor inhibits the functions of 3CLpro and PLpro. Similarly, no direct antiviral activity of famotidine was observed at concentrations of up to 200 µM, when tested against SARS-CoV-2 in two different cell lines, including a human cell line originating from lungs, a primary target of COVID-19. These results rule out famotidine as a direct-acting inhibitor of SARS-CoV-2 replication and warrant further investigation of its molecular mechanism of action in the context of COVID-19.

Reference

https://www.nature.com/articles/s41598-021-84782-w

Long-term monitoring of SARS-CoV-2 RNA in wastewater of the Frankfurt metropolitan area in Southern Germany

Abstract

Wastewater-based epidemiology (WBE) is a great approach that enables us to comprehensively monitor the community to determine the scale and dynamics of infections in a city, particularly in metropolitan cities with a high population density. Therefore, we monitored the time course of the SARS-CoV-2 RNA concentration in raw sewage in the Frankfurt metropolitan area, the European financial center. To determine the SARS-CoV-2 RNA concentration in sewage, 24 h composite samples were continuously collected twice a week from two wastewater treatment plant (WWTP) influents (Niederrad and Sindlingen) serving the Frankfurt metropolitan area and performed RT-qPCR analysis targeting three genes (N gene, S gene, and ORF1ab gene). In August, a resurgence in the SARS-CoV-2 RNA load was observed, reaching 3×10^{13} copies/day, which represented similar levels compared to April with approx. 2×10^{14} copies/day. This corresponds to a continuous increase again in COVID-19 cases in Frankfurt since August, with an average of 28.6 incidences, compared to 28.7 incidences in April. Different temporal dynamics were observed between different

sampling points, indicating local dynamics in COVID-19 cases within the Frankfurt metropolitan area. The SARS-CoV-2 RNA load to the WWTP Niederrad ranged from approx. 4×10^{11} to 1×10^{15} copies/day, the load to the WWTP Sindlingen from approx. 1×10^{11} to 2×10^{14} copies/day, which resulted in a preceding increase in these loading in July ahead of the weekly averaged incidences. The study shows that WBE has the potential as an early warning system for SARS-CoV-2 infections and a monitoring system to identify global hotspots of COVID-19.

Reference

https://www.nature.com/articles/s41598-021-84914-2

Biomaterial-based immunoengineering to fight COVID-19 and infectious diseases

Abstract

Infection by SARS-CoV-2 virus often induces the dysregulation of immune responses, tissue damage, and blood clotting. Engineered biomaterials from the nano to macro scale can provide targeted drug delivery, controlled drug release, local immunomodulation, enhanced immunity, and other desirable functions to coordinate appropriate immune responses and repair tissues. Based on the understanding of COVID-19 disease progression and immune responses to SARS-CoV-2, possible immuno-therapeutic strategies were discussed and highlight biomaterial approaches from the perspectives of preventive immunization, therapeutic immunomodulation, and tissue healing and regeneration. Successful development of biomaterial platforms for immunization and immunomodulation will not only benefit COVID-19 patients, but also have broad applications for a variety of infectious diseases.

Reference

https://www.cell.com/matter/fulltext/S2590-2385(21)00107-7

SARS-CoV-2, SARS-CoV-1, and HIV-1 derived ssRNA sequences activate the NLRP3 inflammasome in human macrophages through a non-classical pathway

Abstract

Macrophages promote an early host response to infection by releasing pro-inflammatory cytokines such as interleukin-1β (IL-1β), TNF, and IL-6. The bioactivity of interleukin-1β is classically dependent upon NLRP3 inflammasome activation which culminates in

caspase-1 activation and pyroptosis. Recent studies suggest a role for NLRP3 inflammasome activation in lung inflammation and fibrosis in both COVID-19 and SARS, and there is evidence of NLRP3 involvement in HIV-1 disease. Here, GU-rich single-stranded RNA (GU-rich RNA) derived from SARS-CoV-2 were shown, SARS-CoV-1 and HIV-1 trigger a TLR8-dependent pro-inflammatory cytokine response from human macrophages in the absence of pyroptosis, with GU-rich RNA from the SARS-CoV-2 spike protein triggering the greatest inflammatory response. Using genetic and pharmacological inhibition, we show that the induction of mature IL-1β is through a non-classical pathway dependent upon caspase-1, caspase-8, the NLRP3 inflammasome, potassium efflux, and autophagy while being independent of TRIF (TICAM1), vitamin D3, and pyroptosis.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00263-7

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: Interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial

Abstract

Background: BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine (3 μg or 6 μg) formulated with a toll-like receptor 7/8 agonist molecule (IMDG) adsorbed to alum (Algel). We previously reported findings from a double-blind, multicentre, randomised, controlled phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 (3 μg with Algel-IMDG, 6 μg with Algel-IMDG, or 6 μg with Algel) and one Algel-only control (no antigen), with the first dose administered on day 0 and the second dose on day 14. The 3 μg and 6 μg with Algel-IMDG formulations were selected for this phase 2 study. Herein, we report interim findings of the phase 2 trial on the immunogenicity and safety of BBV152, with the first dose administered on day 0 and the second dose on day 28.

Methods: A double-blind, randomised, multicentre, phase 2 clinical trial was done to evaluate the immunogenicity and safety of BBV152 in healthy adults and adolescents (aged 12–65 years) at nine hospitals in India. Participants with positive SARS-CoV-2 nucleic acid and serology tests were excluded. Participants were randomly assigned

(1:1) to receive either 3 µg with Algel-IMDG or 6 µg with Algel-IMDG. Block randomisation was done by use of an interactive web response system. Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to treatment group allocation. Two intramuscular doses of vaccine were administered on day 0 and day 28. The primary outcome was SARS-CoV-2 wild-type neutralising antibody titres and seroconversion rates (defined as a post-vaccination titre that was at least four-fold higher than the baseline titre) at 4 weeks after the second dose (day 56), measured by use of the plaque-reduction neutralisation test (PRNT50) and the microneutralisation test (MNT50). The primary outcome was assessed in all participants who had received both doses of the vaccine. Cell-mediated responses were a secondary outcome and were assessed by T-helper-1 (Th1)/Th2 profiling at 2 weeks after the second dose (day 42). Safety was assessed in all participants who received at least one dose of the vaccine. In addition, we report immunogenicity results from a follow-up blood draw collected from phase 1 trial participants at 3 months after they received the second dose (day 104). This trial is registered at ClinicalTrials.gov, NCT04471519.

Findings: Between Sept 5 and 12, 2020, 921 participants were screened, of whom 380 were enrolled and randomly assigned to the 3 µg with Algel-IMDG group (n=190) or 6 µg with Algel-IMDG group (n=190). Geometric mean titres (GMTs; PRNT50) at day 56 were significantly higher in the 6 µg with Algel-IMDG group (197·0 [95% CI 155·6–249·4]) than the 3 µg with Algel-IMDG group (100·9 [74·1–137·4]; p=0·0041). Seroconversion based on PRNT50 at day 56 was reported in 171 (92·9% [95% CI 88·2–96·2] of 184 participants in the 3 µg with Algel-IMDG group and 174 (98·3% [95·1–99·6]) of 177 participants in the 6 µg with Algel-IMDG group. GMTs (MNT50) at day 56 were 92·5 (95% CI 77·7–110·2) in the 3 µg with Algel-IMDG group and 160·1 (135·8–188·8) in the 6 µg with Algel-IMDG group. Seroconversion based on MNT50 at day 56 was reported in 162 (88·0% [95% CI 82·4–92·3]) of 184 participants in the 3 µg with Algel-IMDG group and 171 (96·6% [92·8–98·8]) of 177 participants in the 6 µg with Algel-IMDG group. The 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations elicited T-cell responses that were biased to a Th1 phenotype at day 42. No significant difference in the proportion of participants who had a solicited local or systemic adverse reaction in the 3 µg with Algel-IMDG group (38 [20·0%; 95% CI 14·7–26·5] of 190) and the 6 µg with Algel-IMDG group (40 [21·1%; 15·5–27·5] of 190) was observed on days

0–7 and days 28–35; no serious adverse events were reported in the study. From the phase 1 trial, 3-month post-second-dose GMTs (MNT50) were 39·9 (95% CI 32·0–49·9) in the 3μg with Algel-IMDG group, 69·5 (53·7–89·9) in the 6 μg with Algel-IMDG group, 53·3 (40·1–71·0) in the 6 μg with Algel group, and 20·7 (14·5–29·5) in the Algel alone group.

Interpretation: In the phase 1 trial, BBV152 induced high neutralising antibody responses that remained elevated in all participants at 3 months after the second vaccination. In the phase 2 trial, BBV152 showed better reactogenicity and safety outcomes, and enhanced humoral and cell-mediated immune responses compared with the phase 1 trial. The 6 μg with Algel-IMDG formulation has been selected for the phase 3 efficacy trial.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00070-0/fulltext

Publication Date: Mar 06, 2021

Dynamic blood single-cell immune responses in patients with COVID-19

Abstract

The 2019 coronavirus disease (COVID-19) outbreak caused by the SARS-CoV-2 virus is an ongoing global health emergency. However, the virus' pathogenesis remains unclear, and there is no cure for the disease. We investigated the dynamic changes of blood immune response in patients with COVID-19 at different stages by using 5' gene expression, T cell receptor (TCR), and B cell receptors (BCR) V(D)J transcriptome analysis at a single-cell resolution. We obtained single-cell mRNA sequencing (scRNA-seq) data of 341,420 peripheral blood mononuclear cells (PBMCs) and 185,430 clonotypic T cells and 28,802 clonotypic B cells from 25 samples of 16 patients with COVID-19 for dynamic studies. In addition, we used three control samples. We found expansion of dendritic cells (DCs), CD14+ monocytes, and megakaryocytes progenitor cells (MP)/platelets and a reduction of naïve CD4+ T lymphocytes in patients with COVID-19, along with a significant decrease of CD8+ T lymphocytes, and natural killer cells (NKs) in patients in critical condition. The type I interferon (IFN-I), mitogen-activated protein kinase (MAPK), and ferroptosis pathways were activated while the

disease was active, and recovered gradually after patient conditions improved. Consistent with this finding, the mRNA level of IFN-I signal-induced gene IFI27 was significantly increased in patients with COVID-19 compared with that of the controls in a validation cohort that included 38 patients and 35 controls. The concentration of interferon-α (IFN-α) in the serum of patients with COVID-19 increased significantly compared with that of the controls in an additional cohort of 215 patients with COVID-19 and 106 controls, further suggesting the important role of the IFN-I pathway in the immune response of COVID-19. TCR and BCR sequences analyses indicated that patients with COVID-19 developed specific immune responses against SARS-CoV-2 antigens. Our study reveals a dynamic landscape of human blood immune responses to SARS-CoV-2 infection, providing clues for therapeutic potentials in treating COVID-19.

Reference

https://www.nature.com/articles/s41392-021-00526-2

Publication Date: Mar 05, 2021

Serological evidence of human infection with SARS-CoV-2: A systematic review and meta-analysis

Abstract

Background: A rapidly increasing number of serological surveys for antibodies to SARS-CoV-2 have been reported worldwide. It was aimed to synthesize, combine, and assess this large corpus of data.

Methods: In this systematic review and meta-analysis, we searched PubMed, Embase, Web of Science, and five preprint servers for articles published in English between Dec 1, 2019, and Dec 22, 2020. Studies evaluating SARS-CoV-2 seroprevalence in humans after the first identified case in the area were included. Studies that only reported serological responses among patients with COVID-19, those using known infection status samples, or any animal experiments were all excluded. All data used for analysis were extracted from included papers. Study quality was assessed using a standardised scale. We estimated age-specific, sex-specific, and race-specific seroprevalence by WHO regions and subpopulations with different levels of exposures, and the ratio of

serology-identified infections to virologically confirmed cases. This study is registered with PROSPERO, CRD42020198253.

Findings: 16 506 studies were identified in the initial search, 2523 were assessed for eligibility after removal of duplicates and inappropriate titles and abstracts, and 404 serological studies (representing tests in 5 168 360 individuals) were included in the meta-analysis. In the 82 studies of higher quality, close contacts (18·0%, 95% CI 15·7–20·3) and high-risk health-care workers (17·1%, 9·9–24·4) had higher seroprevalence than did low-risk health-care workers (4·2%, 1·5–6·9) and the general population (8·0%, 6·8–9·2). The heterogeneity between included studies was high, with an overall I2 of 99·9% (p<0·0001). Seroprevalence varied greatly across WHO regions, with the lowest seroprevalence of general populations in the Western Pacific region (1·7%, 95% CI 0·0–5·0). The pooled infection-to-case ratio was similar between the region of the Americas (6·9, 95% CI 2·7–17·3) and the European region (8·4, 6·5–10·7), but higher in India (56·5, 28·5–112·0), the only country in the South-East Asia region with data.

Interpretation: Antibody-mediated herd immunity is far from being reached in most settings. Estimates of the ratio of serologically detected infections per virologically confirmed cases across WHO regions can help provide insights into the true proportion of the population infected from routine confirmation data.

Reference

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00026-7/fulltext

Publication Date: Mar 05, 2021

MR-proADM as prognostic factor of outcome in COVID-19 patients

Abstract

Mid Regional pro-ADM (MR-proADM) is a promising novel biomarker in the evaluation of deteriorating patients and an emergent prognosis factor in patients with sepsis, septic shock and organ failure. It can be induced by bacteria, fungi or viruses. We hypothesized that the assessment of MR-proADM, with or without other inflammatory cytokines, as part of a clinical assessment of COVID-19 patients at hospital admission, may assist in identifying those likely to develop severe disease. A pragmatic retrospective analysis was performed on a complete data set from 111 patients

admitted to Udine University Hospital, in northern Italy, from 25th March to 15th May 2020, affected by SARS-CoV-2 pneumonia. Clinical scoring systems (SOFA score, WHO disease severity class, SIMEU clinical phenotype), cytokines (IL-6, IL-1b, IL-8, TNF-α), and MR-proADM were measured. Demographic, clinical and outcome data were collected for analysis. At multivariate analysis, high MR-proADM levels were significantly associated with negative outcome (death or orotracheal intubation, IOT), with an odds ratio of 4.284 [1.893–11.413], together with increased neutrophil count (OR = 1.029 [1.011–1.049]) and WHO disease severity class (OR = 7.632 [5.871–19.496]). AUROC analysis showed a good discriminative performance of MR-proADM (AUROC: 0.849 [95% Cl 0.771–0.730]; $p < 0.0001$). The optimal value of MR-proADM to discriminate combined event of death or IOT is 0.895 nmol/l, with a sensitivity of 0.857 [95% Cl 0.728–0.987] and a specificity of 0.687 [95% Cl 0.587–0.787]. This study shows an association between MR-proADM levels and the severity of COVID-19. The assessment of MR-proADM combined with clinical scoring systems could be of great value in triaging, evaluating possible escalation of therapies, and admission avoidance or inclusion into trials. Larger prospective and controlled studies are needed to confirm these findings.

Reference

https://www.nature.com/articles/s41598-021-84478-1

Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection

Abstract

The immune response to SARS-CoV-2 is critical in controlling disease, but there is concern that waning immunity may predispose to reinfection. We analyzed the magnitude and phenotype of the SARS-CoV-2-specific T cell response in 100 donors at 6 months following infection. T cell responses were present by ELISPOT and/or intracellular cytokine staining analysis in all donors and characterized by predominant CD4+ T cell responses with strong interleukin (IL)-2 cytokine expression. Median T cell responses were 50% higher in donors who had experienced a symptomatic infection, indicating that the severity of primary infection establishes a ‘set point’ for cellular immunity. T cell responses to spike and nucleoprotein/membrane proteins were

correlated with peak antibody levels. Furthermore, higher levels of nucleoprotein-specific T cells were associated with preservation of nucleoprotein-specific antibody level although no such correlation was observed in relation to spike-specific responses. In conclusion, our data are reassuring that functional SARS-CoV-2-specific T cell responses are retained at 6 months following infection.

Reference

https://www.nature.com/articles/s41590-021-00902-8

Point-of-care bulk testing for SARS-CoV-2 by combining hybridization capture with improved colorimetric LAMP

Abstract

Efforts to contain the spread of SARS-CoV-2 have spurred the need for reliable, rapid, and cost-effective diagnostic methods which can be applied to large numbers of people. However, current standard protocols for the detection of viral nucleic acids while sensitive, require a high level of automation and sophisticated laboratory equipment to achieve throughputs that allow whole communities to be tested on a regular basis. Here we present Cap-iLAMP (capture and improved loop-mediated isothermal amplification) which combines a hybridization capture-based RNA extraction of gargle lavage samples with an improved colorimetric RT-LAMP assay and smartphone-based color scoring. Cap-iLAMP is compatible with point-of-care testing and enables the detection of SARS-CoV-2 positive samples in less than one hour. In contrast to direct addition of the sample to improved LAMP (iLAMP), Cap-iLAMP prevents false positives and allows single positive samples to be detected in pools of 25 negative samples, reducing the reagent cost per test to ~1 Euro per individual.

Reference

https://www.nature.com/articles/s41467-021-21627-0

Impact of evolving practices on SARS-CoV-2 positive mothers and their newborns in the largest public healthcare system in America

Abstract

Objective: The impact of evolving guidelines and clinical practices on SARS-CoV-2-positive dyads across New York City Health and Hospitals during the early peak of COVID-19.

Design: A retrospective cohort study of positive-positive (P/P), positive-negative (P/N), and positive-untested (P/U) dyads delivered from March 1 to May 9, 2020. Wilcoxon rank sum, Chi-squared, and Fisher exact tests were used to analyze demographics, clinical variables, and system-wide management practices.

Result: A total of 2598 mothers delivered. 23.8% (286/1198) of mothers tested for SARS-CoV-2 were positive. 89.7% (260/290) newborns of SARS-CoV-2-positive mothers were tested and 11 were positive. Positive-positive newborns were more likely to be breastfed (81%), be admitted to NICU, and have longer length of stay (7.5 days) than P/N and P/U newborns.

Conclusion: Our study shows that varied testing, feeding, and isolation practices resulted in favorable short-term outcomes for SARS-CoV-2-positive mothers and their newborns. High-risk populations can be safely and effectively treated in resource-limited environments.

Reference

https://www.nature.com/articles/s41372-021-01023-8

Structural basis for inhibition of the SARS-CoV-2 RNA polymerase by suramin

Abstract

The COVID-19 pandemic caused by nonstop infections of SARS-CoV-2 has continued to ravage many countries worldwide. Here we report that suramin, a 100-year-old drug, is a potent inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) and acts by blocking the binding of RNA to the enzyme. In biochemical assays, suramin and its derivatives are at least 20-fold more potent than remdesivir, the currently approved nucleotide drug for treatment of COVID-19. The 2.6 Å cryo-electron microscopy

structure of the viral RdRp bound to suramin reveals two binding sites. One site directly blocks the binding of the RNA template strand and the other site clashes with the RNA primer strand near the RdRp catalytic site, thus inhibiting RdRp activity. Suramin blocks viral replication in Vero E6 cells, although the reasons underlying this effect are likely various. Our results provide a structural mechanism for a nonnucleotide inhibitor of the SARS-CoV-2 RdRp.

Reference

https://www.nature.com/articles/s41594-021-00570-0

IFN signaling and neutrophil degranulation transcriptional signatures are induced during SARS-CoV-2 infection

Abstract

SARS-CoV-2 virus has infected more than 92 million people worldwide resulting in the Coronavirus disease 2019 (COVID-19). Using a rhesus macaque model of SARS-CoV-2 infection, we have characterized the transcriptional signatures induced in the lungs of juvenile and old macaques following infection. Genes associated with Interferon (IFN) signaling, neutrophil degranulation and innate immune pathways are significantly induced in macaque infected lungs, while pathways associated with collagen formation are downregulated, as also seen in lungs of macaques with tuberculosis. In COVID-19, increasing age is a significant risk factor for poor prognosis and increased mortality. Type I IFN and Notch signaling pathways are significantly upregulated in lungs of juvenile infected macaques when compared with old infected macaques. These results are corroborated with increased peripheral neutrophil counts and neutrophil lymphocyte ratio in older individuals with COVID-19 disease. Together, our transcriptomic studies have delineated disease pathways that improve our understanding of the immunopathogenesis of COVID-19.

Reference

https://www.nature.com/articles/s42003-021-01829-4

A novel methodology for epidemic risk assessment of COVID-19 outbreak

Abstract

A novel data-driven framework was proposed for assessing the a-priori epidemic risk of a geographical area and for identifying high-risk areas within a country. The risk index is evaluated as a function of three different components: the hazard of the disease, the exposure of the area and the vulnerability of its inhabitants. As an application, the case of COVID-19 outbreak in Italy was discussed. Each of the twenty Italian regions were characterized by using available historical data on air pollution, human mobility, winter temperature, housing concentration, health care density, population size and age. It was found that the epidemic risk is higher in some of the Northern regions with respect to Central and Southern Italy. The corresponding risk index shows correlations with the available official data on the number of infected individuals, patients in intensive care and deceased patients, and can help explaining why regions such as Lombardia, Emilia-Romagna, Piemonte and Veneto have suffered much more than the rest of the country. Although the COVID-19 outbreak started in both North (Lombardia) and Central Italy (Lazio) almost at the same time, when the first cases were officially certified at the beginning of 2020, the disease has spread faster and with heavier consequences in regions with higher epidemic risk. The framework can be extended and tested on other epidemic data, such as those on seasonal flu, and applied to other countries. A policy model connected with our methodology was presented, which might help policy-makers to take informed decisions.

Reference

https://www.nature.com/articles/s41598-021-82310-4

Changes to the sebum lipidome upon COVID-19 infection observed *via* rapid sampling from the skin

Abstract

Background: The COVID-19 pandemic has led to an unprecedented demand for testing - for diagnosis and prognosis - as well as for investigation into the impact of the disease on the host metabolism. Sebum sampling has the potential to support both needs by looking at what the virus does to us, rather than looking for the virus itself.

Methods: In this pilot study, sebum samples were collected from 67 hospitalised patients (30 COVID-19 positive and 37 COVID-19 negative) by gauze swab. Lipidomics analysis was carried out using liquid chromatography mass spectrometry, identifying 998 reproducible features. Univariate and multivariate statistical analyses were applied to the resulting feature set.

Findings: Lipid levels were depressed in COVID-19 positive participants, indicative of dyslipidemia; p-values of 0·022 and 0·015 were obtained for triglycerides and ceramides respectively, with effect sizes of 0·44 and 0·57. Partial Least Squares-Discriminant Analysis showed separation of COVID-19 positive and negative participants with sensitivity of 57% and specificity of 68%, improving to 79% and 83% respectively when controlled for confounding comorbidities.

Interpretation: COVID-19 dysregulates many areas of metabolism; in this work we show that the skin lipidome can be added to the list. Given that samples can be provided quickly and painlessly, we conclude that sebum is worthy of future consideration for clinical sampling.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00066-3/fulltext

Publication Date: Mar 04, 2021

Polyunsaturated ω-3 fatty acids inhibit ACE2-controlled SARS-CoV-2 binding and cellular entry

Abstract

The strain SARS-CoV-2, newly emerged in late 2019, has been identified as the cause of COVID-19 and the pandemic declared by WHO in early 2020. Although lipids have been shown to possess antiviral efficacy, little is currently known about lipid compounds with anti-SARS-CoV-2 binding and entry properties. To address this issue, overall, 17 polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids, as wells as lipid-soluble vitamins were screened. In performing target-based ligand screening utilizing the RBD-SARS-CoV-2 sequence, we observed that polyunsaturated fatty acids most effectively interfere with binding to hACE2, the receptor for SARS-CoV-2. Using a spike protein pseudo-virus, we also found that linolenic acid and

eicosapentaenoic acid significantly block the entry of SARS-CoV-2. In addition, eicosapentaenoic acid showed higher efficacy than linolenic acid in reducing activity of TMPRSS2 and cathepsin L proteases, but neither of the fatty acids affected their expression at the protein level. Also, neither reduction of hACE2 activity nor binding to the hACE2 receptor upon treatment with these two fatty acids was observed. Although further in vivo experiments are warranted to validate the current findings, our study provides a new insight into the role of lipids as antiviral compounds against the SARS-CoV-2 strain.

Reference

https://www.nature.com/articles/s41598-021-84850-1

Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the global COVID-19 pandemic. Rapidly spreading SARS-CoV-2 variants may jeopardize newly introduced antibody and vaccine countermeasures. Here, using monoclonal antibodies (mAbs), animal immune sera, human convalescent sera and human sera from recipients of the BNT162b2 mRNA vaccine, the impact on antibody neutralization of a panel of authentic SARS-CoV-2 variants were reported including a B.1.1.7 isolate, chimeric strains with South African or Brazilian spike genes and isogenic recombinant viral variants. Many highly neutralizing mAbs engaging the receptor-binding domain or N-terminal domain and most convalescent sera and mRNA vaccine-induced immune sera showed reduced inhibitory activity against viruses containing an E484K spike mutation. As antibodies binding to spike receptor-binding domain and N-terminal domain demonstrate diminished neutralization potency in vitro against some emerging variants, updated mAb cocktails targeting highly conserved regions, enhancement of mAb potency or adjustments to the spike sequences of vaccines may be needed to prevent loss of protection *in vivo*.

Reference

https://www.nature.com/articles/s41591-021-01294-w

Potential neutralizing antibodies discovered for novel corona virus using machine learning

Abstract

The fast and untraceable virus mutations take lives of thousands of people before the immune system can produce the inhibitory antibody. The recent outbreak of COVID-19 infected and killed thousands of people in the world. Rapid methods in finding peptides or antibody sequences that can inhibit the viral epitopes of SARS-CoV-2 will save the life of thousands. To predict neutralizing antibodies for SARS-CoV-2 in a high-throughput manner, in this paper, we use different machine learning (ML) model to predict the possible inhibitory synthetic antibodies for SARS-CoV-2. We collected 1933 virus-antibody sequences and their clinical patient neutralization response and trained an ML model to predict the antibody response. Using graph featurization with variety of ML methods, like XGBoost, Random Forest, Multilayered Perceptron, Support Vector Machine and Logistic Regression, we screened thousands of hypothetical antibody sequences and found nine stable antibodies that potentially inhibit SARS-CoV-2. We combined bioinformatics, structural biology, and Molecular Dynamics (MD) simulations to verify the stability of the candidate antibodies that can inhibit SARS-CoV-2.

Reference

https://www.nature.com/articles/s41598-021-84356-w

A novel highly quantitative and reproducible assay for the detection of anti-SARS-CoV-2 IgG and IgM antibodies

Abstract

The quantitative range and reproducibility of current serological tests for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are not optimized. Herein, we developed a diagnostic test that detects SARS-CoV-2 IgG and IgM with high quantitativeness and reproducibility and low interference. The system was based on the high-sensitivity chemiluminescence enzyme immunoassay (HISCL) platform and detects IgG and IgM specific to SARS-CoV-2 spike and nucleocapsid proteins. Quantification accuracy and reproducibility were evaluated using serially diluted samples from 60 SARS-CoV-2-infected patients. Assay performance was evaluated

using serum samples from the SARS-CoV-2-infected patients and 500 SARS-CoV-2-negative serum samples collected before the emergence of SARS-CoV-2. The system showed high quantification accuracy (range, 102), high reproducibility (within 5%), and no cross-reaction between SARS1- and MERS-S proteins. Detection accuracy was 98.3% and 93.3% for IgG and IgM against spike proteins and 100% and 71.7% for IgG and IgM against nucleocapsid proteins, respectively. Mean antibody levels were > 10 times that in negative samples upon admission and > 100 times that at convalescent periods. Clinical severity upon admission was not correlated with IgG or IgM levels. This highly quantitative, reproducible assay system with high clinical performance may help analyze temporal serological/immunological profiles of SARS-CoV-2 infection and SARS-CoV-2 vaccine effectiveness.

Reference

https://www.nature.com/articles/s41598-021-84387-3

Quantitative and semi-quantitative CT assessments of lung lesion burden in COVID-19 pneumonia

Abstract

This study aimed to clarify and provide clinical evidence for which computed tomography (CT) assessment method can more appropriately reflect lung lesion burden of the COVID-19 pneumonia. A total of 244 COVID-19 patients were recruited from three local hospitals. All the patients were assigned to mild, common and severe types. Semi-quantitative assessment methods, e.g., lobar-, segmental-based CT scores and opacity-weighted score, and quantitative assessment method, i.e., lesion volume quantification, were applied to quantify the lung lesions. All four assessment methods had high inter-rater agreements. At the group level, the lesion load in severe type patients was consistently observed to be significantly higher than that in common type in the applications of four assessment methods (all the $p < 0.001$). In discriminating severe from common patients at the individual level, results for lobe-based, segment-based and opacity-weighted assessments had high true positives while the quantitative lesion volume had high true negatives. In conclusion, both semi-quantitative and quantitative methods have excellent repeatability in measuring inflammatory lesions, and can well distinguish between common type and severe type patients. Lobe-based

CT score is fast, readily clinically available, and has a high sensitivity in identifying severe type patients. It is suggested to be a prioritized method for assessing the burden of lung lesions in COVID-19 patients.

Reference

https://www.nature.com/articles/s41598-021-84561-7

Interferon antagonism by SARS-CoV-2: A functional study using reverse genetics

Abstract

Background: The COVID-19 agent, SARS-CoV-2, is conspecific with SARS-CoV, the causal agent of the severe acute respiratory syndrome epidemic in 2002–03. Although the viruses share a completely homologous repertoire of proteins and use the same cellular entry receptor, their transmission efficiencies and pathogenetic traits differ. We aimed to compare interferon antagonism by SARS-CoV and SARS-CoV-2.

Methods: For this functional study, we infected Vero E6 and Calu-3 cells with strains of SARS-CoV and SARS-CoV-2. Differences in cell line-specific replication (Vero E6 vs Calu-3 cells) were studied and analysed these differences in relation to TMPRSS2-dependent cell entry based on inhibition with the drug camostat mesilate. Viral sensitivity was evaluated towards type I interferon treatment and assessed cytokine induction and type I interferon signalling in the host cells by RT-PCR and analysis of transcription factor activation and nuclear translocation. Based on reverse genetic engineering of SARS-CoV, the contribution of open reading frame 6 (ORF6) was investigated to the observed phenotypic differences in interferon signalling, because ORF6 encodes an interferon signalling antagonist. A luciferase-based interferon-stimulated response element promotor activation assay was done to evaluate the antagonistic capacity of SARS-CoV-2 wild-type ORF6 constructs and three mutants (Gln51Glu, Gln56Glu, or both) that represent amino acid substitutions between SARS-CoV and SARS-CoV-2 protein 6 in the carboxy-terminal domain.

Findings: Overall, replication was higher for SARS-CoV in Vero E6 cells and for SARS-CoV-2 in Calu-3 cells. SARS-CoV-2 was reliant on TMPRSS2, found only in Calu-3 cells, for more efficient entry. SARS-CoV-2 was more sensitive to interferon treatment, less efficient in suppressing cytokine induction via IRF3 nuclear translocation, and

permissive of a higher level of induction of interferon-stimulated genes MX1 and ISG56. SARS-CoV-2 ORF6 expressed in the context of a fully replicating SARS-CoV backbone suppressed MX1 gene induction, but this suppression was less efficient than that by SARS-CoV ORF6. Mutagenesis showed that charged amino acids in residues 51 and 56 shift the phenotype towards more efficient interferon antagonism, as seen in SARS-CoV.

Interpretation: SARS-CoV-2 ORF6 interferes less efficiently with human interferon induction and interferon signalling than SARS-CoV ORF6. Because of the homology of the genes, onward selection for fitness could involve functional optimisation of interferon antagonism. Charged amino acids at positions 51 and 56 in ORF6 should be monitored for potential adaptive changes.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00027-6/fulltext

Sarilumab in patients admitted to hospital with severe or critical COVID-19: A randomised, double-blind, placebo-controlled, phase 3 trial

Abstract

Background: Elevated proinflammatory cytokines are associated with greater COVID-19 severity. We aimed to assess safety and efficacy of sarilumab, an interleukin-6 receptor inhibitor, in patients with severe (requiring supplemental oxygen by nasal cannula or face mask) or critical (requiring greater supplemental oxygen, mechanical ventilation, or extracorporeal support) COVID-19.

Methods: A 60-day, randomised, double-blind, placebo-controlled, multinational phase 3 trial was done at 45 hospitals in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain. We included adults (≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and pneumonia, who required oxygen supplementation or intensive care. Patients were randomly assigned (2:2:1 with permuted blocks of five) to receive intravenous sarilumab 400 mg, sarilumab 200 mg, or placebo. Patients, care providers, outcome assessors, and investigators remained masked to assigned intervention throughout the course of the study. The primary endpoint was time to clinical improvement of two or more points (seven point scale

ranging from 1 [death] to 7 [discharged from hospital]) in the modified intention-to-treat population. The key secondary endpoint was proportion of patients alive at day 29. Safety outcomes included adverse events and laboratory assessments. This study is registered with ClinicalTrials.gov, NCT04327388; EudraCT, 2020-001162-12; and WHO, U1111-1249-6021.

Findings: Between March 28 and July 3, 2020, of 431 patients who were screened, 420 patients were randomly assigned and 416 received placebo (n=84 [20%]), sarilumab 200 mg (n=159 [38%]), or sarilumab 400 mg (n=173 [42%]). At day 29, no significant differences were seen in median time to an improvement of two or more points between placebo (12·0 days [95% CI 9·0 to 15·0]) and sarilumab 200 mg (10·0 days [9·0 to 12·0]; hazard ratio [HR] 1·03 [95% CI 0·75 to 1·40]; log-rank p=0·96) or sarilumab 400 mg (10·0 days [9·0 to 13·0]; HR 1·14 [95% CI 0·84 to 1·54]; log-rank p=0·34), or in proportions of patients alive (77 [92%] of 84 patients in the placebo group; 143 [90%] of 159 patients in the sarilumab 200 mg group; difference −1·7 [−9·3 to 5·8]; p=0·63 vs placebo; and 159 [92%] of 173 patients in the sarilumab 400 mg group; difference 0·2 [−6·9 to 7·4]; p=0·85 vs placebo). At day 29, there were numerical, non-significant survival differences between sarilumab 400 mg (88%) and placebo (79%; difference +8·9% [95% CI −7·7 to 25·5]; p=0·25) for patients who had critical disease. No unexpected safety signals were seen. The rates of treatment-emergent adverse events were 65% (55 of 84) in the placebo group, 65% (103 of 159) in the sarilumab 200 mg group, and 70% (121 of 173) in the sarilumab 400 mg group, and of those leading to death 11% (nine of 84) were in the placebo group, 11% (17 of 159) were in the sarilumab 200 mg group, and 10% (18 of 173) were in the sarilumab 400 mg group.

Interpretation: This trial did not show efficacy of sarilumab in patients admitted to hospital with COVID-19 and receiving supplemental oxygen. Adequately powered trials of targeted immunomodulatory therapies assessing survival as a primary endpoint are suggested in patients with critical COVID-19.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00099-0/fulltext

Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: A national, multicentre prospective cohort study using the ISARIC WHO Clinical Characterisation Protocol UK

Abstract

Background: Studies of patients admitted to hospital with COVID-19 have found varying mortality outcomes associated with underlying respiratory conditions and inhaled corticosteroid use. Using data from a national, multicentre, prospective cohort, we aimed to characterise people with COVID-19 admitted to hospital with underlying respiratory disease, assess the level of care received, measure in-hospital mortality, and examine the effect of inhaled corticosteroid use.

Methods: Data from the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) study was analyzed. All patients admitted to hospital with COVID-19 across England, Scotland, and Wales between Jan 17 and Aug 3, 2020, were eligible for inclusion in this analysis. Patients with asthma, chronic pulmonary disease, or both, were identified and stratified by age (<16 years, 16–49 years, and ≥50 years). In-hospital mortality was measured by use of multilevel Cox proportional hazards, adjusting for demographics, comorbidities, and medications (inhaled corticosteroids, short-acting β-agonists [SABAs], and long-acting β-agonists [LABAs]). Patients with asthma who were taking an inhaled corticosteroid plus LABA plus another maintenance asthma medication were considered to have severe asthma.

Findings: 75 463 patients from 258 participating health-care facilities were included in this analysis: 860 patients younger than 16 years (74 [8·6%] with asthma), 8950 patients aged 16–49 years (1867 [20·9%] with asthma), and 65 653 patients aged 50 years and older (5918 [9·0%] with asthma, 10 266 [15·6%] with chronic pulmonary disease, and 2071 [3·2%] with both asthma and chronic pulmonary disease). Patients with asthma were significantly more likely than those without asthma to receive critical care (patients aged 16–49 years: adjusted odds ratio [OR] 1·20 [95% CI 1·05–1·37]; p=0·0080; patients aged ≥50 years: adjusted OR 1·17 [1·08–1·27]; p<0·0001), and patients aged 50 years and older with chronic pulmonary disease (with or without asthma) were significantly less likely than those without a respiratory condition to

receive critical care (adjusted OR 0·66 [0·60–0·72] for those without asthma and 0·74 [0·62–0·87] for those with asthma; p<0·0001 for both). In patients aged 16–49 years, only those with severe asthma had a significant increase in mortality compared to those with no asthma (adjusted hazard ratio [HR] 1·17 [95% CI 0·73–1·86] for those on no asthma therapy, 0·99 [0·61–1·58] for those on SABAs only, 0·94 [0·62–1·43] for those on inhaled corticosteroids only, 1·02 [0·67–1·54] for those on inhaled corticosteroids plus LABAs, and 1·96 [1·25–3·08] for those with severe asthma). Among patients aged 50 years and older, those with chronic pulmonary disease had a significantly increased mortality risk, regardless of inhaled corticosteroid use, compared to patients without an underlying respiratory condition (adjusted HR 1·16 [95% CI 1·12–1·22] for those not on inhaled corticosteroids, and 1·10 [1·04–1·16] for those on inhaled corticosteroids; p<0·0001). Patients aged 50 years and older with severe asthma also had an increased mortality risk compared to those not on asthma therapy (adjusted HR 1·24 [95% CI 1·04–1·49]). In patients aged 50 years and older, inhaled corticosteroid use within 2 weeks of hospital admission was associated with decreased mortality in those with asthma, compared to those without an underlying respiratory condition (adjusted HR 0·86 [95% CI 0·80−0·92]).

Interpretation: Underlying respiratory conditions are common in patients admitted to hospital with COVID-19. Regardless of the severity of symptoms at admission and comorbidities, patients with asthma were more likely, and those with chronic pulmonary disease less likely, to receive critical care than patients without an underlying respiratory condition. In patients aged 16 years and older, severe asthma was associated with increased mortality compared to non-severe asthma. In patients aged 50 years and older, inhaled corticosteroid use in those with asthma was associated with lower mortality than in patients without an underlying respiratory condition; patients with chronic pulmonary disease had significantly increased mortality compared to those with no underlying respiratory condition, regardless of inhaled corticosteroid use. The results suggest that the use of inhaled corticosteroids, within 2 weeks of admission, improves survival for patients aged 50 years and older with asthma, but not for those with chronic pulmonary disease.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00013-8/fulltext

Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): A randomised, controlled, open-label, adaptive platform trial

Abstract

Background: Azithromycin, an antibiotic with potential antiviral and anti-inflammatory properties, has been used to treat COVID-19, but evidence from community randomised trials is lacking. We aimed to assess the effectiveness of azithromycin to treat suspected COVID-19 among people in the community who had an increased risk of complications.

Methods: In this UK-based, primary care, open-label, multi-arm, adaptive platform randomised trial of interventions against COVID-19 in people at increased risk of an adverse clinical course (PRINCIPLE), we randomly assigned people aged 65 years and older, or 50 years and older with at least one comorbidity, who had been unwell for 14 days or less with suspected COVID-19, to usual care plus azithromycin 500 mg daily for three days, usual care plus other interventions, or usual care alone. The trial had two coprimary endpoints measured within 28 days from randomisation: time to first self-reported recovery, analysed using a Bayesian piecewise exponential, and hospital admission or death related to COVID-19, analysed using a Bayesian logistic regression model. Eligible participants with outcome data were included in the primary analysis, and those who received the allocated treatment were included in the safety analysis. The trial is registered with ISRCTN, ISRCTN86534580.

Findings: The first participant was recruited to PRINCIPLE on April 2, 2020. The azithromycin group enrolled participants between May 22 and Nov 30, 2020, by which time 2265 participants had been randomly assigned, 540 to azithromycin plus usual care, 875 to usual care alone, and 850 to other interventions. 2120 (94%) of 2265 participants provided follow-up data and were included in the Bayesian primary analysis, 500 participants in the azithromycin plus usual care group, 823 in the usual care alone group, and 797 in other intervention groups. 402 (80%) of 500 participants in the azithromycin plus usual care group and 631 (77%) of 823 participants in the usual care alone group reported feeling recovered within 28 days. We found little evidence of a meaningful benefit in the azithromycin plus usual care group in time to first reported

recovery versus usual care alone (hazard ratio 1·08, 95% Bayesian credibility interval [BCI] 0·95 to 1·23), equating to an estimated benefit in median time to first recovery of 0·94 days (95% BCI −0·56 to 2·43). The probability that there was a clinically meaningful benefit of at least 1·5 days in time to recovery was 0·23. 16 (3%) of 500 participants in the azithromycin plus usual care group and 28 (3%) of 823 participants in the usual care alone group were hospitalised (absolute benefit in percentage 0·3%, 95% BCI −1·7 to 2·2). There were no deaths in either study group. Safety outcomes were similar in both groups. Two (1%) of 455 participants in the azothromycin plus usual care group and four (1%) of 668 participants in the usual care alone group reported admission to hospital during the trial, not related to COVID-19.

Interpretation: Our findings do not justify the routine use of azithromycin for reducing time to recovery or risk of hospitalisation for people with suspected COVID-19 in the community. These findings have important antibiotic stewardship implications during this pandemic, as inappropriate use of antibiotics leads to increased antimicrobial resistance, and there is evidence that azithromycin use increased during the pandemic in the UK.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00461-X/fulltext

A meta-analysis on the role of pre-existing chronic disease in the cardiac complications of SARS-CoV-2 infection

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with multiple direct and indirect cardiovascular complications. We sought to analyse the association of host co-morbidities (chronic respiratory illnesses, cardiovascular disease (CVD), hypertension or diabetes mellitus (DM)) with the acute cardiovascular complications associated with SARS-CoV-2 infection. Individual analyses of the majority of studies found median age was higher by ~10 years in patients with cardiovascular complications. Pooled analyses showed development of SARS-CoV-2 cardiovascular complications was significantly increased in patients with chronic respiratory illness (odds ratio (OR) 1.67[1.48,1.88]), CVD (OR 3.37[2.57,4.43]), hypertension (OR 2.68[2.11,3.41]), DM (OR 1.60[1.31,1.95]) and male sex (OR 1.31[1.21,1.42]), findings

that were mostly conserved during sub-analysis of studies stratified into global geographic regions. Age, chronic respiratory illness, CVD, hypertension, DM and male sex may represent prognostic factors for the development of cardiovascular complications in COVID-19 disease, highlighting the need for a multidisciplinary approach to chronic disease patient management.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00232-7

PREVIEW

Publication Date: Mar 10, 2021

The great escape? SARS-CoV-2 variants evading neutralizing responses

In the latest issues of *Cell Host & Microbe and Cell*, three articles describe new mutations in the SARS-CoV-2 Spike receptor binding domain that escape neutralizing responses. These highlight the importance of surveillance of SARS-CoV-2 evolution to anticipate and manage new variants that could impact reinfection, vaccine efficacy, and immunotherapies. For more details, read the link given below.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00089-5

COMMENT

Publication Date: Mar 08, 2021

Adjuvantation helps to optimise COVID-19 vaccine candidate

Abstract

BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine, formulated with a toll-like receptor (TLR) 7/8 agonist molecule (IMDG) adsorbed to alum (Algel), and manufactured and produced by Bharat Biotech (India).2 In The Lancet Infectious Diseases, Raches Ella and colleagues3 report on the safety and immunogenicity of BBV152 in a double-blind, randomised, multicentre, phase 2 trial, and describe the persistence of immune responses at 3 months follow-up from the double-blind, randomised, phase 1 trial.2 The results showed that two intramuscular injections of 6 µg BBV152 with Algel-IMDG administered 4 weeks apart induced seroconversion (plaque-reduction neutralisation test [PRNT50]) in 174 (98·3% [95% CI 95·1–99·6]) of 177 participants, and geometric mean titres (GMT; microneutralisation assay [MNT50]) of neutralising antibodies of 160·1 (95% CI 135·8–188·8) on day 56 (4 weeks after the second dose). BBV152 was also found to induce a persistent immune response, with high neutralising antibody titres observed in phase 1 participants at 3 months after the second dose of 6 µg with Algel-IMDG (GMT [MNT50] 69·5 [95% CI 53·7–89·9]). Compared with other Algel-IMDG-containing vaccine formulations, the greatest T-cell memory response at 3 months follow-up was observed in phase 1 participants who received 6 µg with Algel-IMDG. Of particular note, BBV152 at 6 µg with Algel-IMDG was well tolerated, with 40 (21·1% [95% CI 15·5–27·5]) of 190 participants reporting at least one solicited local or systemic adverse reaction. The 6 µg with Algel-IMDG formulation has already received emergency use authorisation in India and is being evaluated in 25 800 volunteers in a phase 3 efficacy trial.

Overall, Algel-IMDG-adjuvanted BBV152 was safe, immunogenic, and able to induce Th1-biased T-cell responses, and could therefore be a potentially superior vaccine over the alum-adjuvanted inactivated COVID-19 vaccines. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00094-3/fulltext

COVID-19 serosurveys for public health decision making

During the first year of the COVID-19 pandemic, more than 90 million cases were reported globally, with nearly 2 million deaths. Case reporting depends on several factors, including testing capacity, type of tests used, testing strategies, and health-seeking behaviour of the population. Most SARS-CoV-2 infections are mild or asymptomatic in nature and are less likely to be detected by the surveillance system. Therefore, population-based serosurveys are considered as a valuable tool in estimating the proportion of the population previously infected with SARS-CoV-2.

A number of serosurveys have been done in different countries at different timepoints in the pandemic, investigating different population groups (*eg*, general population, health-care workers, contacts), and using different types of laboratory assays. Xinhua Chen and colleagues, in The Lancet Global Health, have synthesized data from serological studies published between Dec 1, 2019, and Dec 22, 2020. On the basis of the data from 82 high-quality studies, they estimated an overall seroprevalence of 8·0% (95% CI 6·8–9·2) in the general population, ranging from 1·7% in the Western Pacific region to 19·6% in the South-East Asia region. The seroprevalence was higher among close contacts of COVID-19 cases (18·0%, 95% CI 15·7–20·3) and health-care workers (17·1%, 9·9–24·4%) than in low-risk health-care workers (4·2%, 1·5–6·9) and the general population.

Seroepidemiological studies provide meaningful information to guide the public health response. Unfortunately, most serological studies done globally were of low quality, with nearly two thirds of studies included in the review using convenience sampling. Large-scale population-based serosurveys are resource-intensive, and allocating scarce public health resources could be challenging for many developing nations. Therefore, well designed, population-based studies with probability sampling, use of laboratory assays with high sensitivity and specificity, and appropriate data analysis (including adjustment for assay characteristics as well as for population demographics) are very important. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00057-7/fulltext

REPORT

Publication Date: Mar 06, 2021

The effect of spike mutations on SARS-CoV-2 neutralization

Multiple severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines show protective efficacy, which is most likely mediated by neutralizing antibodies recognizing the viral entry protein, spike. Because new SARS-CoV-2 variants are emerging rapidly, as exemplified by the B.1.1.7, B.1.351, and P.1 lineages, it is critical to understand whether antibody responses induced by infection with the original SARS-CoV-2 virus or current vaccines remain effective. In this study, neutralization of a series of mutated spike pseudotypes based on divergence from SARS-CoV was evaluated and then compare neutralization of the B.1.1.7 spike pseudotype and individual mutations. Spike-specific monoclonal antibody neutralization is reduced dramatically; in contrast, polyclonal antibodies from individuals infected in early 2020 remain active against most mutated spike pseudotypes, but potency is reduced in a minority of samples. This work highlights that changes in SARS-CoV-2 spike can alter neutralization sensitivity and underlines the need for effective real-time monitoring of emerging mutations and their effect on vaccine efficacy.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00204-7

HEALTH POLICY

Publication Date: Mar 09, 2021

Urgent lessons from COVID 19: Why the world needs a standing, coordinated system and sustainable financing for global research and development

The research and development (R&D) ecosystem has evolved over the past decade to include pandemic infectious diseases, building on experience from multiple recent outbreaks. Outcomes of this evolution have been particularly evident during the COVID-19 pandemic with accelerated development of vaccines and monoclonal antibodies, as well as novel clinical trial designs. These products were developed, trialled, manufactured, and authorised for use in several countries within a year of the pandemic's onset. Many gaps remain, however, that must be bridged to establish a truly efficient and effective end-to-end R&D preparedness and response ecosystem. Foremost among them is a global financing system. In addition, important changes are required for multiple aspects of enabling sciences and product development. For each of these elements we identify priorities for improved and faster functionality. There will be no better time than now to seriously address these needs, however difficult, as the ravages of COVID-19 continue to accelerate with devastating health, social, and economic consequences for the entire community of nations.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00503-1/fulltext