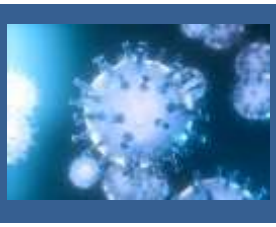
COVID-19

May 13 - 19, 2021



RESEARCH PUBLICATIONS

Publication Date: May 19, 2021

Direct derivation of human alveolospheres for SARS-CoV-2 infection modeling and drug screening

Abstract

Although the main cellular target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is thought to be alveolar cells, the absence of their tractable culture system has precluded the development of a clinically-relevant SARS-CoV-2 infection model. Here, we established an efficient human alveolosphere culture method and sphere-based drug testing platform for SARS-CoV-2. Alveolospheres exhibited indolent growth in a Wnt and R-spondin dependent manner. Gene expression, immunofluorescence and electron microscopy analyses revealed the presence of alveolar cells in alveolospheres. Alveolospheres expressed ACE2 and allowed SARS-CoV-2 to propagate nearly 100,000- fold in three days of infection. While lopinavir and nelfinavir, protease inhibitors used for the treatment of HIV infection, had a modest anti-viral effect on SARS-CoV-2, remdesivir, a nucleotide prodrug, showed anti-viral effect at the concentration comparable to the circulating drug level. These results demonstrated the validity of alveolosphere culture system for the development of therapeutic agents to combat SARS-CoV-2.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00569-6

Remarkable vessel enlargement within lung consolidation in COVID-19 compared to AH1N1 pneumonia: a retrospective study in Italy

Abstract

Purpose: To investigate the early CT findings in COVID-19 pneumonia as compared to influenza A virus H1N1 (AH1N1), with focus on vascular enlargement within consolidation or ground glass opacity (GGO) areas.

Methods: 50 Patients with COVID-19 pneumonia were retrospectively compared to 50 patients with AH1N1 pneumonia diagnosed during the 2009 pandemic. Two radiologists reviewed chest CT scans independently and blindly, with discordance resolved by consensus. Dilated or tortuous vessels within hyperdense lesions were recorded.

Results: COVID-19 pneumonia presented with bilateral (96%), peripheral areas of GGO (22%), consolidation (4%) or combined GGO-consolidation (74%). The vascular enlargement sign in COVID-19 pneumonia was much more commonly present in COVID-19 (45/50, 90%) versus AH1N1 pneumonia (12/50, 24%) ($p<0.001$). Vascular enlargement was more often present in lower lobes with a peripheral distribution.

Conclusions: Vascular enlargement in consolidative / GGO areas may represent a reasonably common early CT marker in COVID-19 patients and is of uncertain etiology. Although speculative, theoretical mechanisms could potentially reflect acute inflammatory changes, pulmonary endothelial activation, or acute stasis. Further studies are necessary to verify specificity and to study if prognostic for clinical outcomes.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)01215-9

SARS-CoV-2 infection induces beta cell transdifferentiation

Abstract

Recent clinical data has suggested a correlation between Coronavirus disease 19 (COVID-19) and diabetes. Here, the detection of SARS-CoV-2 viral antigen was described in pancreatic beta cells in autopsy samples from individuals with COVID-19. Single-cell RNA-sequencing and immunostaining from ex vivo infections confirmed that multiple types of pancreatic islet cells were susceptible to SARS-CoV-2, eliciting a

cellular stress response and the induction of chemokines. Upon SARS-CoV-2 infection, beta cells showed a lower expression of insulin and a higher expression of alpha and acinar cell markers, including glucagon and trypsin1, respectively, suggesting cellular transdifferentiation. Trajectory analysis indicated that SARS-CoV-2 induced eIF2 pathway-mediated beta cell transdifferentiation, a phenotype that could be reversed with trans-integrated stress response inhibitor (trans-ISRIB). Altogether, this study demonstrates an example of SARS-CoV-2 infection causing cell fate change, which provides further insight into the pathomechanisms of COVID-19.

Reference

https://www.cell.com/cell-metabolism/fulltext/S1550-4131(21)00232-1

Diverse functional autoantibodies in patients with COVID-19

Abstract

COVID-19 manifests with a wide spectrum of clinical phenotypes that are characterized by exaggerated and misdirected host immune responses. While pathological innate immune activation is well documented in severe disease, the impact of autoantibodies on disease progression is less defined. Here, a high-throughput autoantibody (AAb) discovery technique called Rapid Extracellular Antigen Profiling (REAP) was used to screen a cohort of 194 SARS-CoV-2 infected COVID-19 patients and healthcare workers for autoantibodies against 2,770 extracellular and secreted proteins (the “exoproteome”). It was found that COVID-19 patients exhibit dramatic increases in autoantibody reactivities compared to uninfected controls, with a high prevalence of autoantibodies against immunomodulatory proteins including cytokines, chemokines, complement components, and cell surface proteins. We established that these autoantibodies perturb immune function and impair virological control by inhibiting immunoreceptor signaling and by altering peripheral immune cell composition, and found that murine surrogates of these autoantibodies exacerbate disease severity in a mouse model of SARS-CoV-2 infection. Analysis of autoantibodies against tissue-associated antigens revealed associations with specific clinical characteristics and disease severity. In summary, these findings implicate a pathological role for exoproteome-directed autoantibodies in COVID-19 with diverse impacts on immune functionality and associations with clinical outcomes.

Reference

https://www.nature.com/articles/s41586-021-03631-y

Multivalent nanoparticle-based vaccines protect hamsters against SARS-CoV-2 after a single immunization

Abstract

The COVID-19 pandemic continues to wreak havoc as worldwide SARS-CoV-2 infection, hospitalization, and death rates climb unabated. Effective vaccines remain the most promising approach to counter SARS-CoV-2. Yet, while promising results are emerging from COVID-19 vaccine trials, the need for multiple doses and the challenges associated with the widespread distribution and administration of vaccines remain concerns. Here, we engineered the coat protein of the MS2 bacteriophage and generated nanoparticles displaying multiple copies of the SARS-CoV-2 spike (S) protein. The use of these nanoparticles as vaccines generated high neutralizing antibody titers and protected Syrian hamsters from a challenge with SARS-CoV-2 after a single immunization with no infectious virus detected in the lungs. This nanoparticle-based vaccine platform thus provides protection after a single immunization and may be broadly applicable for protecting against SARS-CoV-2 and future pathogens with pandemic potential.

Reference

https://www.nature.com/articles/s42003-021-02128-8

A super-potent tetramerized ACE2 protein displays enhanced neutralization of SARS-CoV-2 virus infection

Abstract

Approaches are needed for therapy of the severe acute respiratory syndrome from SARS-CoV-2 coronavirus (COVID-19). Interfering with the interaction of viral antigens with the angiotensin converting enzyme 2 (ACE-2) receptor is a promising strategy by blocking the infection of the coronaviruses into human cells. A novel protein engineering technology was implemented to produce a super-potent tetravalent form of ACE2, coupled to the human immunoglobulin γ1 Fc region, using a self-assembling, tetramerization domain from p53 protein. This high molecular weight Quad protein

(ACE2-Fc-TD) retains binding to the SARS-CoV-2 receptor binding spike protein and can form a complex with the spike protein plus anti-viral antibodies. The ACE2-Fc-TD acts as a powerful decoy protein that out-performs soluble monomeric and dimeric ACE2 proteins and blocks both SARS-CoV-2 pseudovirus and SARS-CoV-2 virus infection with greatly enhanced efficacy. The ACE2 tetrameric protein complex promise to be important for development as decoy therapeutic proteins against COVID-19. In contrast to monoclonal antibodies, ACE2 decoy is unlikely to be affected by mutations in SARS-CoV-2 that are beginning to appear in variant forms. In addition, ACE2 multimeric proteins will be available as therapeutic proteins should new coronaviruses appear in the future because these are likely to interact with ACE2 receptor.

Reference

https://www.nature.com/articles/s41598-021-89957-z

Cross-reactive serum and memory B-cell responses to spike protein in SARS-CoV-2 and endemic coronavirus infection

Abstract

Pre-existing immunity to seasonal endemic coronaviruses could have profound consequences for antibody responses to SARS-CoV-2, induced from natural infection or vaccination. A first step to establish whether pre-existing responses can impact SARS-CoV-2 infection is to understand the nature and extent of cross-reactivity in humans to coronaviruses. Here we compare serum antibody and memory B cell responses to coronavirus spike proteins from pre-pandemic and SARS-CoV-2 convalescent donors using binding and functional assays. We show weak evidence of pre-existing SARS-CoV-2 cross-reactive serum antibodies in pre-pandemic donors. However, we find evidence of pre-existing cross-reactive memory B cells that are activated during SARS-CoV-2 infection. Monoclonal antibodies show varying degrees of cross-reactivity with betacoronaviruses, including SARS-CoV-1 and endemic coronaviruses. We identify one cross-reactive neutralizing antibody specific to the S2 subunit of the S protein. Our results suggest that pre-existing immunity to endemic coronaviruses should be considered in evaluating antibody responses to SARS-CoV-2.

Reference

https://www.nature.com/articles/s41467-021-23074-3

COVID-19 non-pharmaceutical intervention portfolio effectiveness and risk communication predominance

Abstract

Non-pharmaceutical interventions (NPIs) including resource allocation, risk communication, social distancing and travel restriction, are mainstream actions to control the spreading of Coronavirus disease 2019 (COVID-19) worldwide. Different countries implemented their own combinations of NPIs to prevent local epidemics and healthcare system overloaded. Portfolios, as temporal sets of NPIs have various systemic impacts on preventing cases in populations. Here, a probabilistic modeling framework was developed to evaluate the effectiveness of NPI portfolios at the macroscale. A deconvolution method was employed to back-calculate incidence of infections and estimate the effective reproduction number by using the package EpiEstim. It was then evaluated that the effectiveness of NPIs using ratios of the reproduction numbers and considered them individually and as a portfolio systemically. Based on estimates from Japan, we estimated time delays of symptomatic-to-confirmation and infection-to-confirmation as 7.4 and 11.4 days, respectively. These were used to correct surveillance data of other countries. Considering 50 countries, risk communication and returning to normal life were the most and least effective yielding the aggregated effectiveness of 0.11 and − 0.05 that correspond to a 22.4% and 12.2% reduction and increase in case growth. The latter is quantified by the change in reproduction number before and after intervention implementation. Countries with the optimal NPI portfolio are along an empirical Pareto frontier where mean and variance of effectiveness are maximized and minimized independently of incidence levels. Results indicate that implemented interventions, regardless of NPI portfolios, had distinct incidence reductions and a clear timing effect on infection dynamics measured by sequences of reproduction numbers. Overall, the successful suppression of the epidemic cannot work without the non-linear effect of NPI portfolios whose effectiveness optimality may relate to country-specific socio-environmental factors.

Reference

https://www.nature.com/articles/s41598-021-88309-1

Effect of COVID-19 on liver abnormalities: A systematic review and meta-analysis

Abstract

Emerging evidence suggest association of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection with the development of many liver abnormalities. The overarching aim of this study was therefore to assess the available evidence on the clinical effects of SARS-CoV-2 on the profiles of liver chemistries and coagulation in COVID-19 diagnosed patients. All study designs were considered including epidemiological and observational that reported liver function test abnormalities in patients confirmed with SARS-CoV-2 infection. Medline, Embase databases and Google Scholar as well as relevant reviews were searched to identify appropriate studies from inception to 31st of August 2020. The pooled mean was calculated with 95% confidence intervals (95% CI) through a random-effect model meta-analysis. A total of 35 studies with 10,692 participants were considered for the review from which 23 studies with sufficient quantitative data were included in the meta-analysis. The pooled mean for liver enzymes and coagulation parameters did not significantly change in patients diagnosed with COVID-19 and remained within normal range. Notwithstanding potential bias from confounding factors in interpretation of data in this review, findings from the observational studies and case reports suggest that COVID-19 does not appear to have a significant impact on the transaminases or total bilirubin levels of patients with confirmed SARS-CoV-2 infection. Further controlled studies and larger sample size observational studies are needed with adequate reporting of other liver function parameters are warranted.

Reference

https://www.nature.com/articles/s41598-021-89513-9

A novel strategy for SARS-CoV-2 mass screening with quantitative antigen testing of saliva: A diagnostic accuracy study

Abstract

Background: Quantitative RT-PCR (RT-qPCR) of nasopharyngeal swab (NPS) samples for SARS-CoV-2 detection requires medical personnel and is time consuming, and thus is poorly suited to mass screening. In June, 2020, a chemiluminescent enzyme immunoassay (CLEIA; Lumipulse G SARS-CoV-2 Ag kit, Fujirebio, Tokyo, Japan) was developed that can detect SARS-CoV-2 nucleoproteins in NPS or saliva samples within 35 min. In this study, the utility of CLEIA was assessed in mass SARS-CoV-2 screening.

Methods: A diagnostic accuracy study was done to develop a mass-screening strategy for salivary detection of SARS-CoV-2 by CLEIA, enrolling hospitalised patients with clinically confirmed COVID-19, close contacts identified at community health centres, and asymptomatic international arrivals at two airports, all based in Japan. All test participants were enrolled consecutively. The diagnostic accuracy of CLEIA was compared with RT-qPCR, estimated according to concordance (Kendall's coefficient of concordance, W), and sensitivity (probability of CLEIA positivity given RT-qPCR positivity) and specificity (probability of CLEIA negativity given RT-qPCR negativity) for different antigen concentration cutoffs (0·19 pg/mL, 0·67 pg/mL, and 4·00 pg/mL; with samples considered positive if the antigen concentration was equal to or more than the cutoff and negative if it was less than the cutoff). A two-step testing strategy was also assessed, post hoc with CLEIA as an initial test, using separate antigen cutoff values for test negativity and positivity from the predefined cutoff values. The proportion of intermediate results requiring secondary RT-qPCR was then quantified assuming prevalence values of RT-qPCR positivity in the overall tested population of 10%, 30%, and 50%.

Findings: Self-collected saliva was obtained from 2056 participants between June 12 and Aug 6, 2020. Results of CLEIA and RT-qPCR were concordant in 2020 (98·2%) samples (Kendall's W=0·99). Test sensitivity was 85·4% (76 of 89 positive samples; 90% credible interval [CrI] 78·0–90·3) at the cutoff of 0·19 pg/mL; 76·4% (68 of 89; 68·2–82·8) at the cutoff of 0·67 pg/mL; and 52·8% (47 of 89; 44·1–61·3) at the cutoff of

4·0 pg/mL. Test specificity was 91·3% (1796 of 1967 negative samples; 90% CrI 90·2–92·3) at the cutoff of 0·19 pg/mL, 99·2% (1952 of 1967; 98·8–99·5) at the cutoff of 0·67 pg/mL, and 100·0% (1967 of 1967; 99·8–100·0) at the cutoff of 4·00 pg/mL. Using a two-step testing strategy with a CLEIA negativity cutoff of 0·19 pg/mL (to maximise sensitivity) and a CLEIA positivity cutoff of 4·00 pg/mL (to maximise specificity), the proportions of indeterminate results (ie, samples requiring secondary RT-qPCR) would be approximately 11% assuming a prevalence of RT-qPCR positivity of 10%, 16% assuming a prevalence of RT-qPCR positivity of 30%, and 21% assuming a prevalence of RT-qPCR positivity of 50%.

Interpretation: CLEIA testing of self-collected saliva is simple and provides results quickly, and is thus suitable for mass testing. To improve accuracy, we propose a two-step screening strategy with an initial CLEIA test followed by confirmatory RT-qPCR for intermediate concentrations, varying positive and negative thresholds depending on local prevalence. Implementation of this strategy has expedited sample processing at Japanese airports since July, 2020, and might apply to other large-scale mass screening initiatives.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00092-6/fulltext

Seroprevalence of anti-SARS-CoV-2 antibodies in Iquitos, Peru in July and August, 2020: A population-based study

Abstract

Background: Detection of anti-SARS-CoV-2 antibodies among people at risk of infection is crucial for understanding both the past transmission of COVID-19 and vulnerability of the population to continuing transmission and, when done serially, the intensity of ongoing transmission over an interval in a community. It was aimed to estimate the seroprevalence of COVID-19 in a representative population-based cohort in Iquitos, one of the regions with the highest mortality rates from COVID-19 in Peru, where a devastating number of cases occurred in March, 2020.

Methods: A population-based study was done of SARS-CoV-2 transmission in Iquitos at two timepoints: July 13–18, 2020 (baseline), and Aug 13–18, 2020 (1-month follow-up).

A geographically stratified representative sample of the city population was obtained using the 2017 census data, which was updated on Jan 20, 2020. People were included, who were inhabitants of Iquitos since COVID-19 was identified in Peru (March 6, 2020) or earlier. People living in institutions were excluded, people receiving any pharmacological treatment for COVID-19, people with any contraindication for phlebotomy, and health workers or individuals living with an active health worker. We tested each participant for IgG and IgM anti-SARS-CoV-2 antibodies using the COVID-19 IgG/IgM Rapid Test (Zhejiang Orient Gene Biotech, China). Survey analysis methods were used to estimate seroprevalence accounting for the sampling design effect and test performance characteristics.

Findings: 726 Eligible individuals were identified and enrolled a total of 716 participants (99%), distributed across 40 strata (four districts, two sexes, and five age groups). Ten individuals, were excluded who: did not have consent from a parent or legal representative (n=3), had moved to Iquitos after March 6, 2020 (n=3), were in transit (n=2), or had respiratory symptoms (n=1). After adjusting for the study sampling effects and sensitivity and specificity of the test, we estimated a seroprevalence of 70% (95% CI 67–73) at baseline and 66% (95% CI 62–70) at 1 month of follow-up, with a test-retest positivity of 65% (95% CI 61–68), and an incidence of new exposures of 2% (95% CI 1–3). We observed significant differences in the seroprevalence between age groups, with participants aged 18–29 years having lower seroprevalence than those aged younger than 12 years (prevalence ratio 0·85 [95% CI 0·73–0·98]; p=0·029).

Interpretation: After the first epidemic peak, Iquitos had one of the highest rates of seroprevalence of anti-SARS-CoV-2 antibodies worldwide. Nevertheless, the city experienced a second wave starting in January, 2021, probably due to the emergence of the SARS-CoV-2 P1 variant, which has shown higher transmissibility and reinfection rates.

Reference

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00173-X/fulltext

SARS-CoV-2 infects human pancreatic β-cells and elicits β-cell impairment

Abstract

Emerging evidence points towards an intricate relationship between the pandemic of coronavirus disease-2019 (COVID-19) and diabetes. While pre-existing diabetes is associated with severe COVID-19, it is unclear if COVID-19 severity is a cause or consequence of diabetes. To mechanistically link COVID-19 to diabetes, we tested whether insulin-producing pancreatic β-cells can be infected by SARS-CoV-2 and cause β-cell depletion. We found that the SARS-CoV-2 receptor, ACE2 and related entry factors (TMPRSS2, NRP1, TRFC) are expressed in β-cells, with selectively high expression of NRP1. We discovered that SARS-CoV-2 infects human pancreatic β-cells in patients who succumbed to COVID-19 and selectively infects human islet β-cells in vitro. We demonstrated SARS-CoV-2 infection attenuates pancreatic insulin levels and secretion, and induces β-cell apoptosis, each rescued by NRP1 inhibition. Phosphoproteomic pathway analysis of infected islets indicates apoptotic β-cell signaling, similar to that observed in Type 1 diabetes (T1D). In summary, our study shows SARS-CoV-2 can directly induce β-cell killing.

Reference

https://www.cell.com/cell-metabolism/fulltext/S1550-4131(21)00230-8

Type-I interferon signatures in SARS-CoV-2 infected Huh7 cells

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes Coronavirus disease 2019 (COVID-19) has caused a global health emergency. A key feature of COVID-19 is dysregulated interferon-response. Type-I interferon (IFN-I) is one of the earliest antiviral innate immune responses following viral infection and plays a significant role in the pathogenesis of SARS-CoV-2. In this study, using a proteomics-based approach, it was identified that SARS-CoV-2 infection induces delayed and dysregulated IFN-I signaling in Huh7 cells. It was demonstrated that SARS-CoV-2 is able to inhibit RIG-I mediated IFN-β production. The results also confirm the recent findings that IFN-I pretreatment is able to reduce the susceptibility of Huh7 cells to

SARS-CoV-2, but not post-treatment. Moreover, senescent Huh7 cells, in spite of showing accentuated IFN-I response were more susceptible to SARS-CoV-2 infection, and the virus effectively inhibited IFIT1 in these cells. Finally, proteomic comparison between SARS-CoV-2, SARS-CoV, and MERS-CoV revealed a distinct differential regulatory signature of interferon-related proteins emphasizing that therapeutic strategies based on observations in SARS-CoV and MERS-CoV should be used with caution. The findings provide a better understanding of SARS-CoV-2 regulation of cellular interferon response and a perspective on its use as a treatment. Investigation of different interferon-stimulated genes and their role in the inhibition of SARS-CoV-2 pathogenesis may direct novel antiviral strategies.

Reference

https://www.nature.com/articles/s41420-021-00487-z

Diagnostic performance and characteristics of anterior nasal collection for the SARS-CoV-2 antigen test: A prospective study

Abstract

The clinical utility of antigen test using anterior nasal samples has not been well evaluated. A prospective study was conducted in a drive-through testing site located at a PCR center to evaluate the diagnostic performance of the antigen test QuickNavi-COVID19 Ag using anterior nasal samples and to compare the degrees of coughs or sneezes induction and the severity of pain between anterior nasal collection and nasopharyngeal collection. The study included a total of 862 participants, of which 91.6% were symptomatic. The median duration from symptom onset to sample collection was 2.0 days. Fifty-one participants tested positive for severe acute respiratory syndrome coronavirus 2 on reverse transcription PCR (RT-PCR) with nasopharyngeal samples, and all of them were symptomatic. In comparison to the findings of RT-PCR, the antigen test using anterior nasal samples showed 72.5% sensitivity (95% confidence interval [CI] 58.3–84.1%) and 100% specificity (95% CI 99.3–100%). Anterior nasal collection was associated with a significantly lower degree of coughs or sneezes induction and the severity of pain in comparison to nasopharyngeal collection ($p < 0.001$). The antigen test using anterior nasal samples

showed moderate sensitivity in symptomatic patients who were at the early stages of the disease course but was less painful and induced fewer coughs or sneezes.

Reference

https://www.nature.com/articles/s41598-021-90026-8

Implementing a method for engineering multivalency to substantially enhance binding of clinical trial anti-SARS-CoV-2 antibodies to wildtype spike and variants of concern proteins

Abstract

Infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes COVID-19 disease. Therapeutic antibodies are being developed that interact with the viral spike proteins to limit viral infection of epithelium. A method was applied to dramatically improve the performance of anti-SARS-CoV-2 antibodies by enhancing avidity through multimerization using simple engineering to yield tetrameric antibodies. We have re-engineered six anti-SARS-CoV-2 antibodies using the human p53 tetramerization domain, including three clinical trials antibodies casirivimab, imdevimab and etesevimab. The method yields tetrameric antibodies, termed quads, that retain efficient binding to the SARS-CoV-2 spike protein, show up to two orders of magnitude enhancement in neutralization of pseudovirus infection and retain potent interaction with virus variant of concern spike proteins. The tetramerization method is simple, general and its application is a powerful methodological development for SARS-CoV-2 antibodies that are currently in pre-clinical and clinical investigation.

Reference

https://www.nature.com/articles/s41598-021-89887-w

Diffuse trophoblast damage is the hallmark of SARS-CoV-2-associated fetal demise

Abstract

Placental pathology in SARS-CoV-2-infected pregnancies seems rather unspecific. However, the identification of the placental lesions due to SARS-CoV-2 infection would be a significant advance in order to improve the management of these pregnancies and

to identify the mechanisms involved in a possible vertical transmission. The pathological findings in placentas delivered from 198 SARS-CoV-2-positive pregnant women were investigated for the presence of lesions associated with placental SARS-CoV-2 infection. SARS-CoV-2 infection was investigated in placental tissues through immunohistochemistry, and positive cases were further confirmed by in situ hybridization. SARS-CoV-2 infection was also investigated by RT-PCR in 33 cases, including all the immunohistochemically positive cases. Nine cases were SARS-CoV-2-positive by immunohistochemistry, in situ hybridization, and RT-PCR. These placentas showed lesions characterized by villous trophoblast necrosis with intervillous space collapse and variable amounts of mixed intervillous inflammatory infiltrate and perivillous fibrinoid deposition. Such lesions ranged from focal to massively widespread in five cases, resulting in intrauterine fetal death. Two of the stillborn fetuses showed some evidence of SARS-CoV-2 positivity. The remaining 189 placentas did not show similar lesions. The strong association between trophoblastic damage and placenta SARS-CoV-2 infection suggests that this lesion is a specific marker of SARS-CoV-2 infection in placenta. Diffuse trophoblastic damage, massively affecting chorionic villous tissue, can result in fetal death associated with COVID-19 disease.

Reference

https://www.nature.com/articles/s41379-021-00827-5

A rapid, accurate, scalable, and portable testing system for COVID-19 diagnosis

Abstract

The need for rapid, accurate, and scalable testing systems for COVID-19 diagnosis is clear and urgent. Here, a rapid Scalable and Portable Testing (SPOT) system was reported, consisting of a rapid, highly sensitive, and accurate assay and a battery-powered portable device for COVID-19 diagnosis. The SPOT assay comprises a one-pot reverse transcriptase-loop-mediated isothermal amplification (RT-LAMP) followed by PfAgo-based target sequence detection. It is capable of detecting the N gene and E gene in a multiplexed reaction with the limit of detection (LoD) of 0.44 copies/μL and 1.09 copies/μL, respectively, in SARS-CoV-2 virus-spiked saliva samples within 30 min. Moreover, the SPOT system is used to analyze 104 clinical saliva samples and identified 28/30 (93.3% sensitivity) SARS-CoV-2 positive samples (100% sensitivity if

LoD is considered) and 73/74 (98.6% specificity) SARS-CoV-2 negative samples. This combination of speed, accuracy, sensitivity, and portability will enable high-volume, low-cost access to areas in need of urgent COVID-19 testing capabilities.

Reference

https://www.nature.com/articles/s41467-021-23185-x

Is COVID-19 a risk factor for progression of benign prostatic hyperplasia and exacerbation of its related symptoms?: A systematic review

Abstract

Background: To explore the potential mechanisms of SARS-CoV-2 in targeting the prostate gland, leading to exacerbation of benign prostatic hyperplasia (BPH) symptoms and greater risks of BPH complications such as acute urinary retention.

Methods: A categorized and comprehensive search in the literature has been conducted by 10 April 2021 using international databases including PubMed, Embase, Web of Science, Scopus, and Cochrane Library in line with the PRISMA guidelines recommendations. PICO strategy was used to formulate the research question. The following terms were used: urology, COVID-19, coronavirus, BPH, inflammation, androgen receptors, LUTS, IPSS, PSA, and SARS-CoV-2 or a combination of them. Studies with irrelevant purposes and duplicates were excluded. The selected studies were performed on humans and published in English.

Results: The research revealed 89 articles. After title screening and considering exclusion criteria, 52 papers were included for the systematic review. BPH is a common condition affecting older men. SARS-CoV-2 infects the host cell by binding to angiotensin converting enzyme 2 (ACE2). A hyperactivated RAS system during infection with SARS-CoV-2 may lead to activation of pro-inflammatory pathways and increased cytokine release. Thus, this virus can lead to exacerbation of lower urinary tract symptoms (LUTS) and trigger inflammatory processes in the prostate gland. Since androgen receptors (AR) play an important role in the BPH pathophysiology and infection with SARS-CoV-2 may be androgen-mediated, BPH progression and its related symptoms can be a complication of COVID-19 through AR involvement and metabolic disturbances.

Conclusions: Based on the current findings, SARS-CoV-2 can possibly damage the prostate and worsen BPH and its related LUTS through ACE2 signaling, AR-related mechanisms, inflammation, and metabolic derangement. We encourage future studies to investigate the possible role of COVID-19 in the progression of BPH-related LUTS and examine the prostatic status in susceptible patients with relevant available questionnaires (e.g., IPSS) and serum biomarkers (e.g., PSA).

Reference

https://www.nature.com/articles/s41391-021-00388-3

Phase-1 randomized trial of a plant-derived virus-like particle vaccine for COVID-19

Abstract

Several severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are being deployed, but the global need greatly exceeds the supply, and different formulations might be required for specific populations. Here Day 42 interim safety and immunogenicity data was reported from an observer-blinded, dose escalation, randomized controlled study of a virus-like particle vaccine candidate produced in plants that displays the SARS-CoV-2 spike glycoprotein (CoVLP: NCT04450004). The co-primary outcomes were the short-term tolerability/safety and immunogenicity of CoVLP formulations assessed by neutralizing antibody (NAb) and cellular responses. Secondary outcomes in this ongoing study include safety and immunogenicity assessments up to 12 months after vaccination. Adults (18–55 years, n = 180) were randomized at two sites in Quebec, Canada, to receive two intramuscular doses of CoVLP (3.75 µg, 7.5 µg, and 15 µg) 21 d apart, alone or adjuvanted with AS03 or CpG1018. All formulations were well tolerated, and adverse events after vaccination were generally mild to moderate, transient and highest in the adjuvanted groups. There was no CoVLP dose effect on serum NAbs, but titers increased significantly with both adjuvants. After the second dose, NAbs in the CoVLP + AS03 groups were more than tenfold higher than titers in Coronavirus 2019 convalescent sera. Both spike protein-specific interferon-γ and interleukin-4 cellular responses were also induced. This pre-specified interim analysis supports further evaluation of the CoVLP vaccine candidate.

Reference

https://www.nature.com/articles/s41591-021-01370-1

Systemic inflammatory syndrome in COVID-19–SISCoV study: Systematic review and meta-analysis

Abstract

Background: There has been a recent upsurge in the cases of Multisystem inflammatory syndrome in children (MIS-C) associated with Coronavirus disease (COVID-19). Systematic review and meta-analysis were performed on the demographic profile, clinical characteristics, complications, management, and prognosis of this emerging novel entity.

Methods: Using a predefined search strategy incorporating MeSH terms and keywords, all known literature databases were searched up till 10th July 2020. The review was done in accordance with PRISMA guidelines and registered in PROSPERO (CRD4202019757).

Results: Of the 862 identified publications, 18 studies comprising 833 patients were included for meta-analysis. The socio-demographic profile showed male predilection ($p = 0.0085$) with no significant racial predisposition. A higher incidence of gastrointestinal symptoms (603/715, 84.3%), myocarditis (191/309, 61.8%), left ventricular dysfunction (190/422, 45.0%), pericardial (135/436, 31.0%) and neurological symptoms (138/602, 22.9%) was reported. Serological evidence of SARS-CoV-2 had higher sensitivity compared to rtPCR (291/800, 36.4% vs 495/752, 65.8%; $p < 0.001$). Coronary artery anomaly (CAA) was reported in 117/681 in 9 publications (17.2%). A total of 13 (1.6%) fatalities were reported.

Conclusion: Clinicians need to be vigilant in identifying the constellation of these symptoms in children with clinical or epidemiologic SARS-CoV-2 infection. Early diagnosis and treatment lead to a favorable outcome.

Reference

https://www.nature.com/articles/s41390-021-01545-z

Equitable allocation of COVID-19 vaccines in the United States

Abstract

Many vaccine rationing guidelines urge planners to recognize, and ideally reduce, inequities. In the United States, allocation frameworks are determined by each of the Centers for Disease Control and Prevention's 64 jurisdictions (50 states, the District of Columbia, five cities and eight territories). In this study, we analyzed vaccine allocation plans published by 8 November 2020, tracking updates through to 30 March 2021. We evaluated whether jurisdictions adopted proposals to reduce inequity using disadvantage indices and related place-based measures. By 30 March 2021, 14 jurisdictions had prioritized specific zip codes in combination with metrics such as COVID-19 incidence, and 37 jurisdictions (including 34 states) had adopted disadvantage indices, compared to 19 jurisdictions in November 2020. Uptake of indices doubled from 7 to 14 among the jurisdictions with the largest shares of disadvantaged communities. Five applications were distinguished: (1) prioritizing disadvantaged groups through increased shares of vaccines or vaccination appointments; (2) defining priority groups or areas; (3) tailoring outreach and communication; (4) planning the location of dispensing sites; and (5) monitoring receipt. To ensure that equity features centrally in allocation plans, policymakers at the federal, state and local levels should universalize the uptake of disadvantage indices and related place-based measures.

Reference

https://www.nature.com/articles/s41591-021-01379-6

Dynamics of neutralizing antibody responses to SARS-CoV-2 in patients with COVID-19: An observational study

Abstract

Our understanding of the protective immunity, particularly the long-term dynamics of neutralizing antibody (NAbs) response to SARS-CoV-2, is currently limited. A cohort of 545 COVID-19 patients were enrolled from Hubei, China, who were followed up up to 7 months, and determined the dynamics of NAbs to SARS-CoV-2 by using a surrogate virus neutralization test (sVNT). In the validation study, sVNT IC50 titers and the

neutralization rate measured at a single dilution (1:20) were well correlated with FRNT titers (r = 0.85 and 0.84, respectively). The median time to seroconversion of NAbs was 5.5 days post onset of symptoms. The rate of positive sVNT was 52% in the first week, reached 100% in the third week, and remained above 97% till 6 months post onset. Quantitatively, NAbs peaked in the fourth week and only a quarter of patients had an estimated peak titer of >1000. NAbs declined with a half-time of 61 days (95% CI: 49–80 days) within the first two months, and the decay deaccelerated to a half-time of 104 days (95% CI: 86–130 days) afterward. The peak levels of NAbs were positively associated with severity of COVID-19 and age, while negatively associated with serum albumin levels. The observation that the low-moderate peak neutralizing activity and fast decay of NAbs in most naturally infected individuals called for caution in evaluating the feasibility of antibody-based therapy and vaccine durability. NAbs response positively correlated with disease severity, warning for the possibility of repeat infection in patients with mild COVID-19.

Reference

https://www.nature.com/articles/s41392-021-00611-6

Publication Date: May 17, 2021

Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection

Abstract

Predictive models of immune protection from COVID-19 are urgently needed to identify correlates of protection to assist in the future deployment of vaccines. To address this, we analyzed the relationship between *in vitro* neutralization levels and the observed protection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection using data from seven current vaccines and from convalescent cohorts. We estimated the neutralization level for 50% protection against detectable SARS-CoV-2 infection to be 20.2% of the mean convalescent level (95% confidence interval (CI) = 14.4–28.4%). The estimated neutralization level required for 50% protection from severe infection was significantly lower (3% of the mean convalescent level; 95% CI = 0.7–13%, P = 0.0004). Modeling of the decay of the neutralization titer over the first

250 d after immunization predicts that a significant loss in protection from SARS-CoV-2 infection will occur, although protection from severe disease should be largely retained. Neutralization titers against some SARS-CoV-2 variants of concern are reduced compared with the vaccine strain, and our model predicts the relationship between neutralization and efficacy against viral variants. Here, we show that neutralization level is highly predictive of immune protection, and provide an evidence-based model of SARS-CoV-2 immune protection that will assist in developing vaccine strategies to control the future trajectory of the pandemic.

Reference

https://www.nature.com/articles/s41591-021-01377-8

Rapid isolation and immune profiling of SARS-CoV-2 specific memory B cell in convalescent COVID-19 patients *via* LIBRA-seq

Abstract

B-cell response plays a critical role against SARS-CoV-2 infection. However, little is known about the diversity and frequency of the paired SARS-CoV-2 antigen-specific BCR repertoire after SARS-CoV-2 infection. Here, single-cell RNA sequencing and VDJ sequencing were performed using the memory and plasma B cells isolated from five convalescent COVID-19 patients, and analyzed the spectrum and transcriptional heterogeneity of antibody immune responses. Via linking BCR to antigen specificity through sequencing (LIBRA-seq), a distinct activated memory B cell subgroup (CD11chigh CD95high) was identified that had a higher proportion of SARS-CoV-2 antigen-labeled cells compared with memory B cells. The results revealed the diversity of paired BCR repertoire and the non-stochastic pairing of SARS-CoV-2 antigen-specific immunoglobulin heavy and light chains after SARS-CoV-2 infection. The public antibody clonotypes were shared by distinct convalescent individuals. Moreover, several antibodies isolated by LIBRA-seq showed high binding affinity against SARS-CoV-2 receptor-binding domain (RBD) or nucleoprotein (NP) via ELISA assay. Two RBD-reactive antibodies C14646P3S and C2767P3S isolated by LIBRA-seq exhibited high neutralizing activities against both pseudotyped and authentic SARS-CoV-2 viruses *in vitro.* The study provides fundamental insights into B cell response following SARS-CoV-2 infection at the single-cell level.

Reference

https://www.nature.com/articles/s41392-021-00610-7

Safety and efficacy of meplazumab in healthy volunteers and COVID-19 patients: a randomized phase 1 and an exploratory phase 2 trial

Abstract

Recent evidence suggests that CD147 serves as a novel receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Blocking CD147 via anti-CD147 antibody could suppress the in vitro SARS-CoV-2 replication. Meplazumab is a humanized anti-CD147 IgG2 monoclonal antibody, which may effectively prevent SARS-CoV-2 infection in coronavirus disease 2019 (COVID-19) patients. Here, we conducted a randomized, double-blinded, placebo-controlled phase 1 trial to evaluate the safety, tolerability, and pharmacokinetics of meplazumab in healthy subjects, and an open-labeled, concurrent controlled add-on exploratory phase 2 study to determine the efficacy in COVID-19 patients. In phase 1 study, 59 subjects were enrolled and assigned to eight cohorts, and no serious treatment-emergent adverse event (TEAE) or TEAE grade ≥3 was observed. The serum and peripheral blood Cmax and area under the curve showed non-linear pharmacokinetic characteristics. No obvious relation between the incidence or titer of positive anti-drug antibody and dosage was observed in each cohort. The biodistribution study indicated that meplazumab reached lung tissue and maintained >14 days stable with the lung tissue/cardiac blood–pool ratio ranging from 0.41 to 0.32. In the exploratory phase 2 study, 17 COVID-19 patients were enrolled, and 11 hospitalized patients were involved as concurrent control. The meplazumab treatment significantly improved the discharged ($P = 0.005$) and case severity ($P = 0.021$), and reduced the time to virus negative ($P = 0.045$) in comparison to the control group. These results show a sound safety and tolerance of meplazumab in healthy volunteers and suggest that meplazumab could accelerate the recovery of patients from COVID-19 pneumonia with a favorable safety profile.

Reference

https://www.nature.com/articles/s41392-021-00603-6

Differences in coagulopathy indices in patients with severe *versus* non-severe COVID-19: A meta-analysis of 35 studies and 6427 patients

Abstract

Coronavirus disease 2019 (COVID-19) is a highly contagious disease that appeared in China in December 2019 and spread rapidly around the world. Several patients with severe COVID-19 infection can develop a coagulopathy according to the ISTH criteria for disseminated intravascular coagulopathy (DIC) with fulminant activation of coagulation, resulting in widespread microvascular thrombosis and consumption of coagulation factors. A meta-analysis was conducted in order to explore differences in coagulopathy indices in patients with severe and non-severe COVID-19. An electronic search was performed within PubMed, Google Scholar and Scopus electronic databases between December 2019 (first confirmed Covid-19 case) up to April 6th, 2020. The primary endpoint was the difference of D-dimer values between Non-Severe vs Severe disease and Survivors vs Non-Survivors. Furthermore, results on additional coagulation parameters (platelet count, prothrombin time, activated partial thromboplastin time) were also analyzed. The primary analysis showed that mean d-dimer was significantly lower in COVID-19 patients with non-severe disease than in those with severe (SMD − 2.15 [− 2.73 to − 1.56], I2 98%, P < 0.0001). Similarly, we found a lower mean d-dimer in Survivors compared to Non-Survivors (SMD − 2.91 [− 3.87 to − 1.96], I2 98%, P < 0.0001). Additional analysis of platelet count showed higher levels of mean PLT in Non-Severe patients than those observed in the Severe group (SMD 0.77 [0.32 to 1.22], I2 96%, P < 0.001). Of note, a similar result was observed even when Survivors were compared to Non-Survivors (SMD 1.84 [1.16 to 2.53], I2 97%, P < 0.0001). Interestingly, shorter mean PT was found in both Non-Severe (SMD − 1.34 [− 2.06 to − 0.62], I2 98%, P < 0.0002) and Survivors groups (SMD − 1.61 [− 2.69 to − 0.54], I2 98%, P < 0.003) compared to Severe and Non-Survivor patients. In conclusion, the results of the present meta-analysis demonstrate that Severe COVID-19 infection is associated with higher D-dimer values, lower platelet count and prolonged PT. This data suggests a possible role of disseminated intravascular coagulation in the pathogenesis of COVID-19 disease complications.

Reference

https://www.nature.com/articles/s41598-021-89967-x

Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019 (COVID-19)

Abstract

A meta-analysis was performed to determine safety and efficacy of tocilizumab in persons with coronavirus disease-2019 (COVID-19). PubMed, Web of Science and Medline were searched using Boolean operators for studies with the terms coronavirus OR COVID-19 OR 2019-nCoV OR SARS-CoV-2 AND tocilizumab. Review Manager 5.4 was used to analyze data and the modified Newcastle–Ottawa and Jadad scales for quality assessment. 32 studies were identified in 11,487 subjects including three randomized trials and 29 cohort studies with a comparator cohort, including historical controls (N = 5), a matched cohort (N = 12), or concurrent controls (N = 12). Overall, tocilizumab decreased risk of death (Relative Risk [RR] = 0.74; 95% confidence interval [CI], 0.59, 0.93; P = 0.008; I2 = 80%) but not of surrogate endpoints including ICU admission (RR = 1.40 [0.64,3.06]; P = 0.4; I2 = 88%), invasive mechanical ventilation (RR = 0.83 [0.57,1.22]; P = 0.34; I2 = 65%) or secondary infections (RR = 1.30 [0.97,1.74]; P = 0.08; I2 = 65%) and increased interval of hospitalization of subjects discharged alive(mean difference [MD] = 2 days [<1, 4 days]; P = 0.006; I2 = 0). RRs of death in studies with historical controls (RR = 0.28 [0.16,0.49; P < 0.001]; I2 = 62%) or a matched cohort (RR = 0.68 [0.53, 0.87]; P = 0.002; I2 = 42%) were decreased. In contrast, RRs of death in studies with a concurrent control (RR = 1.10 [0.77, 1.56]; P = 0.60; I2 = 85%) or randomized (RR = 1.18 [0.57,2.44]; P = 0.66; I2 = 0) were not decreased. A reduced risk of death was not confirmed in our analyses which questions safety and efficacy of tocilizumab in persons with COVID-19.

Reference

https://www.nature.com/articles/s41375-021-01264-8

Weight trajectories and abdominal adiposity in COVID-19 survivors with overweight/obesity

Abstract

Background: COVID-19 is associated with unintentional weight loss. Little is known on whether and how patients regain the lost weight. Changes in weight and abdominal adiposity were assessed over a three-month follow-up after discharge in COVID-19 survivors.

Methods: In this sub-study of a large prospective observational investigation, we collected data from individuals who had been hospitalized for COVID-19 and re-evaluated at one (V1) and three (V2) months after discharge. Patient characteristics upon admission and anthropometrics, waist circumference and hunger levels assessed during follow-up were analyzed across BMI categories.

Results: One-hundred-eighty-five COVID-19 survivors (71% male, median age 62.1 [54.3; 72.1] years, 80% with overweight/obesity) were included. Median BMI did not change from admission to V1 in normal weight subjects (−0.5 [−1.2; 0.6] kg/m2, $p = 0.08$), but significantly decreased in subjects with overweight (−0.8 [−1.8; 0.3] kg/m2, $p < 0.001$) or obesity (−1.38 [−3.4; −0.3] kg/m2, $p < 0.001$; $p < 0.05$ vs. normal weight or obesity). Median BMI did not change from V1 to V2 in normal weight individuals (+0.26 [−0.34; 1.15] kg/m2, $p = 0.12$), but significantly increased in subjects with overweight (+0.4 [0.0; 1.0] kg/m2, $p < 0.001$) or obesity (+0.89 [0.0; 1.6] kg/m2, $p < 0.001$; $p = 0.01$ vs. normal weight). Waist circumference significantly increased from V1 to V2 in the whole group ($p < 0.001$), driven by the groups with overweight or obesity. At multivariable regression analyses, male sex, hunger at V1 and initial weight loss predicted weight gain at V2.

Conclusions: Patients with overweight or obesity hospitalized for COVID-19 exhibit rapid, wide weight fluctuations that may worsen body composition (abdominal adiposity).

Reference

https://www.nature.com/articles/s41366-021-00861-y

Post-COVID syndrome in non-hospitalised patients with COVID-19: A longitudinal prospective cohort study

Abstract

Background: While the leading symptoms during coronavirus disease 2019 (COVID-19) are acute and the majority of patients fully recover, a significant fraction of patients now increasingly experience long-term health consequences. However, most data available focus on health-related events after severe infection and hospitalisation. We present a longitudinal, prospective analysis of health consequences in patients who initially presented with no or minor symptoms of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Hence, we focus on mild COVID-19 in non-hospitalised patients.

Methods: 958 Patients with confirmed SARS-CoV-2 infection were observed from April 6th to December 2nd 2020 for long-term symptoms and SARS-CoV-2 antibodies. Anosmia, ageusia, fatigue or shortness of breath were identified as most common, persisting symptoms at month 4 and 7 and summarised presence of such long-term health consequences as post-COVID syndrome (PCS). Predictors of long-term symptoms were assessed using an uni- and multivariable logistic regression model.

Findings: 442 and 353 Patients were observed over four and seven months after symptom onset, respectively. Four months post SARS-CoV-2 infection, 8•6% (38/442) of patients presented with shortness of breath, 12•4% (55/442) with anosmia, 11•1% (49/442) with ageusia and 9•7% (43/442) with fatigue. At least one of these characteristic symptoms was present in 27•8% (123/442) and 34•8% (123/353) at month 4 and 7 post-infection, respectively. A lower baseline level of SARS-CoV-2 IgG, anosmia and diarrhoea during acute COVID-19 were associated with higher risk to develop long-term symptoms.

Interpretation: The on-going presence of either shortness of breath, anosmia, ageusia or fatigue as long-lasting symptoms even in non-hospitalised patients was observed at four and seven months post-infection and summarised as post-COVID syndrome (PCS). The continued assessment of patients with PCS will become a major task to define and mitigate the socioeconomic and medical long-term effects of COVID-19.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00099-5/fulltext

Understanding the psychiatric symptoms of COVID-19: A meta-analysis of studies assessing psychiatric symptoms in Chinese patients with and survivors of COVID-19 and SARS by using the Symptom Checklist-90-Revised

Abstract

Understanding the psychiatric symptoms of COVID-19 could facilitate the clinical management of COVID-19 patients. However, the profile of psychiatric symptoms among COVID-19 patients has been understudied. A meta-analysis of studies was performed, assessing psychiatric symptoms of COVID-19 and SARS patients and survivors by using the Symptom Checklist-90-Revised (SCL-90-R), an instrument covering a wide spectrum of psychiatric symptoms. Studies reporting SCL-90-R subscale scores among patients with and survivors of COVID-19 and SARS were retrieved from major English and Chinese literature databases. Patients' pooled SCL-90-R subscale scores were compared to the Chinese normative SCL-90-R data, and Cohen's d values were calculated to indicate the severity of psychiatric symptoms. The Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data was used to assess the quality of the included studies. The search yielded 25 Chinese studies with 1675 acute COVID-19 and 964 acute SARS patients, 30 COVID-19 and 552 SARS survivors during very early recovery (up to 1 month since discharge), 291 SARS survivors during early recovery (1–6 months after discharge), and 48 SARS survivors during late recovery (12 months after discharge). None of the included studies were rated as good quality. The ten SCL-90-R-defined psychiatric symptoms, which were of medium-to-severe severity (d = 0.68–3.01), were all exhibited in acute COVID-19 patients, and the severity of these symptoms decreased to mild-to-medium during very early recovery (d = 0.17–0.73). SARS patients presented eight psychiatric symptoms with mild-to-severe severity during the acute stage (d =0.43–1.88), and thereafter, the severity of symptoms decreased over the follow-up period. However, somatization (d = 0.30) and anxiety (d = 0.28) remained at mild levels during late recovery. A wide variety of severe psychiatric symptoms have been reported by acute COVID-19 patients, and these symptoms, despite decreasing in severity, persist in very

early recovery. The changing trajectory observed with SARS suggests that psychiatric symptoms of COVID-19 may persist for a long time after discharge, and therefore, periodic monitoring of psychiatric symptoms, psychosocial support, and psychiatric treatment (when necessary) may be necessary for COVID-19 patients from the acute to convalescent stages.

Reference

https://www.nature.com/articles/s41398-021-01416-5

Publication Date: May 16, 2021

Highly specific monoclonal antibodies and epitope identification against SARS-CoV-2 nucleocapsid protein for antigen detection tests

Abstract

The ongoing COVID-19 pandemic is a major global public health concern. Although rapid point-of-care testing for detecting viral antigen is important for management of the outbreak, the current antigen tests are less sensitive than nucleic acid testing. In the current study, monoclonal antibodies (mAb) were produced that exclusively react with SARS-CoV-2 and exhibit no cross-reactivity with other human coronaviruses including SARS-CoV. Molecular modeling suggest that the mAbs bind to epitopes present on the exterior surface of the nucleocapsid, making them suitable for detecting SARS-CoV-2 in clinical samples. It was further selected that the optimal pair of anti-SARS-CoV-2 NP mAbs using ELISA, and then use this mAb pair to develop immunochromatographic assay augmented with silver amplification technology. The mAbs recognize the variants of concern (501Y.V1-V3) that are currently in circulation. Due to their high performance, the mAbs of this study can serve as good candidates for developing antigen detection kits for COVID-19.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00154-3

Longitudinal analysis reveals that delayed bystander CD8+ T cell activation and early immune pathology distinguish severe COVID-19 from mild disease

Abstract

The kinetics of the immune changes in COVID-19 across severity groups have not been rigorously assessed. Using immunophenotyping, RNA sequencing and serum cytokine analysis, we analyzed serial samples from 207 SARS-CoV2-infected individuals with a range of disease severities over 12 weeks from symptom onset. An early robust bystander CD8+ T cell immune response, without systemic inflammation, characterized asymptomatic or mild disease. Hospitalized individuals had delayed bystander responses and systemic inflammation that was already evident near symptom onset, indicating that immunopathology may be inevitable in some individuals. Viral load did not correlate with this early pathological response, but did correlate with subsequent disease severity. Immune recovery is complex, with profound persistent cellular abnormalities in severe disease correlating with altered inflammatory responses, with signatures associated with increased oxidative phosphorylation replacing those driven by cytokines tumor necrosis factor (TNF) and interleukin (IL)-6. These late immunometabolic and immune defects may have clinical implications.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00216-8

Publication Date: May 14, 2021

Innate immune and inflammatory responses to SARS-CoV-2: Implications for COVID-19

Abstract

COVID-19 can result in severe disease characterized by significant immunopathology that is spurred by an exuberant, yet dysregulated, innate immune response with a poor adaptive response. A limited and delayed interferon I (IFN-I) and IFN-III response results in exacerbated proinflammatory cytokine production and in extensive cellular infiltrates in the respiratory tract, resulting in lung pathology. The development of effective therapeutics for patients with severe COVID-19 depends on our understanding of the pathological elements of this unbalanced innate immune response. Here, we

review the mechanisms by which SARS-CoV-2 both activates and antagonizes the IFN and inflammatory response following infection, how a dysregulated cytokine and cellular response contributes to immune-mediated pathology in COVID-19, and therapeutic strategies that target elements of the innate response.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00232-8

***JAK*-inhibitors for coronavirus disease-2019 (COVID-19): A meta-analysis**

Abstract

Reports on safety and efficacy of *JAK*-inhibitors in patients with coronavirus infectious disease-2019 (COVID-19) published between January 1st and March 6th 2021 using the Newcastle-Ottawa and Jadad scales were analyzed for quality assessment. Disease severity was used as a proxy for time when *JAK*-inhibitor therapy was started. 6 Cohort studies and 5 clinical trials were identified involving 2367 subjects treated with ruxolitinib (N = 3) or baricitinib 45 (N = 8). Use of *JAK*-inhibitors decreased use of invasive mechanical ventilation (RR = 0.63; [95% Confidence Interval (CI), 0.47, 0.84]; P = 0.002) and had borderline impact on rates of intensive care unit (ICU) admission (RR = 0.24 [0.06, 1.02]; P = 0.05) and acute respiratory distress syndrome (ARDS; RR = 0.50 [0.19, 1.33]; P = 0.16). *JAK*-inhibitors did not decrease length of hospitalization (mean difference (MD) –0.18 [–4.54, 4.18]; P = 0.94). Relative risks of death for both drugs were 0.42 [0.30, 0.59] (P < 0.001), for ruxolitinib, RR = 0.33 (0.13, 0.88; P = 0.03) and for baricitinib RR = 0.44 (0.31, 0.63; P < 0.001). Timing of *JAK*-inhibitor treatment during the course of COVID-19 treatment may be important in determining impact on outcome. However, these data are not consistently reported.

Reference

https://www.nature.com/articles/s41375-021-01266-6

Changes in in-hospital mortality in the first wave of COVID-19: A multicentre prospective observational cohort study using the WHO Clinical Characterisation Protocol UK

Abstract

Background: Mortality rates in hospitalised patients with COVID-19 in the UK appeared to decline during the first wave of the pandemic. It was aimed to quantify potential drivers of this change and identify groups of patients who remain at high risk of dying in hospital.

Methods: In this multicentre prospective observational cohort study, the International Severe Acute Respiratory and Emerging Infections Consortium WHO Clinical Characterisation Protocol UK recruited a prospective cohort of patients with COVID-19 admitted to 247 acute hospitals in England, Scotland, and Wales during the first wave of the pandemic (between March 9 and Aug 2, 2020). All patients aged 18 years and older were included, with clinical signs and symptoms of COVID-19 or confirmed COVID-19 (by RT-PCR test) from assumed community-acquired infection. A three-way decomposition mediation analysis was done using natural effects models to explore associations between week of admission and in-hospital mortality, adjusting for confounders (demographics, comorbidities, and severity of illness) and quantifying potential mediators (level of respiratory support and steroid treatment). The primary outcome was weekly in-hospital mortality at 28 days, defined as the proportion of patients who had died within 28 days of admission of all patients admitted in the observed week, and it was assessed in all patients with an outcome. This study is registered with the ISRCTN Registry, ISRCTN66726260.

Findings: Between March 9, and Aug 2, 2020, 80 713 patients were recruited, of whom 63 972 were eligible and included in the study. Unadjusted weekly in-hospital mortality declined from 32·3% (95% CI 31·8–32·7) in March 9 to April 26, 2020, to 16·4% (15·0–17·8) in June 15 to Aug 2, 2020. Reductions in mortality were observed in all age groups, in all ethnic groups, for both sexes, and in patients with and without comorbidities. After adjustment, there was a 32% reduction in the risk of mortality per 7-week period (odds ratio [OR] 0·68 [95% CI 0·65–0·71]). The higher proportions of patients with severe disease and comorbidities earlier in the first wave (March and April) than in June and July accounted for 10·2% of this reduction. The use of respiratory

support changed during the first wave, with gradually increased use of non-invasive ventilation over the first wave. Changes in respiratory support and use of steroids accounted for 22·2%, OR 0·95 (0·94–0·95) of the reduction in in-hospital mortality.

Interpretation: The reduction in in-hospital mortality in patients with COVID-19 during the first wave in the UK was partly accounted for by changes in the case-mix and illness severity. A significant reduction in in-hospital mortality was associated with differences in respiratory support and critical care use, which could partly reflect accrual of clinical knowledge. The remaining improvement in in-hospital mortality is not explained by these factors, and could be associated with changes in community behaviour, inoculum dose, and hospital capacity strain.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00175-2/fulltext

A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19

Abstract

The emergent 21st century betacoronaviruses, including SARS-CoV-2, lead to clinicopathological manifestations with unusual features, such as early-onset chest pain, pulmonary infarction, and pulmonary and systemic thromboembolism that is pathologically linked to extensive capillary, arteriolar, and venular thrombosis. Early ground glass opacities detected by CT, which are reminiscent of lung infarcts associated with pulmonary embolism, point to a novel vascular pathology in COVID-19. Under physiological conditions, normal parenchymal oxygenation is maintained by three sources: the alveolus itself and dual oxygen supply from the pulmonary and bronchial artery circulations. A model was proposed in which these three components are disrupted in COVID-19 pneumonia, with severe viral alveolitis and concomitant immunothrombotic obstruction of the pulmonary and bronchiolar circulation. Tricompartmental disruption might have two main consequences: systemic clot embolisation from pulmonary vein territory immunothrombosis, and alveolar–capillary barrier disruption with systemic access of thrombogenic viral material. The model encompasses the known pathological and clinical features of severe COVID-19, and

has implications for understanding patient responses to immunomodulatory therapies, which might exert an anti-inflammatory effect within the vascular compartments.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00213-7/fulltext

Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): A single centre, open-label, randomised, controlled trial

Abstract

Background: It was sought to clarify the benefit of cytokine adsorption in patients with COVID-19 supported with venovenous extracorporeal membrane oxygenation (ECMO).

Methods: A single-centre, open-label, randomised, controlled trial was done to investigate cytokine adsorption in adult patients with severe COVID-19 pneumonia requiring ECMO. Patients with COVID-19 selected for ECMO at the Freiburg University Medical Center (Freiburg, Germany) were randomly assigned (1:1) to receive cytokine adsorption using the CytoSorb device or not. Randomisation was computer-generated, allocation was concealed by opaque, sequentially numbered sealed envelopes. The CytoSorb device was incorporated into the ECMO circuit before connection to the patient circuit, replaced every 24 h, and removed after 72 h. The primary endpoint was serum interleukin-6 (IL-6) concentration 72 h after initiation of ECMO analysed by intention to treat. Secondary endpoints included 30-day survival. The trial is registered with ClinicalTrials.gov (NCT04324528) and the German Clinical Trials Register (DRKS00021300) and is closed.

Findings: From March 29, 2020, to Dec 29, 2020, of 34 patients assessed for eligibility, 17 (50%) were treated with cytokine adsorption and 17 (50%) without. Median IL-6 decreased from 357·0 pg/mL to 98·6 pg/mL in patients randomly assigned to cytokine adsorption and from 289·0 pg/mL to 112·0 pg/mL in the control group after 72 h. One patient in each group died before 72 h. Adjusted mean log IL-6 concentrations after 72 h were 0·30 higher in the cytokine adsorption group (95% CI −0·70 to 1·30, p=0·54). Survival after 30 days was three (18%) of 17 with cytokine adsorption and 13 (76%) of 17 without cytokine adsorption (p=0·0016).

Interpretation: Early initiation of cytokine adsorption in patients with severe COVID-19 and venovenous ECMO did not reduce serum IL-6 and had a negative effect on survival. Cytokine adsorption should not be used during the first days of ECMO support in COVID-19.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00177-6/fulltext

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): A randomised controlled, open-label, platform trial

Abstract

Background: Many patients with COVID-19 have been treated with plasma containing anti-SARS-CoV-2 antibodies. It was aimed to evaluate the safety and efficacy of convalescent plasma therapy in patients admitted to hospital with COVID-19.

Methods: This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. The trial is underway at 177 NHS hospitals from across the UK. Eligible and consenting patients were randomly assigned (1:1) to receive either usual care alone (usual care group) or usual care plus high-titre convalescent plasma (convalescent plasma group). The primary outcome was 28-day mortality, analysed on an intention-to-treat basis. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Findings: Between May 28, 2020, and Jan 15, 2021, 11558 (71%) of 16287 patients enrolled in RECOVERY were eligible to receive convalescent plasma and were assigned to either the convalescent plasma group or the usual care group. There was no significant difference in 28-day mortality between the two groups: 1399 (24%) of 5795 patients in the convalescent plasma group and 1408 (24%) of 5763 patients in the usual care group died within 28 days (rate ratio 1·00, 95% CI 0·93–1·07; p=0·95). The 28-day mortality rate ratio was similar in all prespecified subgroups of patients, including in those patients without detectable SARS-CoV-2 antibodies at randomisation. Allocation to convalescent plasma had no significant effect on the proportion of patients discharged from hospital within 28 days (3832 [66%] patients in the convalescent

plasma group vs 3822 [66%] patients in the usual care group; rate ratio 0·99, 95% CI 0·94–1·03; p=0·57). Among those not on invasive mechanical ventilation at randomisation, there was no significant difference in the proportion of patients meeting the composite endpoint of progression to invasive mechanical ventilation or death (1568 [29%] of 5493 patients in the convalescent plasma group vs 1568 [29%] of 5448 patients in the usual care group; rate ratio 0·99, 95% CI 0·93–1·05; p=0·79).

Interpretation: In patients hospitalised with COVID-19, high-titre convalescent plasma did not improve survival or other prespecified clinical outcomes.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00897-7/fulltext

Publication Date: May 13, 2021

Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2

Abstract

As SARS-CoV-2 vaccines are deployed worldwide, a comparative evaluation is important to underpin decision-making. A systematic literature review and meta-analysis of Phase I/II/III human trials and non-human primates (NHP) studies were reported, comparing reactogenicity, immunogenicity and efficacy across different vaccine platforms for comparative evaluation (updated to March 22, 2021). Twenty-three NHP and 32 human studies are included. Vaccines result in mostly mild, self-limiting adverse events. Highest spike neutralizing antibody (nAb) responses are identified for the mRNA-1273-SARS-CoV and adjuvanted NVX-CoV2373-SARS-CoV-2 vaccines. ChAdOx-SARS-CoV-2 produces the highest T cell ELISpot responses. Pre-existing nAb against vaccine viral vector are identified following AdH-5-SARS-CoV-2 vaccination, halving immunogenicity. The mRNA vaccines depend on boosting to achieve optimal immunogenicity especially in the elderly. BNT162b2, and mRNA-1273 achieve >94%, rAd26/5 > 91% and ChAdOx-SARS-CoV-2 > 66.7% efficacy. Across different vaccine platforms there are trade-offs between antibody binding, functional nAb titers, T cell frequency, reactogenicity and efficacy. Emergence of variants makes rapid mass rollout of high efficacy vaccines essential to reduce any selective advantage.

Reference

https://www.nature.com/articles/s41541-021-00336-1

Characterization of an attenuated SARS-CoV-2 variant with a deletion at the S1/S2 junction of the spike protein

Abstract

SARS-CoV-2 is of zoonotic origin and contains a PRRA polybasic cleavage motif which is considered critical for efficient infection and transmission in humans. We previously reported on a panel of attenuated SARS-CoV-2 variants with deletions at the S1/S2 junction of the spike protein. Here, pathogenicity, immunogenicity, and protective ability of a further cell-adapted SARS-CoV-2 variant, Ca-DelMut, were characterized in in vitro and in vivo systems. Ca-DelMut replicates more efficiently than wild type or parental virus in Vero E6 cells, but causes no apparent disease in hamsters, despite replicating in respiratory tissues. Unlike wild type virus, Ca-DelMut causes no obvious pathological changes and does not induce elevation of proinflammatory cytokines, but still triggers a strong neutralizing antibody and T cell response in hamsters and mice. Ca-DelMut immunized hamsters challenged with wild type SARS-CoV-2 are fully protected, with little sign of virus replication in the upper or lower respiratory tract, demonstrating sterilizing immunity.

Reference

https://www.nature.com/articles/s41467-021-23166-0

In silico analysis suggests the RNAi-enhancing antibiotic enoxacin as a potential inhibitor of SARS-CoV-2 infection

Abstract

COVID-19 has currently become the biggest challenge in the world. There is still no specific medicine for COVID-19, which leaves a critical gap for the identification of new drug candidates for the disease. Recent studies have reported that the small-molecule enoxacin exerts an antiviral activity by enhancing the RNAi pathway. The aim of this study is to analyze if enoxacin can exert anti-SARS-CoV-2 effects. Multiple computational tools and databases were exploited to examine (i) whether the RNAi mechanism, as the target pathway of enoxacin, could act on the SARS-CoV-2 genome,

and (ii) microRNAs induced by enoxacin might directly silence viral components as well as the host cell proteins mediating the viral entry and replication. We find that the RNA genome of SARS-CoV-2 might be a suitable substrate for DICER activity. We also highlight several enoxacin-enhanced microRNAs which could target SARS-CoV-2 components, pro-inflammatory cytokines, host cell components facilitating viral replication, and transcription factors enriched in lung stem cells, thereby promoting their differentiation and lung regeneration. Finally, the analyses identify several enoxacin-targeted regulatory modules that were critically associated with exacerbation of the SARS-CoV-2 infection. Overall, the analysis suggests that enoxacin could be a promising candidate for COVID-19 treatment through enhancing the RNAi pathway.

Reference

https://www.nature.com/articles/s41598-021-89605-6

Highly conserved, non-human-like, and cross-reactive SARS-CoV-2 T cell epitopes for COVID-19 vaccine design and validation

Abstract

Natural and vaccine-induced SARS-CoV-2 immunity in humans has been described but correlates of protection are not yet defined. T cells support the SARS-CoV-2 antibody response, clear virus-infected cells, and may be required to block transmission. In this study, we identified peptide epitopes associated with SARS-CoV-2 T-cell immunity. Using immunoinformatic methods, T-cell epitopes from spike, membrane, and envelope were selected for maximal HLA-binding potential, coverage of HLA diversity, coverage of circulating virus, and minimal potential cross-reactivity with self. Direct restimulation of PBMCs collected from SARS-CoV-2 convalescents confirmed 66% of predicted epitopes, whereas only 9% were confirmed in naive individuals. However, following a brief period of epitope-specific T-cell expansion, both cohorts demonstrated robust T-cell responses to 97% of epitopes. HLA-DR3 transgenic mouse immunization with peptides co-formulated with poly-ICLC generated a potent Th1-skewed, epitope-specific memory response, alleviating safety concerns of enhanced respiratory disease associated with Th2 induction. Taken together, these epitopes may be used to improve our understanding of natural and vaccine-induced immunity, and to facilitate the

development of T-cell-targeted vaccines that harness pre-existing SARS-CoV-2 immunity.

Reference

https://www.nature.com/articles/s41541-021-00331-6

Screening of core filter layer for the development of respiratory mask to combat COVID-19

Abstract

The severe outbreak of respiratory coronavirus disease 2019 has increased the significant demand of respiratory mask and its use become ubiquitous worldwide to control this unprecedented respiratory pandemic. The performance of a respiratory mask depends on the efficiency of the filter layer which is mostly made of polypropylene melt blown non-woven (PP-MB-NW). So far, very limited characterization data are available for the PPE-MB-NW in terms to achieve desired particulate filtration efficiency (PFE) against 0.3 μm size, which are imperative in order to facilitate the right selection of PP-MB-NW fabric for the development of mask. In present study, eight different kinds of PP-MB-NW fabrics (Sample A–H) of varied structural morphology are chosen. The different PP-MB-NW were characterized for its pore size and distribution by mercury porosimeter and BET surface area analyzer was explored first time to understand the importance of blind pore in PFE. The PP-MB-NW samples were characterized using scanning electron microscopy so as to know the surface morphology. The filtration efficiency, pressure drop and breathing resistance of various PP-MB-NW fabric samples are investigated in single and double layers combination against the particle size of 0.3, 0.5 and 1 μm. The samples which are having low pore dia, high solid fraction volume, and low air permeability has high filtration efficiency (> 90%) against 0.3 μm particle with high pressure drop (16.3–21.3 mm WC) and breathing resistance (1.42–1.92 mbar) when compared to rest of the samples. This study will pave the way for the judicial selection of right kind of filter layer i.e., PP-MB-NW fabric for the development of mask and it will be greatly helpful in manufacturing of mask in this present pandemic with desired PFE indicating considerable promise for defense against respiratory pandemic.

Reference

https://www.nature.com/articles/s41598-021-89503-x

Q493K and Q498H Substitutions in Spike promote adaptation of SARS-CoV-2 in mice

Abstract

Background: An ideal animal model to study SARS-coronavirus 2 (SARS-CoV-2) pathogenesis and evaluate therapies and vaccines should reproduce SARS-CoV-2 infection and recapitulate lung disease like those seen in humans. The angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2, but mice are resistant to the infection because their ACE2 is incompatible with the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein.

Methods: SARS-CoV-2 was passaged in BALB/c mice to obtain mouse-adapted virus strain. Complete genome deep sequencing of different generations of viruses was performed to characterize the dynamics of the adaptive mutations in SARS-CoV-2. Indirect immunofluorescence analysis and Biolayer interferometry experiments determined the binding affinity of mouse-adapted SARS-CoV-2 WBP-1 RBD to mouse ACE2 and human ACE2. Finally, we tested whether TLR7/8 agonist Resiquimod (R848) could also inhibit the replication of WBP-1 in the mouse model.

Findings: The mouse-adapted strain WBP-1 showed increased infectivity in BALB/c mice and led to severe interstitial pneumonia. We characterized the dynamics of the adaptive mutations in SARS-CoV-2 and demonstrated that Q493K and Q498H in RBD significantly increased its binding affinity towards mouse ACE2. Additionally, the study tentatively found that the TLR7/8 agonist Resiquimod was able to protect mice against WBP-1 challenge. Therefore, this mouse-adapted strain is a useful tool to investigate COVID-19 and develop new therapies.

Interpretation: It was found for the first time that the Q493K and Q498H mutations in the RBD of WBP-1 enhanced its interactive affinities with mACE2. The mouse-adapted SARS-CoV-2 provides a valuable tool for the evaluation of novel antiviral and vaccine strategies. This study also tentatively verified the antiviral activity of TLR7/8 agonist Resiquimod against SARS-CoV-2 *in vitro* and *in vivo*.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00174-2/fulltext

Structural basis of ribosomal frameshifting during translation of the SARS-CoV-2 RNA genome

Abstract

Programmed ribosomal frameshifting is a key event during translation of the SARS-CoV-2 RNA genome allowing synthesis of the viral RNA-dependent RNA polymerase and downstream proteins. Here we present the cryo-electron microscopy structure of a translating mammalian ribosome primed for frameshifting on the viral RNA. The viral RNA adopts a pseudoknot structure that lodges at the entry to the ribosomal mRNA channel to generate tension in the mRNA and promote frameshifting, whereas the nascent viral polyprotein forms distinct interactions with the ribosomal tunnel. Biochemical experiments validate the structural observations and reveal mechanistic and regulatory features that influence frameshifting efficiency. Finally, compounds previously shown to reduce frameshifting were compared with respect to their ability to inhibit SARS-CoV-2 replication, establishing coronavirus frameshifting as a target for antiviral intervention.

Reference

https://science.sciencemag.org/content/early/2021/05/12/science.abf3546

CORRESPONDANCE

Publication Date: May 19, 2021

SARS-CoV-2 B.1.1.7 and B.1.351 spike variants bind human ACE2 with increased affinity

Genomic surveillance efforts have uncovered SARS-CoV-2 variants with mutations in the viral spike glycoprotein, which binds the human angiotensin-converting enzyme 2 (ACE2) receptor to facilitate viral entry. Such variants represent a public health challenge during the COVID-19 pandemic because they increase viral transmission and disease severity. The B.1.351 variant, first identified in South Africa, has three notable mutations in the spike receptor-binding domain (RBD)—namely, K417N, E484K, and N501Y—whereas the B.1.1.7 variant, first identified in the UK, carries the N501Y mutation. B.1.351 is of particular concern for its potential resistance to antibodies elicited by previous SARS-CoV-2 infection and vaccination. Several mechanisms might account for increased variant transmissibility, such as increased spike protein density, greater furin cleavage accessibility, and enhanced spike protein binding affinity for the ACE2 receptor. To test whether the B.1.351 and B.1.1.7 variants bind ACE2 with increased affinity, binding of purified recombinant B.1.351 and B.1.1.7 RBD was compared with binding of the Hu-1 RBD, which was originally identified in Wuhan (SCoV2) using microscale thermophoresis. The B.1.1.7 RBD bound ACE2 with 1·98-times greater affinity than the SCoV2 RBD (mean equilibrium dissociation constant [Kd] 203·7 nM [SD 57·1] *vs* 402·5 nM [112·1]; p=0·0521). The B.1.351 RBD bound ACE2 with 4·62-times greater affinity than the SCoV2 RBD (mean Kd 87·6 nM [SD 25·5] vs 402·5 nM [112·1]; p=0·0009). These data are consistent with a model in which variant spike proteins mediate increased transmissibility of the B.1.1.7 and B.1.351 variants, at least in part, by enhancing ACE2 binding affinity in line with *in-silico* predictions. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00262-0/fulltext

COVID-19 vaccines: Effectiveness and number needed to treat

In a *Lancet Microbe* Comment, Piero Olliaro and colleagues suggest that reporting relative risk reduction (RRR) for vaccination does not reflect entirely its therapeutic performance and consider the solw use of RRR a reporting bias. In addition, they propose that absolute risk reduction (ARR) should be reported as a measure of the vaccine's effectiveness. The authors end up comparing the numbers needed to vaccinate to prevent one case of COVID-19 among the vaccines, which derives from the absolute reductions. However, this suggestion might have a paradoxical effect in misleading perception of treatment performance. This approach disregards three epidemiological facts.

First, number needed to treat (NNT) is not an intrinsic property of a treatment, it is rather a property of the population that receives a treatment: for a constant relative risk reduction, populations of different baseline risks will have different absolute reductions. Therefore, NNT comparison of different treatments across studies should be avoided, because sample populations will always have baseline risk variations. Indeed, this approach is the actual reporting bias. Second, the authors raise a concern that different levels of background risk might change relative risk reduction of studies. This statement disregards the constant property of relative risk repeatedly demonstrated by subgroup analysis of clinical trials and meta-scientific evaluations of a treatment across studies of different baseline risks. For example, statins, anti-hypertensive therapy, and aspirin have the same relative risk reduction across the baseline risks of primary or secondary prevention. Finally, effectiveness—a real-world property—is about clinical decision making, and not to be derived from efficacy studies (randomised controlled studies). As a clinician or an epidemiologist, one should multiply the RRR (intrinsic property of a treatment) by the baseline risk of a given population or patient, individualising the ARR and NNT. They are not scientific concepts, they are circumstantial information.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00119-1/fulltext

REPORT

Publication Date: May 18, 2021

Clonal analysis of immunodominance and cross-reactivity of the CD4 T cell response to SARS-CoV-2

The identification of CD4+ T cell epitopes is instrumental for the design of subunit vaccines for broad protection against coronaviruses. Here we demonstrate in COVID-19-recovered individuals a robust CD4+ T cell response to naturally processed SARS-CoV-2 spike (S) and nucleoprotein (N), including effector, helper, and memory T cells. By characterizing 2943 S-reactive T cell clones from 34 individuals, we found that 34% of clones and 93% of individuals recognized a conserved immunodominant S346-365 region within the RBD comprising nested HLA-DR- and HLA-DP-restricted epitopes. Using pre- and post-COVID-19 samples and S proteins from endemic coronaviruses, we identify cross-reactive T cells targeting multiple S protein sites. The immunodominant and cross-reactive epitopes identified can inform vaccination strategies to counteract emerging SARS-CoV-2 variants.

Reference

https://science.sciencemag.org/content/early/2021/05/17/science.abg8985

Publication Date: May 13, 2021

A SARS-CoV-2 targeted siRNA-nanoparticle therapy for COVID-19

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in humans. Despite several emerging vaccines, there remains no verifiable therapeutic targeted specifically to the virus. Here we present a highly effective siRNA therapeutic against SARS-CoV-2 infection using a novel lipid nanoparticle delivery system. Multiple small-interfering RNAs (siRNAs) targeting highly conserved regions of the SARS-CoV-2 virus were screened and three candidate siRNAs emerged that effectively inhibit virus by greater than 90% either alone or in combination with one another. It was simultaneously developed and screened two novel lipid nanoparticle formulations for the delivery of these candidate siRNA

therapeutics to the lungs, an organ that incurs immense damage during SARS-CoV-2 infection. Encapsulation of siRNAs in these LNPs followed by *in vivo* injection demonstrated robust repression of virus in the lungs and a pronounced survival advantage to the treated mice. The LNP-siRNA approaches are scalable and can be administered upon the first sign of SARS-CoV-2 infection in humans. It was suggested that an siRNA-LNP therapeutic approach could prove highly useful in treating COVID-19 disease as an adjunctive therapy to current vaccine strategies.

Reference

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(21)00256-2

SARS-CoV-2 infects human adult donor eyes and hESC-derived ocular epithelium

The SARS-CoV-2 pandemic has caused unparalleled disruption of global behavior and significant loss of life. To minimize SARS-CoV-2 spread, understanding the mechanisms of infection from all possible routes of entry is essential. While aerosol transmission is thought to be the primary route of spread, viral particles have been detected in ocular fluid, suggesting that the eye may be a vulnerable point of viral entry. To this end, we confirmed SARS-CoV-2 entry factor and antigen expression in post-mortem COVID-19 patient ocular surface tissue and observed productive viral replication in cadaver samples and eye organoid cultures, most notably in limbal regions. Transcriptional analysis of ex vivo infected ocular surface cells and hESC-derived eye cultures revealed robust induction of NF-κB in infected cells as well as diminished type I/III interferon signaling. Together these data suggest that the eye can be directly infected by SARS-CoV-2 and implicate limbus as a portal for viral entry.

Reference

https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(21)00186-7

Engineering mesenchymal stromal cells with neutralizing and anti-inflammatory capability against SARS-CoV-2 infection

The emergence of the novel human severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has led to the pandemic of coronavirus disease 2019 (COVID-19), which has markedly affected global health and economy. Both uncontrolled viral replication

and proinflammatory cytokine storm can cause severe tissue damage in patients with COVID-19. SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) as its entry receptor. In this study, ACE2 extracellular domain-Fc and scFv-IL6R-Fc fusion proteins were generated to differentially neutralize viruses and ameliorate the cytokine storm. The hACE21-740-Fc fusion protein showed a potent inhibitory effect on pseudotyped SARS-CoV-2 entry and a good safety profile in mice. In addition, scFv-IL6R-Fc strongly blocked interleukin-6 signal activation. It was also established a mesenchymal stromal cell MSC-based hACE21-740-Fc and scFv-IL6R-Fc delivery system, which could serve as a potential therapy strategy for urgent clinical needs of patients with COVID-19.

Reference

https://www.cell.com/molecular-therapy-family/methods/fulltext/S2329-0501(21)00088-7

SARS-CoV-2 genomic surveillance identifies naturally occurring truncation of ORF7a that limits immune suppression

Over 950,000 whole genome sequences of SARS-CoV-2 have been determined for viruses isolated from around the world. These sequences have been critical for understanding the spread and evolution of SARS-CoV-2. Using global phylogenomics, we show that mutations frequently occur in the C-terminal end of ORF7a. One of these mutant viruses from a patient sample were isolated and used viral challenge experiments to link this isolate (ORF7aΔ115) to a growth defect. ORF7a has been implicated in immune modulation, and it was shown that the C-terminal truncation negates anti-immune activities of the protein, which results in elevated type I interferon response to the viral infection. Collectively, this work indicates that ORF7a mutations occur frequently and that these changes affect viral mechanisms responsible for suppressing the immune response.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00543-X

PERSPECTIVE

Publication Date: May 18, 2021

COVID-19 vaccines: Progress and understanding on quality control and evaluation

The outbreak of COVID-19 has posed a huge threat to global health and economy. Countermeasures have revolutionized norms for working, socializing, learning, and travel. Importantly, vaccines have been considered as most effective tools to combat with COVID-19. As of the beginning of 2021, >200 COVID-19 vaccine candidates, covering nearly all existing technologies and platforms, are being research and development (R&D) by multiple manufacturers worldwide. This has posed a huge obstacle to the quality control and evaluation of those candidate vaccines, especially in China, where five vaccine platforms are deployed in parallel. To accelerate the R&D progress of COVID-19 vaccines, the guidances on R&D of COVID-19 vaccine have been issued by National Regulatory Authorities or organizations worldwide. The Center for Drug Evaluation and national quality control laboratory in China have played a leading role in launching the research on quality control and evaluation in collaboration with relevant laboratories involved in the vaccine R&D, which greatly supported the progression of vaccines R&D, and accelerated the approval for emergency use and conditional marketing of currently vaccine candidates. In this paper, the progress and experience gained in quality control and evaluation of COVID-19 vaccines developed in China are summarized, which might provide references for the R&D of current and next generation of COVID-19 vaccines worldwide.

Reference

https://www.nature.com/articles/s41392-021-00621-4

NEWS LETTER

Publication Date: May 19, 2021

Mix-and-match COVID vaccines trigger potent immune response

Vaccinating people with both the Oxford–AstraZeneca and Pfizer–BioNTech COVID-19 vaccines produces a potent immune response against the virus SARS-CoV-2, researchers conducting a study in Spain have found. Preliminary results from the trial of more than 600 people are the first to show the benefits of combining different coronavirus vaccines. A UK trial of a similar strategy reported safety data last week, and is expected to deliver further findings on immune responses soon.

Because of safety concerns, several European countries are already recommending that some or all people who were given a first dose of the vaccine developed by the University of Oxford, UK, and AstraZeneca in Cambridge, UK, get another vaccine for their second dose. Researchers hope that such mix-and-match COVID-19 vaccination regimens will trigger stronger, more robust immune responses than will two doses of a single vaccine, while simplifying immunization efforts for countries facing fluctuating supplies of the various vaccines. It appears that the Pfizer vaccine boosted antibody responses remarkably in one-dose AstraZeneca vaccines. This is all around wonderful news," says Zhou Xing, an immunologist at McMaster University in Hamilton, Canada. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-021-01359-3

Publication Date: May 17, 2021

COVID vaccines can block variant hitting Asia, lab study finds

First detected in India last October, the variant B.1.617 was this year linked to a rapid rise in cases in a handful of Indian states and has now been found in more than 40 countries. The subtypes B.1.617.1 and B.1.617.2 have both been detected with increasing frequency in India in the past few months; both carry two mutations linked to

increased transmissibility. Because of their quick spread, scientists are keen to find out whether the various forms of B.1.617 undermine COVID-19 vaccines.

For their experiments, Suthar and his team used B.1.617.1 itself, making their assay a ‘gold standard’ test for vaccine efficacy. The researchers combined the virus with antibody-laden blood serum from people who had received either the Pfizer vaccine or that made by Moderna of Cambridge, Massachusetts, both based on mRNA. This allowed the team to study how well antibodies induced by vaccination could ‘neutralize’ the virus, or block it from infecting cells. The team’s data show that antibodies generated by vaccination are seven times less effective at blocking B.1.617.1 than at neutralizing the coronavirus strain that circulated early in the pandemic. But antibodies from all 25 vaccinated people were able to neutralize B.1.617.1 to some extent. Hence, these assays using live SARS-CoV-2 offer a hope that the vaccines made by Pfizer and Moderna will protect against a viral strain first seen in India.

Reference

https://www.nature.com/articles/d41586-021-01359-3

HIGHLIGHTS

Publication Date: May 18, 2021

SARS-CoV-2 vaccines: Anamnestic response in previously infected recipients

The continued evolution of SARS-CoV-2 has raised questions regarding the ability of prior immunity to early pandemic strains to afford protection against emerging variants. In a recent study, Stamatatos *et al.* demonstrate that currently approved mRNA vaccines elicit antibodies capable of neutralizing heterologous antigen and they further show that single-dose vaccination triggers an anamnestic response in individuals with pre-existing anti-RBD IgG developed through previous SARS-CoV-2 infection. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41422-021-00516-7

PERSONAL VIEW

Publication Date: Apr 18, 2021

Ongoing and future COVID-19 vaccine clinical trials: challenges and opportunities

Large-scale deployment of COVID-19 vaccines will seriously affect the ongoing phases 2 and 3 randomised placebo-controlled trials assessing SARS-CoV-2 vaccine candidates. The effect will be particularly acute in high-income countries where the entire adult or older population could be vaccinated by late 2021. Regrettably, only a small proportion of the population in many low-income and middle-income countries will have access to available vaccines. Sponsors of COVID-19 vaccine candidates currently in phase 2 or initiating phase 3 trials in 2021 should consider continuing the research in countries with limited affordability and availability of COVID-19 vaccines. Several ethical principles must be implemented to ensure the equitable, non-exploitative, and respectful conduct of trials in resource-poor settings. Once sufficient knowledge on the immunogenicity response to COVID-19 vaccines is acquired, non-inferiority immunogenicity trials—comparing the immune response of a vaccine candidate to that of an authorised vaccine—would probably be the most common trial design. Until then, placebo-controlled, double-blind, crossover trials will continue to play a role in the development of new vaccine candidates. WHO or the Council for International Organizations of Medical Sciences should define an ethical framework for the requirements and benefits for trial participants and host communities in resource-poor settings that should require commitment from all vaccine candidate sponsors from high-income countries.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00263-2/fulltext