

COVID-19

Mar 11-17, 2021



RESEARCH PUBLICATIONS

Publication Date: Mar 17, 2021

Common variants at 21q22.3 locus influence *MX1* and *TMPRSS2* gene expression and susceptibility to severe COVID-19

Abstract

The established risk factors of coronavirus disease 2019 (COVID-19) are advanced age, male sex and comorbidities, but they do not fully explain the wide spectrum of disease manifestations. Genetic factors implicated in the host antiviral response provide for novel insights into its pathogenesis.

An in-depth genetic analysis of chromosome 21 exploiting the genome-wide association study data was performed, including 6,406 individuals hospitalized for COVID-19 and 902,088 controls with European genetic ancestry from the COVID-19 Host Genetics Initiative. It was found that five single nucleotide polymorphisms within *TMPRSS2* and near *MX1* gene show associations with severe COVID-19. The minor alleles of the five SNPs correlated with a reduced risk of developing severe COVID-19 and high level of *MX1* expression in blood. The findings demonstrate that host genetic factors can influence the different clinical presentations of COVID-19 and that *MX1* could be a potential therapeutic target.

Reference

[https://www.cell.com/science/fulltext/S2589-0042\(21\)00290-X](https://www.cell.com/science/fulltext/S2589-0042(21)00290-X)

Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19

Abstract

COVID-19 has been associated with cardiac injury and dysfunction. While both myocardial inflammatory cell infiltration and myocarditis with myocyte injury have been reported in patients with fatal COVID-19, clinical–pathologic correlations remain limited. The objective was to determine the relationships between cardiac pathological changes in patients dying from COVID-19 and cardiac infection by SARS-CoV-2, laboratory measurements, clinical features, and treatments. In a retrospective study, 41 consecutive autopsies of patients with fatal COVID-19 were analyzed for the associations between cardiac inflammation, myocarditis, cardiac infection by SARS-CoV-2, clinical features, laboratory measurements, and treatments. Cardiac infection was assessed by in situ hybridization and NanoString transcriptomic profiling. Cardiac infection by SARS-CoV-2 was present in 30/41 cases: virus+ with myocarditis (n = 4), virus+ without myocarditis (n = 26), and virus– without myocarditis (n = 11). In the cases with cardiac infection, SARS-CoV-2+ cells in the myocardium were rare, with a median density of 1 cell/cm². Virus+ cases showed higher densities of myocardial CD68+ macrophages and CD3+ lymphocytes, as well as more electrocardiographic changes (23/27 vs 4/10; P = 0.01). Myocarditis was more prevalent with IL-6 blockade than with nonbiologic immunosuppression, primarily glucocorticoids (2/3 vs 0/14; P = 0.02). Overall, SARS-CoV-2 cardiac infection was less prevalent in patients treated with nonbiologic immunosuppression (7/14 vs 21/24; P = 0.02). Myocardial macrophage and lymphocyte densities overall were positively correlated with the duration of symptoms but not with underlying comorbidities. In summary, cardiac infection with SARS-CoV-2 is common among patients dying from COVID-19 but often with only rare infected cells. Cardiac infection by SARS-CoV-2 is associated with more cardiac inflammation and electrocardiographic changes. Nonbiologic immunosuppression is associated with lower incidences of myocarditis and cardiac infection by SARS-CoV-2.

Reference

<https://www.nature.com/articles/s41379-021-00790-1>

Evaluation of reopening strategies for educational institutions during COVID-19 through agent based simulation

Abstract

Many educational institutions have partially or fully closed all operations to cope with the challenges of the ongoing COVID-19 pandemic. In this paper, strategies were explored that such institutions can adopt to conduct safe reopening and resume operations during the pandemic. The research is motivated by the University of Illinois at Urbana-Champaign's (UIUC's) SHIELD program, which is a set of policies and strategies, including rapid saliva-based COVID-19 screening, for ensuring safety of students, faculty and staff to conduct in-person operations, at least partially. Specifically, we study how rapid bulk testing, contact tracing and preventative measures such as mask wearing, sanitization, and enforcement of social distancing can allow institutions to manage the epidemic spread. This work combines the power of analytical epidemic modeling, data analysis and agent-based simulations to derive policy insights. An analytical model was developed that takes into account the asymptomatic transmission of COVID-19, the effect of isolation via testing (both in bulk and through contact tracing) and the rate of contacts among people within and outside the institution. Next, data were used from the UIUC SHIELD program and 85 other universities to estimate parameters that describe the analytical model. Using the estimated parameters, finally agent-based simulations were conducted with various model parameters to evaluate testing and reopening strategies. The parameter estimates from UIUC and other universities show similar trends. For example, infection rates at various institutions grow rapidly in certain months and this growth correlates positively with infection rates in counties where the universities are located. Infection rates are also shown to be negatively correlated with testing rates at the institutions. Through agent-based simulations, we demonstrate that the key to designing an effective reopening strategy is a combination of rapid bulk testing and effective preventative measures such as mask wearing and social distancing. Multiple other factors help to reduce infection load, such as efficient contact tracing, reduced delay between testing and result revelation, tests with less false negatives and targeted testing of high-risk class among others. This paper contributes to the nascent literature on combating the COVID-19 pandemic and is especially relevant for educational institutions and similarly large organizations. An

analytical model was provided that can be used to estimate key parameters from data, which in turn can be used to simulate the effect of different strategies for reopening. The relative effect of different strategies was quantified such as bulk testing, contact tracing, reduced infectivity and contact rates in the context of educational institutions. Specifically, it was shown that for the estimated average base infectivity of 0.025 ($R_0 = 1.82$), a daily number of tests to population ratio T/N of 0.2, i.e., once a week testing for all individuals, is a good indicative threshold. However, this test to population ratio is sensitive to external infectivities, internal and external mobilities, delay in getting results after testing, and measures related to mask wearing and sanitization, which affect the base infection rate.

Reference

<https://www.nature.com/articles/s41598-021-84192-y>

Structural basis for bivalent binding and inhibition of SARS-CoV-2 infection by human potent neutralizing antibodies

Abstract

Neutralizing monoclonal antibodies (nAbs) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represent promising candidates for clinical intervention against coronavirus disease 2019 (COVID-19). A large number of nAbs were isolated from SARS-CoV-2-infected individuals capable of disrupting proper interaction between the receptor binding domain (RBD) of the viral spike (S) protein and the receptor angiotensin converting enzyme 2 (ACE2). However, the structural basis for their potent neutralizing activity remains unclear. Here, we report cryo-EM structures of the ten most potent nAbs in their native full-length IgG-form or in both IgG-form and Fab-form bound to the trimeric S protein of SARS-CoV-2. The bivalent binding of the full-length IgG is found to associate with more RBDs in the “up” conformation than the monovalent binding of Fab, perhaps contributing to the enhanced neutralizing activity of IgG and triggering more shedding of the S1 subunit from the S protein. Comparison of a large number of nAbs identified common and unique structural features associated with their potent neutralizing activities. This work provides a structural basis for further understanding the mechanism of nAbs, especially through revealing the bivalent binding and its correlation with more potent neutralization and the shedding of S1 subunit.

Reference

<https://www.nature.com/articles/s41422-021-00487-9>

A conserved immunogenic and vulnerable site on the coronavirus spike protein delineated by cross-reactive monoclonal antibodies

Abstract

The coronavirus spike glycoprotein, located on the virion surface, is the key mediator of cell entry and the focus for development of protective antibodies and vaccines. Structural studies show exposed sites on the spike trimer that might be targeted by antibodies with cross-species specificity. Here two human monoclonal antibodies were isolated from immunized humanized mice that display a remarkable cross-reactivity against distinct spike proteins of betacoronaviruses including SARS-CoV, SARS-CoV-2, MERS-CoV and the endemic human coronavirus HCoV-OC43. Both cross-reactive antibodies target the stem helix in the spike S2 fusion subunit which, in the prefusion conformation of trimeric spike, forms a surface exposed membrane-proximal helical bundle. Both antibodies block MERS-CoV infection in cells and provide protection to mice from lethal MERS-CoV challenge in prophylactic and/or therapeutic models. The work highlights an immunogenic and vulnerable site on the betacoronavirus spike protein enabling elicitation of antibodies with unusual binding breadth.

Reference

<https://www.nature.com/articles/s41467-021-21968-w>

Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): An investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial

Abstract

Background: In patients with COVID-19, granulocyte-macrophage colony stimulating factor (GM-CSF) might be a mediator of the hyperactive inflammatory response associated with respiratory failure and death. It was aimed to evaluate whether mavrilimumab, a monoclonal antibody to the GM-CSF receptor, would improve outcomes in patients with COVID-19 pneumonia and systemic hyperinflammation.

Methods: This investigator-initiated, multicentre, double-blind, randomised trial was done at seven hospitals in the USA. Inclusion required hospitalisation, COVID-19 pneumonia, hypoxaemia, and a C-reactive protein concentration of more than 5 mg/dL. Patients were excluded if they required mechanical ventilation. Patients were randomly assigned (1:1) centrally, with stratification by hospital site, to receive mavrimumab 6 mg/kg as a single intravenous infusion, or placebo. Participants and all clinical and research personnel were masked to treatment assignment. The primary endpoint was the proportion of patients alive and off supplemental oxygen therapy at day 14. The primary outcome and safety were analysed in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT04399980, NCT04463004, and NCT04492514.

Findings: Between May 28 and Sept 15, 2020, 40 patients were enrolled and randomly assigned to mavrimumab (n=21) or placebo (n=19). A trial of 60 patients was planned, but given slow enrolment, the study was stopped early to inform the natural history and potential treatment effect. At day 14, 12 (57%) patients in the mavrimumab group were alive and off supplemental oxygen therapy compared with nine (47%) patients in the placebo group (odds ratio 1.48 [95% CI 0.43–5.16]; p=0.76). There were no treatment-related deaths, and adverse events were similar between groups.

Interpretation: There was no significant difference in the proportion of patients alive and off oxygen therapy at day 14, although benefit or harm of mavrimumab therapy in this patient population remains possible given the wide confidence intervals, and larger trials should be completed.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(21\)00070-9/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00070-9/fulltext)

Excess mortality for men and women above age 70 according to level of care during the first wave of COVID-19 pandemic in Sweden: A population-based study

Abstract

Background: Both age and comorbidity are established risk factors for death among those infected with COVID-19. Because they often co-exist, it is difficult to assess if age is a risk factor on its own.

Methods: An administrative register data was used of the total Swedish population from 01/2015 until 07/2020. The population aged 70+ was stratified into three groups according to level of care (in care homes, with home care, and in independent living). Within these groups, the level of excess mortality in 2020 was explored by estimating expected mortality with Poisson regression and compared it to observed levels. It was investigated if excess mortality has been of the same magnitude in the three groups, and if age constitutes a risk factor for death during the pandemic regardless of level of care.

Findings: Individuals living in care homes experienced the highest excess mortality (75–>100% in April, 25–50% in May, 0–25% in June, depending on age). Individuals with home care showed the second highest magnitude (30–60% in April, 15–40% in May, 0–25% in June), while individuals in independent living experienced excess primarily at the highest ages (5–50% in April, 5–50% in May, 0–25% in June). Although mortality rates increased, the age-pattern of mortality during the pandemic resembled the age-pattern observed in previous years.

Interpretation: Stepwise elevated excess mortality was found by level of care during the first wave of the COVID-19 pandemic in Sweden, suggesting that level of frailty or comorbidities plays a more important role than age for COVID-19 associated deaths. Part of our findings are likely attributable to differences in exposure to the virus between individuals receiving formal care and those living independently, and not only different case fatality between the groups. Although age is a strong predictor for mortality, the relative effect of age on mortality was no different during the pandemic than before. It was believe that this is an important contribution to the discussion of the pandemic, its consequences, and which groups need the most protection.

Reference

[https://www.thelancet.com/journals/lanepi/article/PIIS2666-7762\(21\)00049-1/fulltext](https://www.thelancet.com/journals/lanepi/article/PIIS2666-7762(21)00049-1/fulltext)

Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: A population-level observational study

Abstract

Background: The degree to which infection with SARS-CoV-2 confers protection towards subsequent reinfection is not well described. In 2020, as part of Denmark's extensive, free-of-charge PCR-testing strategy, approximately 4 million individuals (69% of the population) underwent 10.6 million tests. Using these national PCR-test data from 2020, we estimated protection towards repeat infection with SARS-CoV-2.

Methods: In this population-level observational study, we collected individual-level data on patients who had been tested in Denmark in 2020 from the Danish Microbiology Database and analysed infection rates during the second surge of the COVID-19 epidemic, from Sept 1 to Dec 31, 2020, by comparison of infection rates between individuals with positive and negative PCR tests during the first surge (March to May, 2020). For the main analysis, we excluded people who tested positive for the first time between the two surges and those who died before the second surge. We did an alternative cohort analysis, in which infection rates were compared throughout the year between those with and without a previous confirmed infection at least 3 months earlier, irrespective of date. It was also investigated whether differences were found by age group, sex, and time since infection in the alternative cohort analysis. Rate ratios (RRs) adjusted for potential confounders and estimated protection against repeat infection as $1 - \text{RR}$, were calculated.

Findings: During the first surge (ie, before June, 2020), 533 381 people were tested, of whom 11 727 (2.20%) were PCR positive, and 525 339 were eligible for follow-up in the second surge, of whom 11 068 (2.11%) had tested positive during the first surge. Among eligible PCR-positive individuals from the first surge of the epidemic, 72 (0.65% [95% CI 0.51–0.82]) tested positive again during the second surge compared with 16 819 (3.27% [3.22–3.32]) of 514 271 who tested negative during the first surge (adjusted RR 0.195 [95% CI 0.155–0.246]). Protection against repeat infection was 80.5% (95% CI 75.4–84.5). The alternative cohort analysis gave similar estimates (adjusted RR 0.212 [0.179–0.251], estimated protection 78.8% [74.9–82.1]). In the

alternative cohort analysis, among those aged 65 years and older, observed protection against repeat infection was 47·1% (95% CI 24·7–62·8). We found no difference in estimated protection against repeat infection by sex (male 78·4% [72·1–83·2] vs female 79·1% [73·9–83·3]) or evidence of waning protection over time (3–6 months of follow-up 79·3% [74·4–83·3] vs ≥7 months of follow-up 77·7% [70·9–82·9]).

Interpretation: The findings could inform decisions on which groups should be vaccinated and advocate for vaccination of previously infected individuals because natural protection, especially among older people, cannot be relied on.

Reference

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00575-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00575-4/fulltext)

SARS-CoV-2 infection and transmission in primary schools in England in June–December, 2020 (sKIDs): An active, prospective surveillance study

Abstract

Background: Little is known about the risk of SARS-CoV-2 infection and transmission in educational settings. Public Health England initiated a study, COVID-19 Surveillance in School KIDs (sKIDs), in primary schools when they partially reopened from June 1, 2020, after the first national lockdown in England to estimate the incidence of symptomatic and asymptomatic SARS-CoV-2 infection, seroprevalence, and seroconversion in staff and students.

Methods: sKIDs, an active, prospective, surveillance study, included two groups: the weekly swabbing group and the blood sampling group. The swabbing group underwent weekly nasal swabs for at least 4 weeks after partial school reopening during the summer half-term (June to mid-July, 2020). The blood sampling group additionally underwent blood sampling for serum SARS-CoV-2 antibodies to measure previous infection at the beginning (June 1–19, 2020) and end (July 3–23, 2020) of the summer half-term, and, after full reopening in September, 2020, and at the end of the autumn term (Nov 23–Dec 18, 2020). Predictors of SARS-CoV-2 antibody positivity using logistic regression, were tested. Antibody seroconversion rates for participants were calculated, who were seronegative in the first round and were tested in at least two rounds.

Findings: During the summer half-term, 11 966 participants (6727 students, 4628 staff, and 611 with unknown staff or student status) in 131 schools had 40 501 swabs taken. Weekly SARS-CoV-2 infection rates were 4.1 (one of 24 463; 95% CI 0.1–21.8) per 100 000 students and 12.5 (two of 16 038; 1.5–45.0) per 100 000 staff. At recruitment, in 45 schools, 91 (11.2%; 95% CI 7.9–15.1) of 816 students and 209 (15.1%; 11.9–18.9) of 1381 staff members were positive for SARS-CoV-2 antibodies, similar to local community seroprevalence. Seropositivity was not associated with school attendance during lockdown ($p=0.13$ for students and $p=0.20$ for staff) or staff contact with students ($p=0.37$). At the end of the summer half-term, 603 (73.9%) of 816 students and 1015 (73.5%) of 1381 staff members were still participating in the surveillance, and five (four students, one staff member) seroconverted. By December, 2020, 55 (5.1%; 95% CI 3.8–6.5) of 1085 participants who were seronegative at recruitment (in June, 2020) had seroconverted, including 19 (5.6%; 3.4–8.6) of 340 students and 36 (4.8%; 3.4–6.6) of 745 staff members ($p=0.60$).

Interpretation: In England, SARS-CoV-2 infection rates were low in primary schools following their partial and full reopening in June and September, 2020.

Reference

[https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(21\)00061-4/fulltext](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00061-4/fulltext)

Publication Date: Mar 16, 2021

Neutralizing and protective human monoclonal antibodies recognizing the N-terminal domain of the SARS-CoV-2 spike protein

Abstract

Most human monoclonal antibodies (mAbs) neutralizing SARS-CoV-2 recognize the spike (S) protein receptor-binding domain and block virus interactions with the cellular receptor angiotensin-converting enzyme 2. A panel of human mAbs binding were described to diverse epitopes on the N-terminal domain (NTD) of S protein from SARS-CoV-2 convalescent donors and found a minority of these possessed neutralizing activity. Two mAbs (COV2-2676 and COV2-2489) inhibited infection of authentic SARS-CoV-2 and recombinant VSV/SARS-CoV-2 viruses. Their binding epitopes were mapped by alanine-scanning mutagenesis and selection of functional SARS-CoV-2 S

neutralization escape variants. Mechanistic studies showed that these antibodies neutralize in part by inhibiting a post-attachment step in the infection cycle. COV2-2676 and COV2-2489 offered protection either as prophylaxis or therapy, and Fc effector functions were required for optimal protection. Thus, natural infection induces a subset of potent NTD-specific mAbs that leverage neutralizing and Fc-mediated activities to protect against SARS-CoV-2 infection using multiple functional attributes.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00357-3](https://www.cell.com/cell/fulltext/S0092-8674(21)00357-3)

A dual antibody test for accurate surveillance of SARS-CoV-2 exposure rates

Abstract

As Nasal swabs followed by reverse-transcription polymerase chain reaction (RT-PCR) detection of SARS-CoV-2 have been at the forefront of screening programs to identify and isolate COVID-19 cases. However, the requirement for specialized laboratories and trained personnel limits testing capacity. The broad range of COVID-19 clinical manifestations, including asymptomatic infections, has further disrupted traditional epidemiological surveillance, with confirmed COVID-19 cases likely capturing only a subset of the true exposure rate. Population-based serological assays can aid the quantification of the proportion of the population presenting antibodies against SARS-CoV-2 and thus exposed and potentially immune. Due to the delay in antibody production in response to infection, antibody testing is not a suitable screening tool. However, antibody testing has a critical role in successful epidemic surveillance, implementation of public health and containment measures, and evaluation of the impact of these measures.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00039-2](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00039-2)

Virological and immunological features of SARS-CoV-2-infected children who develop neutralizing antibodies

Abstract

As the global COVID-19 pandemic progresses, it is paramount to gain knowledge on adaptive immunity to SARS-CoV-2 in children to define immune correlates of protection upon immunization or infection. Anti-SARS-CoV-2 antibodies and their neutralizing activity (PRNT) were analyzed in 66 COVID-19-infected children at 7 (± 2) days after symptom onset. Individuals with specific humoral responses presented faster virus clearance and lower viral load associated with a reduced in vitro infectivity. It was demonstrated that the frequencies of SARS-CoV-2-specific CD4⁺CD40L⁺ T cells and Spike-specific B cells were associated with the anti-SARS-CoV-2 antibodies and the magnitude of neutralizing activity. The plasma proteome confirmed the association between cellular and humoral SARS-CoV-2 immunity, and PRNT⁺ patients show higher viral signal transduction molecules (SLAMF1, CD244, CLEC4G). This work sheds lights on cellular and humoral anti-SARS-CoV-2 responses in children, which may drive future vaccination trial endpoints and quarantine measures policies.

Reference

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(21\)00166-2](https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00166-2)

N-Terminal domain antigenic mapping reveals a site of vulnerability for SARS-CoV-2

Abstract

SARS-CoV-2 spike (S) glycoprotein contains an immunodominant receptor-binding domain (RBD) targeted by most neutralizing antibodies (Abs) in COVID-19 patient plasma. Little is known about neutralizing Abs binding to epitopes outside the RBD and their contribution to protection. Here, we describe 41 human monoclonal Abs (mAbs) derived from memory B cells, which recognize the SARS-CoV-2 S N-terminal domain (NTD) and show that a subset of them neutralize SARS-CoV-2 ultrapotently. An antigenic map of the SARS-CoV-2 NTD was defined and identifies a supersite (designated site i) recognized by all known NTD-specific neutralizing mAbs. These mAbs inhibit cell-to-cell fusion, activate effector functions, and protect Syrian hamsters

from SARS-CoV-2 challenge, albeit selecting escape mutants in some animals. Indeed, several SARS-CoV-2 variants, including the B.1.1.7, B.1.351 and P1 lineages, harbor frequent mutations within the NTD supersite suggesting ongoing selective pressure and the importance of NTD-specific neutralizing mAbs for protective immunity and vaccine design.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00356-1](https://www.cell.com/cell/fulltext/S0092-8674(21)00356-1)

SARS-CoV-2 evolution in an immunocompromised host reveals shared neutralization escape mechanisms

Abstract

Many individuals mount nearly identical antibody responses to SARS-CoV-2. To gain insight into how the viral spike (S) protein receptor-binding domain (RBD) might evolve in response to common antibody responses, mutations were studied occurring during virus evolution in a persistently infected immunocompromised individual. Antibody Fab/RBD structures were used to predict, and pseudotypes to confirm, that mutations found in late-stage evolved S variants confer resistance to a common class of SARS-CoV-2 neutralizing antibodies we isolated from a healthy COVID-19 convalescent donor. Resistance extends to the polyclonal serum immunoglobulins of four out of four healthy convalescent donors we tested and to monoclonal antibodies in clinical use. It was further shown that affinity maturation is unimportant for wildtype virus neutralization but is critical to neutralization breadth. As the mutations we studied foreshadowed emerging variants that are now circulating across the globe, our results have implications to the long-term efficacy of S-directed countermeasures.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00355-X](https://www.cell.com/cell/fulltext/S0092-8674(21)00355-X)

BET inhibition blocks inflammation-induced cardiac dysfunction and SARS-CoV-2 infection

Abstract

Cardiac injury and dysfunction occur in COVID-19 patients and increase the risk of mortality. Causes are ill defined, but could be direct cardiac infection and/or inflammation-induced dysfunction. To identify mechanisms and cardio-protective drugs, we use a state-of-the-art pipeline combining human cardiac organoids with phosphoproteomics and single nuclei RNA sequencing. An inflammatory ‘cytokine-storm’, a cocktail of interferon gamma, interleukin 1 β and poly(I:C), induced diastolic dysfunction were identified. Bromodomain-containing protein 4 is activated along with a viral response that is consistent in both human cardiac organoids and hearts of SARS-CoV-2 infected K18-hACE2 mice. Bromodomain and extraterminal family inhibitors (BETi) recover dysfunction in hCO and completely prevent cardiac dysfunction and death in a mouse cytokine-storm model. Additionally, BETi decreases transcription of genes in the viral response, decreases ACE2 expression and reduces SARS-CoV-2 infection of cardiomyocytes. Together, BETi, including the FDA breakthrough designated drug apabetalone, are promising candidates to prevent COVID-19 mediated cardiac damage.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00354-8](https://www.cell.com/cell/fulltext/S0092-8674(21)00354-8)

The impact of environmental variables on the spread of COVID-19 in the Republic of Korea

Abstract

Corona virus disease 2019 (COVID-19) has been declared a global pandemic and is a major public health concern worldwide. In this study, the role of environmental factors was determined, such as climate and air pollutants, in the transmission of COVID-19 in the Republic of Korea. We collected epidemiological and environmental data from two regions of the Republic of Korea, namely Seoul metropolitan region (SMR) and Daegu-Gyeongbuk region (DGR) from February 2020 to July 2020. The data was then analyzed to identify correlations between each environmental factor with confirmed daily

COVID-19 cases. Among the various environmental parameters, the duration of sunshine and ozone level were found to positively correlate with COVID-19 cases in both regions. However, the association of temperature variables with COVID-19 transmission revealed contradictory results when comparing the data from SMR and DGR. Moreover, statistical bias may have arisen due to an extensive epidemiological investigation and altered socio-behaviors that occurred in response to a COVID-19 outbreak. Nevertheless, our results suggest that various environmental factors may play a role in COVID-19 transmission.

Reference

<https://www.nature.com/articles/s41598-021-85493-y>

Myoglobin and C-reactive protein are efficient and reliable early predictors of COVID-19 associated mortality

Abstract

Since the emergence of SARS-CoV-2, numerous studies have been attempting to determine biomarkers, which could rapidly and efficiently predict COVID-19 severity, however there is lack of consensus on a specific one. This retrospective cohort study is a comprehensive analysis of the initial symptoms, comorbidities and laboratory evaluation of patients, diagnosed with COVID-19 in Huoshenshan Hospital, Wuhan, from 4th February to 12th March, 2020. Based on the data collected from 63 severely ill patients from the onset of symptoms till the full recovery or demise, we found not only age (average 70) but also blood indicators as significant risk factors associated with multiple organ failure. The blood indices of all patients showed hepatic, renal, cardiac and hematopoietic dysfunction with imbalanced coagulatory biomarkers. It was noticed that the levels of LDH (85%, $P < .001$), HBDH (76%, $P < .001$) and CRP (65%, $P < .001$) were significantly elevated in deceased patients, indicating hepatic impairment. Similarly, increased CK (15%, $P = .002$), Cre (37%, $P = 0.102$) and CysC (74%, $P = 0.384$) indicated renal damage. Cardiac injury was obvious from the significantly elevated level of Myoglobin (52%, $P < .01$), Troponin-I (65%, $P = 0.273$) and BNP (50%, $P = .787$). SARS-CoV-2 disturbs the hemolymphatic system as WBC# (73%, $P = .002$) and NEUT# (78%, $P < .001$) were significantly elevated in deceased patients. Likewise, the level of D-dimer (80%, $P < .171$), PT (87%, $P = .031$) and TT (57%, $P = .053$) was

elevated, indicating coagulatory imbalances. Myoglobin and CRP were identified as specific risk factors related to mortality and highly correlated to organ failure in COVID-19 disease.

Reference

<https://www.nature.com/articles/s41598-021-85426-9>

Metabolic dysfunction and immunometabolism in COVID-19 pathophysiology and therapeutics

Abstract

The COVID-19 pandemic has emerged as a public health crisis and has placed a significant burden on healthcare systems. Patients with underlying metabolic dysfunction, such as type 2 diabetes mellitus and obesity, are at a higher risk for COVID-19 complications, including multi-organ dysfunction, secondary to a deranged immune response, and cellular energy deprivation. These patients are at a baseline state of chronic inflammation associated with increased susceptibility to the severe immune manifestations of COVID-19, which are triggered by the cellular hypoxic environment and cytokine storm. The altered metabolic profile and energy generation of immune cells affect their activation, exacerbating the imbalanced immune response. Key immunometabolic interactions may inform the development of an efficacious treatment for COVID-19. Novel therapeutic approaches with repurposed drugs, such as PPAR agonists, or newly developed molecules such as the antagomirs, which block microRNA function, have shown promising results. Those treatments, alone or in combination, target both immune and metabolic pathways and are ideal for septic COVID-19 patients with an underlying metabolic condition.

Reference

<https://www.nature.com/articles/s41366-021-00804-7>

Learning from HIV-1 to predict the immunogenicity of T cell epitopes in SARS-CoV-2

Abstract

A physics-based learning model was described for predicting the immunogenicity of Cytotoxic-T-Lymphocyte (CTL) epitopes derived from diverse pathogens including SARS-CoV-2. The model was trained and optimized on the relative immunodominance of CTL epitopes in Human Immunodeficiency Virus infection. Its accuracy was tested against experimental data from COVID-19 patients. The model predicts that only some SARS-CoV-2 epitopes predicted to bind to HLA molecules are immunogenic. The immunogenic CTL epitopes across all SARS-CoV-2 proteins are predicted to provide broad population coverage, but those from the SARS-CoV-2 spike protein alone are unlikely to do so. The model also predicts that several immunogenic SARS-CoV-2 CTL epitopes are identical to seasonal coronaviruses circulating in the population and such cross-reactive CD8+ T cells can indeed be detected in pre-pandemic blood donors, suggesting that some level of CTL immunity against COVID-19 may be present in some individuals prior to SARS-CoV-2 infection.

Reference

[https://www.cell.com/iscience/fulltext/S2589-0042\(21\)00279-0](https://www.cell.com/iscience/fulltext/S2589-0042(21)00279-0)

Therapeutic potential of metformin in COVID-19: Reasoning for its protective role

Abstract

SARS-CoV-2 infections present with increased disease severity and poor clinical outcomes in diabetic patients compared with their non-diabetic counterparts. Diabetes/hyperglycemia-triggered endothelial dysfunction and hyperactive inflammatory and immune responses are correlated to two- to three-fold higher intensive care hospitalizations and more than twice the mortality among diabetic COVID-19 patients. While comorbidities such as obesity, cardiovascular disease, and hypertension worsen the prognosis of diabetic COVID-19 patients, COVID-19 infections are also associated

with new-onset diabetes, severe metabolic complications, and increased thrombotic events in the backdrop of aberrant endothelial function. While several antidiabetic medications are used to manage blood glucose levels, the multi-faceted ability of metformin was discussed to control blood glucose levels, attenuate endothelial dysfunction, inhibit viral entry, and infection and modify inflammatory and immune responses during SARS-CoV-2 infections. These actions make it a viable candidate for drug repurposing and the higher ground against the SARS-CoV-2 induced tsunami in diabetic COVID-19 patients.

Reference

[https://www.cell.com/trends/microbiology/fulltext/S0966-842X\(21\)00063-9](https://www.cell.com/trends/microbiology/fulltext/S0966-842X(21)00063-9)

Publication Date: Mar 12, 2021

The silent pandemic: Emergent antibiotic resistances following the global response to SARS-CoV-2

Abstract

The ongoing SARS-CoV-2 pandemic has highlighted the importance of the rapid development of vaccines and antivirals. However, the potential for the emergence of antibiotic resistances due to the increased use of antibacterial cleaning products and therapeutics presents an additional, underreported threat. Most antibacterial cleaners contain simple quaternary ammonium compounds (QACs), however these compounds are steadily becoming less effective as antibacterial agents. QACs are extensively used in SARS-CoV-2 related sanitization in clinical and household settings. Similarly, due to the danger of secondary infections, antibiotic therapeutics are increasingly used as a component of COVID-19 treatment regimens, even in the absence of a bacterial infection diagnosis. The increased use of antibacterial agents as cleaners and therapeutics is anticipated to lead to novel resistances in the coming years.

Reference

[https://www.cell.com/iscience/fulltext/S2589-0042\(21\)00272-8](https://www.cell.com/iscience/fulltext/S2589-0042(21)00272-8)

Potent SARS-CoV-2 neutralizing antibodies directed against spike N-terminal domain target a single supersite

Abstract

Numerous antibodies that neutralize SARS-CoV-2 have been identified, and these generally target either the receptor-binding domain (RBD) or the N-terminal domain (NTD) of the viral spike. While RBD-directed antibodies have been extensively studied, far less is known about NTD-directed antibodies. Here cryo-EM and crystal structures for seven potent NTD-directed neutralizing antibodies were reported in the complex with spike or isolated NTD. These structures defined several antibody classes, with at least one observed in multiple convalescent donors. The structures revealed all seven antibodies target a common surface, bordered by glycans N17, N74, N122, and N149. This site – formed primarily by a mobile β -hairpin and several flexible loops – was highly electropositive, located at the periphery of the spike, and the largest glycan-free surface of NTD facing away from the viral membrane. Thus, in contrast to neutralizing RBD-directed antibodies that recognize multiple non-overlapping epitopes, potent NTD-directed neutralizing antibodies appear to target a single supersite.

Reference

[https://www.cell.com/cell-host-microbe/fulltext/S1931-3128\(21\)00133-5](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00133-5)

Linear epitope landscape of the SARS-CoV-2 Spike protein constructed from 1,051 COVID-19 patients

Abstract

To fully decipher the immunogenicity of the SARS-CoV-2 Spike protein, it is essential to assess which part is highly immunogenic in a systematic way. A linear epitope landscape of the Spike protein was generated by analysing the serum IgG response of 1,051 COVID-19 patients with a peptide microarray. Two regions were revealed that were rich in linear epitopes, *i.e.*, CTD and a region close to the S2' cleavage site and fusion peptide. Unexpectedly, It was found that the RBD lacks linear epitope. We reveal that the number of responsive peptides is highly variable among patients and correlates with disease severity. Some peptides are moderately associated with severity and clinical outcome. By immunizing mice, linear-epitope-specific antibodies were obtained;

however, no significant neutralizing activity against the authentic virus was observed for these antibodies. This landscape will facilitate our understanding of SARS-CoV-2-specific humoral responses and might be useful for vaccine refinement.

Reference

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(21\)00229-1](https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00229-1)

Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity

Abstract

Vaccination elicits immune responses capable of potently neutralizing SARS-CoV-2. However, ongoing surveillance has revealed the emergence of variants harboring mutations in spike, the main target of neutralizing antibodies. To understand the impact of these variants, we evaluated the neutralization potency of 99 individuals that received one or two doses of either BNT162b2 or mRNA-1273 vaccines against pseudoviruses representing 10 globally circulating strains of SARS-CoV-2. Five of the 10 pseudoviruses, harboring receptor-binding domain mutations, including K417N/T, E484K, and N501Y, were highly resistant to neutralization. Cross-neutralization of B.1.351 variants was comparable to SARS-CoV and bat-derived WIV1-CoV, suggesting that a relatively small number of mutations can mediate potent escape from vaccine responses. While the clinical impact of neutralization resistance remains uncertain, these results highlight the potential for variants to escape from neutralizing humoral immunity and emphasize the need to develop broadly protective interventions against the evolving pandemic.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00298-1](https://www.cell.com/cell/fulltext/S0092-8674(21)00298-1)

Longitudinal profiling of respiratory and systemic immune responses reveals myeloid cell-driven lung inflammation in severe COVID-19

Abstract

Immune response dynamics in COVID-19 and its severe manifestations have largely been studied in circulation. Here, the relationship between immune processes were examined in the respiratory tract and circulation through longitudinal phenotypic, transcriptomic and cytokine profiling of paired airway and blood samples from patients with severe COVID-19 relative to healthy controls. In COVID-19 airways, T cells exhibited activated, tissue-resident, and protective profiles; higher T cell frequencies correlated with survival and younger age. Myeloid cells in COVID-19 airways featured hyper-inflammatory signatures and higher frequencies of these cells correlated with mortality and older age. In COVID-19 blood, aberrant CD163+ monocytes predominated over conventional monocytes, and were found in corresponding airway samples and in damaged alveoli. High levels of myeloid chemoattractants in airways suggest recruitment of these cells through a CCL2-CCR2 chemokine axis. The findings provide insights into immune processes driving COVID-19 lung pathology with therapeutic implications for targeting inflammation in the respiratory tract.

Reference

[https://www.cell.com/immunity/fulltext/S1074-7613\(21\)00117-5](https://www.cell.com/immunity/fulltext/S1074-7613(21)00117-5)

New dimensions for hospital services and early detection of disease: A Review from the Lancet Commission into liver disease in the UK

Abstract

This Review, in addressing the unacceptably high mortality of patients with liver disease admitted to acute hospitals, reinforces the need for integrated clinical services. The masterplan described is based on regional, geographically sited liver centres, each linked to four to six surrounding district general hospitals—a pattern of care similar to that successfully introduced for stroke services. The plan includes the establishment of a lead and deputy lead clinician in each acute hospital, preferably a hepatologist or gastroenterologist with a special interest in liver disease, who will have prime

responsibility for organising the care of admitted patients with liver disease on a 24/7 basis. Essential for the plan is greater access to intensive care units and high-dependency units, in line with the reconfiguration of emergency care due to the COVID-19 pandemic. This Review strongly recommends full implementation of alcohol care teams in hospitals and improved working links with acute medical services. Recommendations from paediatric liver services were endorsed to improve overall survival figures by diagnosing biliary atresia earlier based on stool colour charts and better caring for patients with impaired cognitive ability and developmental mental health problems. Pilot studies of earlier diagnosis have shown encouraging progress, with 5–6% of previously undiagnosed cases of severe fibrosis or cirrhosis identified through use of a portable FibroScan in primary care. Similar approaches to the detection of early asymptomatic disease are described in accounts from the devolved nations, and the potential of digital technology in improving the value of clinical consultation and screening programmes in primary care is highlighted. The striking contribution of comorbidities, particularly obesity and diabetes (with excess alcohol consumption known to be a major factor in obesity), to mortality in COVID-19 reinforces the need for fiscal and other long delayed regulatory measures to reduce the prevalence of obesity. These measures include the food sugar levy and the introduction of the minimum unit price policy to reduce alcohol consumption. Improving public health, this Review emphasises, will not only mitigate the severity of further waves of COVID-19, but is crucial to reducing the unacceptable burden from liver disease in the UK.

Reference

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32396-5/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32396-5/fulltext)

Discovery and functional interrogation of SARS-CoV-2 RNA-host protein interactions

Abstract

SARS-CoV-2 is the cause of a pandemic with growing global mortality. Using comprehensive identification of RNA-binding proteins by mass spectrometry (ChIRP-MS), 309 host proteins were identified that bind the SARS-CoV-2 RNA during active infection. Integration of this data with ChIRP-MS data from three other RNA viruses defined viral specificity of RNA-host protein interactions. Targeted CRISPR screens

revealed that the majority of functional RNA-binding proteins protect the host from virus-induced cell death, and comparative CRISPR screens across seven RNA viruses revealed shared and SARS-specific antiviral factors. Finally, by combining the RNA-centric approach and functional CRISPR screens, a physical and functional connection between SARS-CoV-2 and mitochondria were demonstrated, highlighting this organelle as a general platform for antiviral activity. Altogether, these data provide a comprehensive catalog of functional SARS-CoV-2 RNA-host protein interactions, which may inform studies to understand the host-virus interface and nominate host pathways that could be targeted for therapeutic benefit.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00297-X](https://www.cell.com/cell/fulltext/S0092-8674(21)00297-X)

CORRESPONDANCE

Publication Date: Mar 17, 2021

Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice

The novel coronavirus SARS-CoV-2 has infected more than 104 million individuals and resulted in more than 2.2 million deaths worldwide as of February 7, 2021 (<https://covid19.who.int>). The COVID-19 pandemic highlights the need for safe and effective vaccines against SARS-CoV-2 infection. Several licensed vaccines and multiple vaccine candidates currently in clinical trials have shown different strengths and weaknesses (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>). Herein, the pilot-scale production of a recombinant subunit vaccine (RBD-Fc Vacc) was reported with the receptor-binding domain of the SARS-CoV-2 S protein fused with the Fc domain of human IgG1. The immunogenicity of the SARS-CoV-2 RBD, which is located in the S1 subunit and is crucial in mediating viral entry into host cells by binding to the ACE2 receptor, has been determined to induce neutralizing antibodies without evident antibody-dependent enhancement effects¹ and can protect animals against SARS-CoV-2 infection². The Fc fusion protein has been recently used as an important backbone for drug development due to its advantages of rapid purification, a relatively long half-life, and the ability to increase the immunogenicity of target antigens³. In addition, Fc promotes the correct folding of the fusion protein and enhances binding to antigen-presenting cells⁴. We have previously developed Fc-fused protein vaccines against MERS, SARS-CoV, and H5N1 influenza and found that Fc-fused proteins are more immunogenic than those lacking fused Fc^{5,6}. The advantages of recombinant protein vaccines, including safety (no viral genome integration, which ensures safe handling) and higher cost efficiency than other types of vaccines⁷, make them competitive vaccine candidates. In the present study, a recombinant vaccine containing an RBD-Fc fusion (RBD-Fc Vacc) was developed, which is currently being assessed in randomized controlled phase I/II human clinical trials. In this study, the data showed the efficacy of RBD-Fc Vacc in protecting against SARS-CoV-2 infection in nonhuman primates and mice. For more details, read the link given below.

Reference

<https://www.nature.com/articles/s41423-021-00658-z>

Malnutrition risk in hospitalised COVID-19 patients receiving CPAP

Continuous positive airway pressure (CPAP) that is delivered by face mask or hood is increasingly used in patients with COVID-19 who have been admitted to hospital, often on general or respiratory wards. Oral intake of food and drink in patients with COVID-19 might have been and will often continue to be poor due to disease-associated anorexia, nausea, and impairment of taste. Full-face or hood CPAP also makes it impossible to eat and drink without mask removal, which can be associated with decreased arterial oxygen saturation. Staff might also fear that the use of nasogastric feeding can cause mask air leaks or promote gastric distension and aspiration due to aerophagia.

Such issues are in fact readily managed, and the British Association for Parenteral and Enteral Nutrition has produced practical guidelines. However, NHS England and NHS Improvement advocate opioid administration when CPAP is used to reduce the sensation of breathlessness and high tidal volumes, an intervention that can impair gut motility. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00447-5/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00447-5/fulltext)

Publication Date: Mar 16, 2021

Brazil: Boost COVID-19 vaccine uptake in Indigenous people

Low uptake of COVID-19 vaccination in Brazil's Indigenous people is concerning: death rates from the disease in these communities are estimated to be more than double the national average. Urgent action to increase vaccination must counter misinformation, build trust and ensure easy access.

Acceptance rates to COVID-19 vaccines go from almost 90% in China to less than 55% in Russia, and are around 85% in Brazil. Rates also vary between ethnic groups. So far, six million Brazilians have been vaccinated. Indigenous people are a priority group. But only around half of them have been vaccinated. Reserved doses have been released to others, such as non-Indigenous elderly people. Practical difficulties with the roll-out are

compounded by the spread of frightening fake news through social media in these communities, fuelled by anti-science rhetoric at the highest levels. It is imperative that regional and local leaders co-develop communication and education programmes about coronavirus vaccination with communities to protect people from misinformation ('pre-bunking') and to debunk it. The Articulation of Indigenous Peoples of Brazil has been leading the way. For more details, read the link given below.

Reference

<https://www.nature.com/articles/d41586-021-00689-6>

Placebo use and unblinding in COVID-19 vaccine trials: Recommendations of a WHO Expert Working Group

The Working Group has concluded that although there is a scientific imperative to continue trials of vaccines against COVID-19 after a candidate vaccine is granted an EUD, there is also an ethical imperative to ensure that trial participants who are at substantial risk of infection with the coronavirus SARS-CoV-2, and severe COVID-19 morbidity or mortality—such as healthcare workers at high to very high risk of acquiring and transmitting the disease, and people above 65 years of age—are in a position to access an EUD vaccine as soon as practically possible, should they wish to do so. Candidate vaccines granted an EUD will probably be deployed in a phased manner to ensure the prioritization of those deemed to be at considerable risk. In settings in which candidate vaccines are introduced under an EUD, investigators should explain the scientific benefit of continued trial participation and the implications of unblinding to trial participants deemed to be at substantial risk of infection, severe morbidity or mortality. Participants should then be offered the opportunity to be unblinded, so that they can make an informed decision about whether to withdraw from the trial and access an EUD vaccine programmatically as soon as practically possible, should they wish to do so. Trial participants who are not deemed to be at substantial risk of SARS-CoV-2 infection and COVID-19 morbidity or mortality and who do not meet prevailing eligibility criteria to access a candidate vaccine granted an EUD should be informed of the scientific benefits of continuing with the trial and should be encouraged to remain enrolled, with full acknowledgment of their right to withdraw from a trial at any point, without penalty. The continued enrollment of as many participants as possible, for as long as possible,

will have considerable scientific and public health utility, as doing so will yield invaluable longer-term data on the safety and efficacy of candidate vaccines. Continued enrollment could also highlight the potential risk of emerging variants of SARS-CoV-2 of concern in relation to those previously unexposed to the virus, those previously infected and recent vaccinees. For more details, read the link given below.

Reference

<https://www.nature.com/articles/s41591-021-01299-5>

Arthritis after SARS-CoV-2 infection

In COVID-19, the pivotal cytokines that provoke severe disease in the lung are similar to those usually targeted by drugs used for treating rheumatoid arthritis. Although COVID-19 is not yet considered as a trigger for rheumatoid arthritis, this similarity has led to the suspicion that COVID-19 might be a risk factor for inducing a rheumatoid arthritis flare. Recently, arthralgia and arthritis have been reported after SARS-CoV-2 infection in three patients that were negative for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). In this Correspondence, a man was described who developed arthritis after COVID-19.

On February 20, 2020, a 67-year-old non-smoking man attended a routine clinical check-up at the Shymkent Medical Center for Joint Diseases in Shymkent (Kazakhstan). He did not complain of any joint pain or swelling and testing for RF, which was requested as a routine evaluation, was negative. On May 26, 2020, he developed fever, anosmia, shortness of breath, and weakness: chest x-rays showed bilateral interstitial pneumonia (appendix p 1) with 83% oxygen saturation. An RT-PCR for SARS-CoV-2 was positive, and the patient was diagnosed with COVID-19. On June 1, 2020, he was admitted to a provisional COVID-19 hospital in Shymkent (Kazakhstan). After 7 days of treatment with ceftriaxone (1 g per day for 4 days), azithromycin (0.5 g per day for 4 days), and non-steroidal anti-inflammatory drugs (three ibuprofen tablets taken per day when necessary), he was discharged from hospital. On July 2, 2020, he developed morning stiffness (>30 min) and symmetric polyarthritis of the knees and hands (appendix p 2). Testing showed a Disease Activity Score of 28 joints with C-reactive protein (DAS28-CRP) of 7.35. Furthermore, a high RF concentration (411 IU/mL, normal range <18 IU/mL), a high erythrocyte sedimentation rate (59 mm/h), and

a high concentration of CRP (55 mg/L, normal range <5 mg/L) were reported, but ACPA concentration was low (19.2 U/mL, normal range <20 U/mL). A serological anti-SARS-CoV-2 rapid test (COVID-19 IgG/IgM antibody test; Humasis, Anyang, Korea) was positive for IgG and IgA. A diagnosis of early rheumatoid arthritis was made, and treatment with methotrexate (15 mg per week) and methylprednisolone (8 mg per day) was started. After 1 month, the patient's erythrocyte sedimentation rate was 28 mm/h, and the concentration of CRP was reduced but still high (18 mg/L), with a low joint DAS28-CRP of 2.8. An x-ray did not show any parenchymal lesions (appendix p 1), but a chest CT (appendix p 3) detected residual signs of polysegmental pneumonia in the resolution stage, chronic bronchitis, and emphysema. A quantitative serological SARS-CoV-2 antibody test was negative for IgA (0.1 conventional units) but positive for IgG (13.3 conventional units). ACPA concentration was high (104 U/mL). In October 2020, the patient was still receiving treatment with methotrexate and methylprednisolone, was in remission (DAS28-CRP 2.2), and he returned to work.

The patient survived COVID-19 with a standard treatment approach. An association between COVID-19 and the onset of reactive arthritis has been previously postulated.² Approximately 1 month after the resolution of COVID-19 symptoms, the patient developed arthritis with a high RF and, almost 5 months later, a progressive increase of ACPA. However, it is unknown if the persistence of SARS-CoV-2 infection, detected in this patient with the CT via signs of pneumonia in a resolution phase, could have been a factor triggering the onset of arthritis. Moreover, the response to methotrexate and corticosteroids was satisfactory, with remission of joint disease when the patient was still positive for IgG and IgA anti-SARS-CoV-2 antibodies. This case might suggest that SARS-CoV-2 was involved in triggering RF-positive and ACPA-positive arthritis, which might be diagnosed as rheumatoid arthritis, but we cannot rule out the possibility that the onset of this arthritis could have been coincidental. However, previous reports of the presence of autoantibodies after SARS-CoV-2 infection might suggest that this virus might also act as a trigger of arthritis or other autoimmune diseases. Long-term observation of patients affected by COVID-19 might provide an answer to this challenging question.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(21\)00067-9/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00067-9/fulltext)

COMMENT

Publication Date: Mar 17, 2021

COVID-19 highlights the model dilemma in biomedical research

Scientists worldwide struggle to identify suitable animal models to study SARS-CoV-2 infections. Interspecies-related differences, such as host specificity, divergent immune responses, or the unavailability of species-specific reagents hamper the research. Human-based models, such as micro-engineered multi-organs-on-chip, may hold the solution. For more details, read the link given below.

Reference

<https://www.nature.com/articles/s41578-021-00305-z>

Granulocyte-macrophage colony stimulating factor in COVID-19: Friend or foe?

A biphasic model of COVID-19 is now well-established, with an initial viraemic phase, followed by a host hyperinflammatory phase in a subgroup of patients with an inappropriate, excessive immune response associated with high mortality, which might respond to immunomodulatory therapy. Randomised controlled trials (eg, RECOVERY and REMAP-CAP) have shown the efficacy of corticosteroids and interleukin (IL)-6 blockade in reducing mortality in patients with severe COVID-19, although there have been mixed results with IL-6 inhibition.

Granulocyte-macrophage colony stimulating factor (GM-CSF) is an immunoregulatory cytokine that exemplifies the complexity and challenges of drug trials in COVID-19, given its role in both the pro-inflammatory hypercytokinaemia leading to monocyte and macrophage activation, and in antiviral immunity. There is rationale for both therapeutic blockade and recombinant administration of GM-CSF, and there is accumulating evidence for targeting GM-CSF in patients with severe COVID-19. Bronchoalveolar lavage fluid analysis from patients with severe COVID-19 has shown clonally expanded tissue-resident memory-like Th17 cells with a potentially pathogenic profile of cytokine expression of GM-CSF and IL-17A; these memory-like Th17 cells are thought to interact with lung macrophages and cytotoxic CD8⁺ T cells, and are associated with disease severity and lung damage.⁶ High GM-CSF protein concentrations in the serum of

patients with COVID-19 is associated with a more severe clinical course. Additionally, inhibiting GM-CSF might have advantages over targeting IL-6 with respect to safety, because there might be less pronounced pharmacodynamic suppression of C-reactive protein and fever, which can facilitate the detection of secondary infection. Cohort studies have shown an efficacy signal for drugs targeting GM-CSF (lenzilumab) or its receptor (mavrilimumab), but robust controlled trial data have been eagerly anticipated. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(21\)00078-3/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00078-3/fulltext)

REPORT

Publication Date: Mar 17, 2021

A single intranasal dose of chimpanzee adenovirus-vectored vaccine protects against SARS-CoV-2 infection in rhesus macaques

Abstract

The deployment of a vaccine that limits transmission and disease likely will be required to end the Coronavirus Disease 2019 (COVID-19) pandemic. The protective activity of an intranasally-administered chimpanzee adenovirus-vectored vaccine was described, encoding a pre-fusion stabilized spike (S) protein (ChAd-SARS-CoV-2-S) in the upper and lower respiratory tract of mice expressing the human angiotensin-converting enzyme 2 (ACE2) receptor. Here, the immunogenicity and protective efficacy of this vaccine was shown in non-human primates. Rhesus macaques were immunized with ChAd-Control or ChAd-SARS-CoV-2-S and challenged one month later by combined intranasal and intrabronchial routes with SARS-CoV-2. A single intranasal dose of ChAd-SARS-CoV-2-S induces neutralizing antibodies and T cell responses and limits or prevents infection in the upper and lower respiratory tract after SARS-CoV-2 challenge. As this single intranasal dose vaccine confers protection against SARS-CoV-2 in non-human primates, it is a promising candidate for limiting SARS-CoV-2 infection and transmission in humans.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00046-X](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00046-X)

Antiviral drug screen identifies DNA-damage response inhibitor as potent blocker of SARS-CoV-2 replication

SARS-CoV-2 has currently precipitated the COVID-19 global health crisis. A medium-throughput drug screening system was developed and identified a small molecule library of 34 of 430 protein kinase inhibitors that were capable of inhibiting SARS-CoV-2 cytopathic effect in human epithelial cells. These drug inhibitors are in various stages of clinical trials. We detected key proteins involved in cellular signaling pathways mTOR-PI3K-AKT, ABL-BCR/MAPK, and DNA-Damage Response that are critical for SARS-

CoV-2 infection. A drug-protein interaction based secondary screen confirmed compounds such as the ATR kinase inhibitor berzosertib and torin2 with anti SARS-CoV-2 activity. Berzosertib exhibited potent antiviral activity against SARS-CoV-2 in multiple cell types and blocked replication at post-entry step. Berzosertib inhibited replication of SARS-CoV-1 and MERS-CoV as well. The study highlights key promising kinase inhibitors to constrain coronavirus replication as a host-directed therapy in the treatment of COVID-19 and beyond as well as provides an important mechanism of host-pathogen interactions.

Reference

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(21\)00254-0](https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00254-0)

Publication Date: Mar 16, 2021

Structural impact on SARS-CoV-2 spike protein by D614G substitution

Substitution for aspartic acid by glycine at position 614 in the spike (S) protein of severe acute respiratory syndrome coronavirus 2 appears to facilitate rapid viral spread. The G614 strain and its recent variants are now the dominant circulating forms. It was reported here cryo-EM structures of a full-length G614 S trimer, which adopts three distinct prefusion conformations differing primarily by the position of one receptor-binding domain. A loop disordered in the D614 S trimer wedges between domains within a protomer in the G614 spike. This added interaction appears to prevent premature dissociation of the G614 trimer, effectively increasing the number of functional spikes and enhancing infectivity, and to modulate structural rearrangements for membrane fusion. These findings extend the understanding of viral entry and suggest an improved immunogen for vaccine development.

Reference

<https://science.sciencemag.org/content/early/2021/03/16/science.abf2303>

Bacterial pulmonary superinfections are associated with longer duration of ventilation in critically ill COVID-19 patients

Abstract

The impact of secondary bacterial infections (superinfections) in COVID-19 is not well understood. In this prospective monocentric cohort study, it was aimed to investigate the impact of superinfections in COVID-19 patients with acute respiratory distress syndrome. Patients are assessed for concomitant microbial infections by longitudinal analysis of tracheobronchial secretions, bronchoalveolar lavages and blood cultures. In 45 critically ill patients, we identify 19 patients with superinfections (42.2%). Superinfections are detected on day 10 after intensive care admission. The proportion of participants alive and off invasive mechanical ventilation at study day 28 (ventilator-free days (VFDs) at 28 days) is substantially lower in patients with superinfection (subhazard ratio 0.37, 95%-CI 0.15-0.90, $p=0.028$). Patients with pulmonary superinfections have a higher incidence of bacteraemia, virus reactivations, yeast colonization, and required intensive care treatment for a longer time. Superinfections are frequent and associated with reduced VFDs at 28 days despite a high rate of empirical antibiotic therapy.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00045-8](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00045-8)

Long-term persistence of RBD-positive memory B cells encoding neutralising antibodies in SARS-CoV-2 infection

Abstract

Considerable concerns relating to the duration of protective immunity against SARS-CoV-2 exist, with evidence of antibody titres declining rapidly after infection and reports of reinfection. Here the antibody responses were monitored against SARS-CoV-2 receptor binding domain (RBD) for up to six months after infection. While antibody titres are maintained, about 13% of the cohort's neutralising responses return to background. However, encouragingly in a selected subset of 13 participants, 12 have detectable RBD-specific memory B cells and these generally are increasing out to 6 months.

Furthermore, we are able to generate monoclonal antibodies with SARS-CoV-2 neutralising capacity from these memory B cells. Overall the study suggests that the loss of neutralising antibodies in plasma may be countered by the maintenance of neutralising capacity in the memory B cell repertoire.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00044-6](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00044-6)

SPOTLIGHT

Publication Date: Mar 16, 2021

High COVID-19 death rates in prisons in England and Wales, and the need for early vaccination

Institutional settings such as prisons are high-risk environments for infectious disease outbreaks and need to be given high priority in the rollout of COVID-19 vaccines. Prisons are typically overcrowded, access to sanitation is inconsistent, and people in prisons have contact with a large staff pool.

Early modelling suggested a worst-case scenario of more than 77 000 COVID-19 cases and 2000 deaths in prisons across England and Wales, if explosive prison outbreaks were not prevented. From March, 2020, UK prisons implemented extensive physical distancing and infection control measures. For example, many people in prison have been required to remain in their cells for 23 h per day for the past year, family visits have not been permitted, and many education, work, and rehabilitation opportunities have been stopped. Other changes have included reduced transfers of people between prisons and cohorting or quarantining those who are vulnerable, symptomatic, or returning from hospital.

Reference

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(21\)00137-5/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00137-5/fulltext)