

COVID-19

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RESEARCH PUBLICATIONS

Publication Date: Feb 10, 2021

mRNA Vaccine-elicited antibodies to SARS-CoV-2 and circulating variants

Abstract

The antibody and memory B cell responses of a cohort of 20 volunteers was reported, who have received the Moderna (mRNA-1273) or Pfizer–BioNTech (BNT162b2) vaccine against SARS-CoV-2. Eight weeks after the second injection of vaccine, volunteers showed high levels of IgM and IgG anti-SARS-CoV-2 spike protein (S) and receptor-binding-domain (RBD) binding titre. Moreover, the plasma neutralizing activity and relative numbers of RBD-specific memory B cells of vaccinated volunteers were equivalent to those of individuals who had recovered from natural infection. However, activity against SARS-CoV-2 variants that encode E484K-, N501Y- or K417N/E484K/N501-mutant S was reduced by a small—but significant—margin. The monoclonal antibodies elicited by the vaccines potently neutralize SARS-CoV-2, and target a number of different RBD epitopes in common with monoclonal antibodies isolated from infected donors. However, neutralization by 14 of the 17 most-potent monoclonal antibodies that we tested was reduced or abolished by the K417N, E484K or N501Y mutation. Notably, these mutations were selected when we cultured recombinant vesicular stomatitis virus expressing SARS-CoV-2 S in the presence of the monoclonal antibodies elicited by the vaccines. Together, these results suggest that the monoclonal antibodies in clinical use should be tested against newly arising variants, and that mRNA vaccines may need to be updated periodically to avoid a potential loss of clinical efficacy.

Reference

<https://www.nature.com/articles/s41586-021-03324-6>

Morphometry of SARS-CoV and SARS-CoV-2 particles in ultrathin plastic sections of infected Vero cell cultures

Abstract

SARS-CoV-2 is the causative of the COVID-19 disease, which has spread pandemically around the globe within a few months. It is therefore necessary to collect fundamental information about the disease, its epidemiology and treatment, as well as about the virus itself. While the virus has been identified rapidly, detailed ultrastructural analysis of virus cell biology and architecture is still in its infancy. The virus morphology and morphometry of SARS-CoV-2 was therefore studied in comparison to SARS-CoV as it appears in Vero cell cultures by using conventional thin section electron microscopy and electron tomography. Both virus isolates, SARS-CoV Frankfurt 1 and SARS-CoV-2 Italy-INMI1, were virtually identical at the ultrastructural level and revealed a very similar particle size distribution with a median of about 100 nm without spikes. Maximal spike length of both viruses was 23 nm. The number of spikes per virus particle was about 30% higher in the SARS-CoV than in the SARS-CoV-2 isolate. This result complements a previous qualitative finding, which was related to a lower productivity of SARS-CoV-2 in cell culture in comparison to SARS-CoV.

Reference

<https://www.nature.com/articles/s41598-021-82852-7>

Role of IgG against N-protein of SARS-CoV2 in COVID19 clinical outcomes

Abstract

The Nucleocapsid Protein (N Protein) of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2) is located in the viral core. Immunoglobulin G (IgG) targeting N protein is detectable in the serum of infected patients. The effect of high titers of IgG against N-protein on clinical outcomes of SARS-CoV2 disease has not been described. We studied 400 RT-PCR confirmed SARS-CoV2 patients to determine independent factors associated with poor outcomes, including Medical Intensive Care Unit (MICU) admission, prolonged MICU stay and hospital admissions, and in-hospital mortality. Serum IgG against the N protein and correlated its concentrations with clinical outcomes were also measured. It was found that several factors, including Charlson

comorbidity Index (CCI), high levels of IL6, and presentation with dyspnea were associated with poor clinical outcomes. It was shown that higher CCI and higher IL6 levels were independently associated with in-hospital mortality. Anti-N protein IgG was detected in the serum of 55 (55%) patients at the time of admission. A high concentration of antibodies, defined as signal to cut off ratio (S/Co) > 1.5 (75 percentile of all measurements), was found in 25 (25%) patients. The multivariable logistic regression models showed that between being an African American, higher CCI, lymphocyte counts, and S/Co ratio > 1.5, only S/Co ratio were independently associated with MICU admission and longer length of stay in hospital. This study recommends that titers of IgG targeting N-protein of SARS-CoV2 at admission is a prognostic factor for the clinical course of disease and should be measured in all patients with SARS-CoV2 infection.

Reference

<https://www.nature.com/articles/s41598-021-83108-0>

Rapid seroconversion and persistent functional IgG antibodies in severe COVID-19 patients correlates with an IL-12p70 and IL-33 signature

Abstract

Despite ongoing efforts to characterize the host response toward SARS-CoV-2, a major gap in our knowledge still exists regarding the magnitude and duration of the humoral response. Analysis of the antibody response in mild versus moderate/severe patients, using our new developed quantitative electrochemiluminescent assay for detecting IgM/IgA/IgG antibodies toward SARS-CoV-2 antigens, revealed a rapid onset of IgG/IgA antibodies, specifically in moderate/severe patients. IgM antibodies against the viral receptor binding domain, but not against nucleocapsid protein, were detected at early stages of the disease. Furthermore, we observed a marked reduction in IgM/IgA antibodies over-time. Adapting our assay for ACE2 binding-competition, demonstrated that the presence of potentially neutralizing antibodies is correlated with IgG/IgA. Finally, analysis of the cytokine profile in COVID-19 patients revealed unique correlation of an IL-12p70/IL33 and IgG seroconversion, which correlated with disease severity. In summary, our comprehensive analysis has major implications on the understanding and monitoring of SARS-CoV-2 infections.

Reference

<https://www.nature.com/articles/s41598-021-83019-0>

Genomic mutations and changes in protein secondary structure and solvent accessibility of SARS-CoV-2 (COVID-19 virus)

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic virus that has caused the global COVID-19 pandemic. Tracing the evolution and transmission of the virus is crucial to respond to and control the pandemic through appropriate intervention strategies. This paper reports and analyses genomic mutations in the coding regions of SARS-CoV-2 and their probable protein secondary structure and solvent accessibility changes, which are predicted using deep learning models. Prediction results suggest that mutation D614G in the virus spike protein, which has attracted much attention from researchers, is unlikely to make changes in protein secondary structure and relative solvent accessibility. Based on 6324 viral genome sequences, we create a spreadsheet dataset of point mutations that can facilitate the investigation of SARS-CoV-2 in many perspectives, especially in tracing the evolution and worldwide spread of the virus. Our analysis results also show that coding genes E, M, ORF6, ORF7a, ORF7b and ORF10 are most stable, potentially suitable to be targeted for vaccine and drug development.

Reference

<https://www.nature.com/articles/s41598-021-83105-3>

Potential health and economic impacts of dexamethasone treatment for patients with COVID-19

Abstract

Dexamethasone can reduce mortality in hospitalised COVID-19 patients needing oxygen and ventilation by 18% and 36%, respectively. Here, we estimate the potential number of lives saved and life years gained if this treatment were to be rolled out in the UK and globally, as well as the cost-effectiveness of implementing this intervention. Assuming SARS-CoV-2 exposure levels of 5% to 15%, we estimate that, for the UK, approximately 12,000 (4,250 - 27,000) lives could be saved between July and

December 2020. Assuming that dexamethasone has a similar effect size in settings where access to oxygen therapies is limited, this would translate into approximately 650,000 (240,000 - 1,400,000) lives saved globally over the same time period. If dexamethasone acts differently in these settings, the impact could be less than half of this value. To estimate the full potential of dexamethasone in the global fight against COVID-19, it is essential to perform clinical research in settings with limited access to oxygen and/or ventilators, for example in low- and middle-income countries.

Reference

<https://www.nature.com/articles/s41467-021-21134-2>

Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: A randomized, double-blind, placebo-controlled phase 2 trial

Abstract

Treatment of severe Coronavirus Disease 2019 (COVID-19) is challenging. We performed a phase 2 trial to assess the efficacy and safety of human umbilical cord-mesenchymal stem cells (UC-MSCs) to treat severe COVID-19 patients with lung damage, based on our phase 1 data. In this randomized, double-blind, and placebo-controlled trial, we recruited 101 severe COVID-19 patients with lung damage. They were randomly assigned at a 2:1 ratio to receive either UC-MSCs (4×10^7 cells per infusion) or placebo on day 0, 3, and 6. The primary endpoint was an altered proportion of whole lung lesion volumes from baseline to day 28. Other imaging outcomes, 6-minute walk test (6-MWT), maximum vital capacity, diffusing capacity, and adverse events were recorded and analyzed. In all, 100 COVID-19 patients were finally received either UC-MSCs ($n = 65$) or placebo ($n = 35$). UC-MSCs administration exerted numerical improvement in whole lung lesion volume from baseline to day 28 compared with the placebo (the median difference was -13.31% , 95% CI -29.14% , 2.13% , $P = 0.080$). UC-MSCs significantly reduced the proportions of solid component lesion volume compared with the placebo (median difference: -15.45% ; 95% CI -30.82% , -0.39% ; $P = 0.043$). The 6-MWT showed an increased distance in patients treated with UC-MSCs (difference: 27.00 m; 95% CI 0.00 , 57.00 ; $P = 0.057$). The incidence of adverse events was similar in the two groups. These results suggest that UC-MSCs

treatment is a safe and potentially effective therapeutic approach for COVID-19 patients with lung damage. A phase 3 trial is required to evaluate effects on reducing mortality and preventing long-term pulmonary disability.

Reference

<https://www.nature.com/articles/s41392-021-00488-5>

Time-resolved systems immunology reveals a late juncture linked to fatal COVID-19

Abstract

COVID-19 exhibits extensive patient-to-patient heterogeneity. To link immune response variation to disease severity and outcome over time, we longitudinally assessed circulating proteins as well as 188 surface protein markers, transcriptome, and T cell receptor sequence simultaneously in single peripheral immune cells from COVID-19 patients. Conditional-independence network analysis revealed primary correlates of disease severity, including gene expression signatures of apoptosis in plasmacytoid dendritic cells and attenuated inflammation but increased fatty acid metabolism in CD56dimCD16hi NK cells linked positively to circulating interleukin (IL)-15. CD8+ T cell activation was apparent without signs of exhaustion. Although cellular inflammation was depressed in severe patients early after hospitalization, it became elevated by days 17–23 post symptom onset, suggestive of a late wave of inflammatory responses. Furthermore, circulating protein trajectories at this time were divergent between and predictive of recovery versus fatal outcomes. Our findings stress the importance of timing in the analysis, clinical monitoring, and therapeutic intervention of COVID-19.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00168-9](https://www.cell.com/cell/fulltext/S0092-8674(21)00168-9)

Persistence of SARS-CoV-2-specific B and T cell responses in convalescent COVID-19 patients 6–8 months after the infection

Abstract

Background: Monitoring the adaptive immune responses during the natural course of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection provides

useful information for the development of vaccination strategies against this virus and its emerging variants. We thus profiled the serum anti-SARS-CoV-2 antibody (Ab) levels and specific memory B and T cell responses in convalescent coronavirus disease 2019 (COVID-19) patients.

Methods: A total of 119 samples from 88 convalescent donors who experienced mild to critical disease were tested for the presence of elevated anti-spike and anti-receptor binding domain Ab levels over a period of 8 months. In addition, the levels of SARS-CoV-2 neutralizing Abs and specific memory B and T cell responses were tested in a subset of samples.

Findings: Anti-SARS-CoV-2 Abs were present in 85% of the samples collected within 4 weeks after the onset of symptoms in COVID-19 patients. Levels of specific immunoglobulin M (IgM)/IgA Abs declined after 1 month, while levels of specific IgG Abs and plasma neutralizing activities remained relatively stable up to 6 months after diagnosis. Anti-SARS-CoV-2 IgG Abs were still present, although at a significantly lower level, in 80% of the samples collected at 6–8 months after symptom onset. SARS-CoV-2-specific memory B and T cell responses developed with time and were persistent in all of the patients followed up for 6–8 months.

Conclusions: Our data suggest that protective adaptive immunity following natural infection of SARS-CoV-2 may persist for at least 6–8 months, regardless of disease severity. Development of medium- or long-term protective immunity through vaccination may thus be possible.

Reference

[https://www.cell.com/med/fulltext/S2666-6340\(21\)00038-6](https://www.cell.com/med/fulltext/S2666-6340(21)00038-6)

Publication Date: Feb 09, 2021

Tipiracil binds to uridine site and inhibits Nsp15 endoribonuclease NendoU from SARS-CoV-2

Abstract

SARS-CoV-2 Nsp15 is a uridine-specific endoribonuclease with C-terminal catalytic domain belonging to the EndoU family that is highly conserved in coronaviruses. As

endoribonuclease activity seems to be responsible for the interference with the innate immune response, Nsp15 emerges as an attractive target for therapeutic intervention. Here the first structures with bound nucleotides were reported and showed how the enzyme specifically recognizes uridine moiety. In addition to a uridine site we present evidence for a second base binding site that can accommodate any base. The structure with a transition state analog, uridine vanadate, confirms interactions key to catalytic mechanisms. In the presence of manganese ions, the enzyme cleaves unpaired RNAs. This acquired knowledge was instrumental in identifying Tipiracil, an FDA approved drug that is used in the treatment of colorectal cancer, as a potential anti-COVID-19 drug. Using crystallography, biochemical, and whole-cell assays, we demonstrate that Tipiracil inhibits SARS-CoV-2 Nsp15 by interacting with the uridine binding pocket in the enzyme's active site. Our findings provide new insights for the development of uracil scaffold-based drugs.

Reference

<https://www.nature.com/articles/s42003-021-01735-9>

Evidence for SARS-CoV-2 related coronaviruses circulating in bats and pangolins in Southeast Asia

Abstract

Among the many questions unanswered for the COVID-19 pandemic are the origin of SARS-CoV-2 and the potential role of intermediate animal host(s) in the early animal-to-human transmission. The discovery of RaTG13 bat coronavirus in China suggested a high probability of a bat origin. Here we report molecular and serological evidence of SARS-CoV-2 related coronaviruses (SC2r-CoVs) actively circulating in bats in Southeast Asia. Whole genome sequences were obtained from five independent bats (*Rhinolophus acuminatus*) in a Thai cave yielding a single isolate (named RacCS203) which is most related to the RmYN02 isolate found in *Rhinolophus malayanus* in Yunnan, China. SARS-CoV-2 neutralizing antibodies were also detected in bats of the same colony and in a pangolin at a wildlife checkpoint in Southern Thailand. Antisera raised against the receptor binding domain (RBD) of RmYN02 was able to cross-neutralize SARS-CoV-2 despite the fact that the RBD of RacCS203 or RmYN02 failed to bind ACE2. Although the origin of the virus remains unresolved, our study extended

the geographic distribution of genetically diverse SC2r-CoVs from Japan and China to Thailand over a 4800-km range. Cross-border surveillance is urgently needed to find the immediate progenitor virus of SARS-CoV-2.

Reference

<https://www.nature.com/articles/s41467-021-21240-1>

SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801

Abstract

All coronaviruses known to have recently emerged as human pathogens probably originated in bats. Here we use a single experimental platform based on immunodeficient mice implanted with human lung tissue (hereafter, human lung-only mice (LoM)) to demonstrate the efficient *in vivo* replication of severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as well as two endogenous SARS-like bat coronaviruses that show potential for emergence as human pathogens. Virus replication in this model occurs in bona fide human lung tissue and does not require any type of adaptation of the virus or the host. Our results indicate that bats contain endogenous coronaviruses that are capable of direct transmission to humans. The detailed analysis of *in vivo* infection with SARS-CoV-2 in human lung tissue from LoM showed a predominant infection of human lung epithelial cells, including type-2 pneumocytes that are present in alveoli and ciliated airway cells. Acute infection with SARS-CoV-2 was highly cytopathic and induced a robust and sustained type-I interferon and inflammatory cytokine and chemokine response. Finally, we evaluated a therapeutic and pre-exposure prophylaxis strategy for SARS-CoV-2 infection. The results show that therapeutic and prophylactic administration of EIDD-2801—an oral broad-spectrum antiviral agent that is currently in phase II/III clinical trials—markedly inhibited SARS-CoV-2 replication *in vivo*, and thus has considerable potential for the prevention and treatment of COVID-19.

Reference

<https://www.nature.com/articles/s41586-021-03312-w>

Lasting antibody and T cell responses to SARS-CoV-2 in COVID-19 patients three months after infection

Abstract

The dynamics, duration, and nature of immunity produced during SARS-CoV-2 infection are still unclear. Here, virus-neutralising antibody, specific antibodies were longitudinally measured against the spike (S) protein, receptor-binding domain (RBD), and the nucleoprotein (N) of SARS-CoV-2, as well as T cell responses, in 25 SARS-CoV-2-infected patients up to 121 days post-symptom onset (PSO). All patients seroconvert for IgG against N, S, or RBD, as well as IgM against RBD, and produce neutralising antibodies (NAb) by 14 days PSO, with the peak levels attained by 15–30 days PSO. Anti-SARS-CoV-2 IgG and NAb remain detectable and relatively stable 3–4 months PSO, whereas IgM antibody rapidly decay. Approximately 65% of patients have detectable SARS-CoV-2-specific CD4+ or CD8+ T cell responses 3–4 months PSO. Our results thus provide critical evidence that IgG, NAb, and T cell responses persist in the majority of patients for at least 3–4 months after infection.

Reference

<https://www.nature.com/articles/s41467-021-21155-x>

Histone deacetylase inhibitors suppress ACE2 and ABO simultaneously, suggesting a preventive potential against COVID-19

Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide as a pandemic throughout 2020. Since the virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor for cellular entry, increment of ACE2 would lead to an increased risk of SARS-CoV-2 infection. At the same time, an association of the ABO blood group system with COVID-19 has also been highlighted: there is increasing evidence to suggest that non-O individuals are at higher risk of severe COVID-19 than O individuals. These findings imply that simultaneous suppression of ACE2 and ABO would be a promising approach for prevention or treatment of COVID-19. Notably, we have previously clarified that histone deacetylase inhibitors (HDACIs) are able to suppress ABO expression in vitro. Against

this background, it was further evaluated that the effect of HDACIs on cultured epithelial cell lines, and found that HDACIs suppress both ACE2 and ABO expression simultaneously. Furthermore, the amount of ACE2 protein was shown to be decreased by one of the clinically-used HDACIs, panobinostat, which has been reported to reduce B-antigens on cell surfaces. On the basis of these findings, we conclude that panobinostat could have the potential to serve as a preventive drug against COVID-19.

Reference

<https://www.nature.com/articles/s41598-021-82970-2>

Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread within the human population. Although SARS-CoV-2 is a novel coronavirus, most humans had been previously exposed to other antigenically distinct common seasonal human coronaviruses (hCoVs) before the coronavirus disease 2019 (COVID-19) pandemic. Here, we quantified levels of SARS-CoV-2-reactive antibodies and hCoV-reactive antibodies in serum samples collected from 431 humans before the COVID-19 pandemic. We then quantified pre-pandemic antibody levels in serum from a separate cohort of 251 individuals who became PCR-confirmed infected with SARS-CoV-2. Finally, we longitudinally measured hCoV and SARS-CoV-2 antibodies in the serum of hospitalized COVID-19 patients. The studies indicated that most individuals possessed hCoV-reactive antibodies before the COVID-19 pandemic. We determined that ~20% of these individuals possessed non-neutralizing antibodies that cross-reacted with SARS-CoV-2 spike and nucleocapsid proteins. These antibodies were not associated with protection against SARS-CoV-2 infections or hospitalizations, but they were boosted upon SARS-CoV-2 infection.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00160-4](https://www.cell.com/cell/fulltext/S0092-8674(21)00160-4)

In vivo structural characterization of the SARS-CoV-2 RNA genome identifies host proteins vulnerable to repurposed drugs

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the ongoing coronavirus disease 2019 (COVID-19) pandemic. Understanding of the RNA virus and its interactions with host proteins could improve therapeutic interventions for COVID-19. By using icSHAPE, we determined the structural landscape of SARS-CoV-2 RNA in infected human cells and from refolded RNAs, as well as the regulatory untranslated regions of SARS-CoV-2 and six other coronaviruses. Several structural elements predicted *in silico* were validated and discovered structural features that affect the translation and abundance of subgenomic viral RNAs in cells. The structural data informed a deep-learning tool to predict 42 host proteins that bind to SARS-CoV-2 RNA. Strikingly, antisense oligonucleotides targeting the structural elements and FDA-approved drugs inhibiting the SARS-CoV-2 RNA binding proteins dramatically reduced SARS-CoV-2 infection in cells derived from human liver and lung tumors. Our findings thus shed light on coronavirus and reveal multiple candidate therapeutics for COVID-19 treatment.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00160-4](https://www.cell.com/cell/fulltext/S0092-8674(21)00160-4)

COVID-19 Immune signatures reveal stable antiviral T-cell function despite declining humoral responses

Abstract

Cellular and humoral immunity to SARS-CoV-2 is critical to control primary infection and correlates with severity of disease. The role of SARS-CoV-2-specific T cell immunity, its relationship to antibodies, and pre-existing immunity against endemic coronaviruses (huCoV), which has been hypothesized to be protective, were investigated in 82 healthy donors (HDs), 204 recovered (RCs), and 92 active COVID-19 patients (ACs). ACs had high amounts of anti-SARS-CoV-2 nucleocapsid and spike IgG but lymphopenia and overall reduced antiviral T cell responses due to the inflammatory milieu, expression of inhibitory molecules (PD-1, Tim-3) as well as effector caspase-3, -7, and -8 activity in T

cells. SARS-CoV-2-specific T cell immunity conferred by polyfunctional, mainly interferon- γ -secreting CD4⁺ T cells remained stable throughout convalescence, whereas humoral responses declined. Immune responses toward huCoV in RCs with mild disease and strong cellular SARS-CoV-2 T cell reactivity imply a protective role of pre-existing immunity against huCoV.

Reference

[https://www.cell.com/immunity/fulltext/S1074-7613\(21\)00031-5](https://www.cell.com/immunity/fulltext/S1074-7613(21)00031-5)

Nanoluciferase complementation-based bioreporter reveals the importance of N-linked glycosylation of SARS-CoV-2 S for viral entry

Abstract

The ongoing COVID-19 pandemic has highlighted the immediate need for the development of antiviral therapeutics targeting different stages of the SARS-CoV-2 life cycle. A bioluminescence-based bioreporter was developed to interrogate the interaction between the SARS-CoV-2 viral spike (S) protein and its host entry receptor, angiotensin-converting enzyme 2 (ACE2). The bioreporter assay is based on a nanoluciferase complementation reporter, composed of two subunits, large BiT and small BiT, fused to the S receptor-binding domain (RBD) of the SARS-CoV-2 S protein and ACE2 ectodomain, respectively. Using this bioreporter, we uncovered critical host and viral determinants of the interaction, including a role for glycosylation of asparagine residues within the RBD in mediating successful viral entry. The importance of N-linked glycosylation was demonstrated to the RBD's antigenicity and immunogenicity. The study demonstrates the versatility of our bioreporter in mapping key residues mediating viral entry as well as screening inhibitors of the ACE2-RBD interaction. The findings point toward targeting RBD glycosylation for therapeutic and vaccine strategies against SARS-CoV-2.

Reference

[https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016\(21\)00074-5](https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(21)00074-5)

Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera

Abstract

Three severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses were engineered containing key spike mutations from the newly emerged United Kingdom (UK) and South African (SA) variants: N501Y from UK and SA; 69/70-deletion + N501Y + D614G from UK; and E484K + N501Y + D614G from SA. Neutralization geometric mean titers (GMTs) of 20 BNT162b2 vaccine-elicited human sera against the three mutant viruses were 0.81- to 1.46-fold of the GMTs against parental virus, indicating small effects of these mutations on neutralization by sera elicited by two BNT162b2 doses.

Reference

<https://www.nature.com/articles/s41591-021-01270-4>

SARS-CoV-2 D614G spike mutation increases entry efficiency with enhanced ACE2-binding affinity

Abstract

The causative agent of the COVID-19 pandemic, SARS-CoV-2, is steadily mutating during continuous transmission among humans. Such mutations can occur in the spike (S) protein that binds to the ACE2 receptor and is cleaved by TMPRSS2. However, whether S mutations affect SARS-CoV-2 cell entry remains unknown. Here, we show that naturally occurring S mutations can reduce or enhance cell entry via ACE2 and TMPRSS2. A SARS-CoV-2 S-pseudotyped lentivirus exhibits substantially lower entry than that of SARS-CoV S. Among S variants, the D614G mutant shows the highest cell entry, as supported by structural and binding analyses. Nevertheless, the D614G mutation does not affect neutralization by antisera against prototypic viruses. Taken together, we conclude that the D614G mutation increases cell entry by acquiring higher affinity to ACE2 while maintaining neutralization susceptibility. Based on these findings, further worldwide surveillance is required to understand SARS-CoV-2 transmissibility among humans.

Reference

<https://www.nature.com/articles/s41467-021-21118-2>

Potent neutralization of clinical isolates of SARS-CoV-2 D614 and G614 variants by a monomeric, sub-nanomolar affinity nanobody

Abstract

Despite unprecedented global efforts to rapidly develop SARS-CoV-2 treatments, in order to reduce the burden placed on health systems, the situation remains critical. Effective diagnosis, treatment, and prophylactic measures are urgently required to meet global demand: recombinant antibodies fulfill these requirements and have marked clinical potential. Here, we describe the fast-tracked development of an alpaca Nanobody specific for the receptor-binding-domain (RBD) of the SARS-CoV-2 Spike protein with potential therapeutic applicability. A rapid method was presented for nanobody isolation that includes an optimized immunization regimen coupled with VHH library E. coli surface display, which allows single-step selection of Nanobodies using a simple density gradient centrifugation of the bacterial library. The selected single and monomeric Nanobody, W25, binds to the SARS-CoV-2 S RBD with sub-nanomolar affinity and efficiently competes with ACE-2 receptor binding. Furthermore, W25 potently neutralizes SARS-CoV-2 wild type and the D614G variant with IC₅₀ values in the nanomolar range, demonstrating its potential as antiviral agent.

Reference

<https://www.nature.com/articles/s41598-021-82833-w>

Distinct mechanisms for TMPRSS2 expression explain organ-specific inhibition of SARS-CoV-2 infection by enzalutamide

Abstract

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly become a global public health threat. The efficacy of several repurposed drugs has been evaluated in clinical trials. Among these drugs, a second-generation antiandrogen agent, enzalutamide, was proposed because it reduces the expression of transmembrane serine protease 2 (TMPRSS2), a key component mediating SARS-CoV-2-driven entry, in prostate cancer

cells. However, definitive evidence for the therapeutic efficacy of enzalutamide in COVID-19 is lacking. Here, the antiviral efficacy of enzalutamide were evaluated in prostate cancer cells, lung cancer cells, human lung organoids and Ad-ACE2-transduced mice. Tmprss2 knockout significantly inhibited SARS-CoV-2 infection in vivo. Enzalutamide effectively inhibited SARS-CoV-2 infection in human prostate cells, however, such antiviral efficacy was lacking in human lung cells and organoids. Accordingly, enzalutamide showed no antiviral activity due to the AR-independent TMPRSS2 expression in mouse and human lung epithelial cells. Moreover, we observed distinct AR binding patterns between prostate cells and lung cells and a lack of direct binding of AR to TMPRSS2 regulatory locus in human lung cells. Thus, our findings do not support the postulated protective role of enzalutamide in treating COVID-19 through reducing TMPRSS2 expression in lung cells.

Reference

<https://www.nature.com/articles/s41467-021-21171-x>

Quantitative assays reveal cell fusion at minimal levels of SARS-CoV-2 spike protein and fusion from without

Abstract

Cell entry of the pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mediated by its spike protein S. As a main antigenic determinant, S protein is in focus of various therapeutic strategies. Besides particle-cell fusion, S mediates fusion between infected and uninfected cells resulting in syncytia formation. Here, sensitive assay systems were presented with a high dynamic range and high signal-to-noise ratios covering not only particle-cell and cell-cell fusion but also fusion from without (FFWO). In FFWO, S-containing viral particles induce syncytia independently of de novo synthesis of S. Neutralizing antibodies, as well as sera from convalescent patients, inhibited particle-cell fusion with high efficiency. Cell-cell fusion, in contrast, was only moderately inhibited despite requiring levels of S protein below the detection limit of flow cytometry and Western blot. The data indicate that syncytia formation as pathological consequence during coronavirus disease 2019 (COVID-19) can proceed at low levels of S protein and may not be effectively prevented by antibodies.

Reference

[https://www.cell.com/iscience/fulltext/S2589-0042\(21\)00138-3](https://www.cell.com/iscience/fulltext/S2589-0042(21)00138-3)

Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies

Abstract

The evolution of SARS-CoV-2 could impair recognition of the virus by human antibody-mediated immunity. To facilitate prospective surveillance for such evolution, we map how convalescent plasma antibodies are impacted by all mutations to the spike's receptor-binding domain (RBD), the main target of plasma neutralizing activity. Binding by polyclonal plasma antibodies is affected by mutations in three main epitopes in the RBD, but longitudinal samples reveal that the impact of these mutations on antibody binding varies substantially both among individuals and within the same individual over time. Despite this inter- and intra-person heterogeneity, the mutations that most reduce antibody binding usually occur at just a few sites in the RBD's receptor-binding motif. The most important site is E484, where neutralization by some plasma is reduced >10-fold by several mutations, including one in the emerging 20H/501Y.V2 and 20J/501Y.V3 SARS-CoV-2 lineages. Going forward, these plasma escape maps can inform surveillance of SARS-CoV-2 evolution.

Reference

[https://www.cell.com/cell-host-microbe/fulltext/S1931-3128\(21\)00082-2](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00082-2)

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Transcriptomic profiling of SARS-CoV-2 infected human cell lines identifies HSP90 as target for COVID-19 therapy

Abstract

Detailed knowledge of the molecular biology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is crucial for understanding of viral replication, host responses, and disease progression. Here, we report gene expression profiles of three SARS-CoV- and SARS-CoV-2-infected human cell lines. SARS-CoV-2 elicited an approximately two-fold higher stimulation of the innate immune response compared to

SARS-CoV in the human epithelial cell line Calu-3, including induction of miRNA-155. Single-cell RNA sequencing of infected cells showed that genes induced by virus infections were broadly upregulated, whereas interferon beta/lambda genes, a pro-inflammatory cytokines such as IL-6, were expressed only in small subsets of infected cells. Temporal analysis suggested that transcriptional activities of interferon regulatory factors precede those of nuclear factor κ B. Lastly, we identified heat shock protein 90 (HSP90) as a protein relevant for the infection. Inhibition of the HSP90 activity resulted in a reduction of viral replication and pro-inflammatory cytokine expression in primary human airway epithelial cells.

Reference

[https://www.cell.com/iscience/fulltext/S2589-0042\(21\)00119-X](https://www.cell.com/iscience/fulltext/S2589-0042(21)00119-X)

Publication Date: Feb 05, 2021

Rapid electrochemical detection of coronavirus SARS-CoV-2

Abstract

Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diagnosis of COVID-19 depends on quantitative reverse transcription PCR (qRT-PCR), which is time-consuming and requires expensive instrumentation. Here, we report an ultrasensitive electrochemical biosensor based on isothermal rolling circle amplification (RCA) for rapid detection of SARS-CoV-2. The assay involves the hybridization of the RCA amplicons with probes that were functionalized with redox active labels that are detectable by an electrochemical biosensor. The one-step sandwich hybridization assay could detect as low as 1 copy/ μ L of N and S genes, in less than 2 h. Sensor evaluation with 106 clinical samples, including 41 SARS-CoV-2 positive and 9 samples positive for other respiratory viruses, gave a 100% concordance result with qRT-PCR, with complete correlation between the biosensor current signals and quantitation cycle (Cq) values. In summary, this biosensor could be used as an on-site, real-time diagnostic test for COVID-19.

Reference

<https://www.nature.com/articles/s41467-021-21121-7>

Structure and binding properties of Pangolin-CoV spike glycoprotein inform the evolution of SARS-CoV-2

Abstract

Coronaviruses of bats and pangolins have been implicated in the origin and evolution of the pandemic SARS-CoV-2. We show that spikes from Guangdong Pangolin-CoVs, closely related to SARS-CoV-2, bind strongly to human and pangolin ACE2 receptors. We also report the cryo-EM structure of a Pangolin-CoV spike protein and show it adopts a fully-closed conformation and that, aside from the Receptor-Binding Domain, it resembles the spike of a bat coronavirus RaTG13 more than that of SARS-CoV-2.

Reference

<https://www.nature.com/articles/s41467-021-21006-9>

A computational framework of host-based drug repositioning for broad-spectrum antivirals against RNA viruses

Abstract

RNA viruses are responsible for many zoonotic diseases that post great challenges for public health. Effective therapeutics against these viral infections remain limited. Here, we deployed a computational framework for host-based drug repositioning to predict potential antiviral drugs from 2,352 approved drugs and 1,062 natural compounds embedded in herbs of traditional Chinese medicine. By systematically interrogating public genetic screening data, we comprehensively cataloged host dependency genes (HDGs) that are indispensable for successful viral infection corresponding to 10 families and 29 species of RNA viruses. We then utilized these HDGs as potential drug targets and interrogated extensive drug-target interactions through database retrieval, literature mining, and de novo prediction using artificial intelligence-based algorithms. Repurposed drugs or natural compounds were proposed against many viral pathogens such as coronaviruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), flaviviruses, and influenza viruses. This study helps to prioritize promising drug candidates for in-depth evaluation against these virus-related diseases.

Reference

[https://www.cell.com/iscience/fulltext/S2589-0042\(21\)00116-4](https://www.cell.com/iscience/fulltext/S2589-0042(21)00116-4)

Molecular recognition in the infection, replication, and transmission of COVID-19-causing SARS-CoV-2: An emerging interface of infectious disease, biological chemistry, and nanoscience

Abstract

A coronavirus (CoV) commonly known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and causing COVID-19 (coronavirus disease of 2019) has become a pandemic following an outbreak in Wuhan. Although mutations in the SARS-CoV-2 spike glycoprotein (SGP) are obvious from comparative genome studies, the novel infectious nature of the virus, its new variants detected in the UK, and outside and recovery–death ratios of COVID-19 inspired us to review the mechanisms of the infection, replication, release, and transmission of progeny virions and the immune response in the host cell. In addition to the specificity of SARS-CoV-2 binding to angiotensin-converting enzyme 2 receptor and transmembrane protease serine 2, the varied symptoms and severity of the infection by the original and mutated forms of the virus suggest the significance of correlating the host innate and adaptive immunity with the binding of the virus to the mannose receptor via lipopolysaccharides (LPSs), toll-like receptors via LPS/proteins/RNA, and sialic acid (Sia) via hemagglutinin, or sugar-acid segments of glycans. HA-to-Sia binding is considered based on the innate Sia N-acetylneuraminic acid and the acquired Sia N-glycolylneuraminic acid in the epithelial cells and the sialidase/neuraminidase- or esterase-hydrolyzed release and transmission of CoVs. Furthermore, the cytokine storms common to aged humans infected with SARS-CoV-2 and aged macaques infected with SARS-CoV encourage us to articulate the mechanism by which the nuclear capsid protein and RNAs bypass the pattern recognition-induced secretion of interferons (IFNs), which stimulate IFN genes through the Janus-activated kinase-signal transducer and activator of a transcription pathway, leading to the secretion of antiviral proteins such as myxovirus resistance protein A/B. By considering the complexities of the structure, and the infectious nature of the virus and the structures and functions of the molecules involved in CoV infection, replication, and immune response, a new interface among virology, immunology, chemistry, imaging technology, drug delivery, and nanoscience is proposed and will be developed. This interface can be an essential platform for researchers, technologists, and

physicians to collaborate and develop vaccines and medicines against COVID-19 and other pandemics in the future.

Reference

<https://www.nature.com/articles/s41427-020-00275-8>

Phylogenetic analysis of SARS-CoV-2 in Boston highlights the impact of superspreading events

Abstract

Analysis of 772 complete severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genomes from early in the Boston-area epidemic revealed numerous introductions of the virus, a small number of which led to most cases. The data revealed two superspreading events. One, in a skilled nursing facility, led to rapid transmission and significant mortality in this vulnerable population but little broader spread, whereas other introductions into the facility had little effect. The second, at an international business conference, produced sustained community transmission and was exported, resulting in extensive regional, national, and international spread. The two events also differed substantially in the genetic variation they generated, suggesting varying transmission dynamics in superspreading events. Our results show how genomic epidemiology can help to understand the link between individual clusters and wider community spread.

Reference

<https://science.sciencemag.org/content/371/6529/eabe3261>

Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection

Abstract

Understanding immune memory to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical for improving diagnostics and vaccines and for assessing the likely future course of the COVID-19 pandemic. Multiple compartments of circulating immune memory to SARS-CoV-2 in 254 samples were analyzed from 188 COVID-19 cases, including 43 samples at ≥ 6 months after infection. Immunoglobulin G (IgG) to the

spike protein was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month after symptom onset. SARS-CoV-2-specific CD4+ T cells and CD8+ T cells declined with a half-life of 3 to 5 months. By studying antibody, memory B cell, CD4+ T cell, and CD8+ T cell memory to SARS-CoV-2 in an integrated manner, we observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics.

Reference

<https://science.sciencemag.org/content/371/6529/eabf4063>

Publication Date: Feb 04, 2021

Dynamics of binding ability prediction between spike protein and human ACE2 reveals the adaptive strategy of SARS-CoV-2 in humans

Abstract

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a novel coronavirus causing the COVID-19 pandemic in 2020. High adaptive plasticity on the spike protein of SARS-CoV-2 enables it to transmit across different host species. In the present study, we collected 2092 high-quality genome sequences of SARS-CoV-2 from 160 regions in over 50 countries and reconstructed their phylogeny. The polymorphic interaction between spike protein and human ACE2 (hACE2) were also analyzed. Phylogenetic analysis of SARS-CoV-2 suggests that SARS-CoV-2 is probably originated from a recombination event on the spike protein between a bat coronavirus and a pangolin coronavirus that endows it humans infectivity. Compared with other regions in the S gene of SARS-CoV-2, the direct-binding sites of the receptor-binding domain (RBD) is more conserved. We focused on 3,860 amino acid mutations in spike protein RBD (T333-C525) of SARS-CoV-2 and simulated their differential stability and binding affinity to hACE2 (S19-D615). The results indicate no preference for SARS-CoV-2 infectivity on people of different ethnic groups. The variants in the spike protein of SARS-CoV-2 may also be a good indicator demonstrating the transmission route of SARS-CoV-2 from its natural reservoir to human hosts.

Reference

<https://www.nature.com/articles/s41598-021-82938-2>

Nasopharyngeal SARS-CoV-2 viral loads in young children do not differ significantly from those in older children and adults

Abstract

The role of children in the spread of the SARS-CoV-2 coronavirus has become a matter of urgent debate as societies in the US and abroad consider how to safely reopen schools. Small studies have suggested higher viral loads in young children. Here a multicenter investigation was presented on over five thousand SARS-CoV-2 cases confirmed by real-time reverse transcription (RT) PCR assay. Notably, no discernable difference was found in amount of viral nucleic acid among young children and adults.

Reference

<https://www.nature.com/articles/s41598-021-81934-w>

DNA-launched RNA replicon vaccines induce potent anti-SARS-CoV-2 immune responses in mice

Abstract

The outbreak of the SARS-CoV-2 virus and its rapid spread into a global pandemic made the urgent development of scalable vaccines to prevent coronavirus disease (COVID-19) a global health and economic imperative. Here, the immunogenicity of two alphavirus-based DNA-launched self-replicating (DREP) vaccine candidates encoding either SARS-CoV-2 spike glycoprotein (DREP-S) or a spike ectodomain trimer stabilized in prefusion conformation (DREP-Secto) were characterized and compared. We observed that the two DREP constructs were immunogenic in mice inducing both binding and neutralizing antibodies as well as T cell responses. Interestingly, the DREP coding for the unmodified spike turned out to be more potent vaccine candidate, eliciting high titers of SARS-CoV-2 specific IgG antibodies that were able to efficiently neutralize pseudotyped virus after a single immunization. In addition, both DREP constructs were able to efficiently prime responses that could be boosted with a heterologous spike protein immunization. These data provide important novel insights into SARS-CoV-2 vaccine design using a rapid response DNA vaccine platform. Moreover, they encourage the use of mixed vaccine modalities as a strategy to combat SARS-CoV-2.

Reference

<https://www.nature.com/articles/s41598-021-82498-5>

Saliva is more sensitive than nasopharyngeal or nasal swabs for diagnosis of asymptomatic and mild COVID-19 infection

Abstract

It was aimed to test the sensitivity of naso-oropharyngeal saliva and self-administered nasal (SN) swab compared to nasopharyngeal (NP) swab for COVID-19 testing in a large cohort of migrant workers in Singapore. The utility of next-generation sequencing (NGS) for diagnosis of COVID-19 was also tested. Saliva, NP and SN swabs were collected from subjects who presented with acute respiratory infection, their asymptomatic roommates, and prior confirmed cases who were undergoing isolation at a community care facility in June 2020. All samples were tested using RT-PCR. SARS-CoV-2 amplicon-based NGS with phylogenetic analysis was done for 30 samples. 200 Subjects were recruited, of which 91 and 46 were tested twice and thrice respectively. In total, 62.0%, 44.5%, and 37.7% of saliva, NP and SN samples were positive. Cycle threshold (Ct) values were lower during the earlier period of infection across all sample types. The percentage of test-positive saliva was higher than NP and SN swabs. It was found a strong correlation between viral genome coverage by NGS and Ct values for SARS-CoV-2. Phylogenetic analyses revealed Clade O and lineage B.6 known to be circulating in Singapore. Saliva was found to be a sensitive and viable sample for COVID-19 diagnosis.

Reference

<https://www.nature.com/articles/s41598-021-82787-z>

A novel box for aerosol and droplet guarding and evacuation in respiratory infection (BADGER) for COVID-19 and future outbreaks

Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected millions and killed more than 1.7 million people worldwide as of December 2020. Healthcare providers are at increased risk of infection when caring for patients with COVID-19. The mechanism of

transmission of SARS-CoV-2 is beginning to emerge as airborne spread in addition to direct droplet and indirect contact as main routes of transmission. Here, the design, construction, and testing of the BADGER (Box for Aerosol and Droplet Guarding and Evacuation in Respiratory Infection), an affordable, scalable device was reported that contains droplets and aerosol particles, thus minimizing the risk of infection to healthcare providers. A semi-sealed environment is created inside the BADGER, which is placed over the head of the patient and maintains at least 12-air changes per hour using in-wall vacuum suction. Multiple hand-ports enable healthcare providers to perform essential tasks on a patient's airway and head. Overall, the BADGER has the potential to contain large droplets and small airborne particles as demonstrated by simulated qualitative and quantitative assessments to provide an additional layer of protection for healthcare providers treating COVID-19 and future respiratory contagions.

Reference

<https://www.nature.com/articles/s41598-021-82675-6>

Integrated immune dynamics define correlates of COVID-19 severity and antibody responses

Abstract

SARS-CoV-2 causes a spectrum of COVID-19 disease, the immunological basis of which remains ill defined. We analyzed 85 SARS-CoV-2-infected individuals at acute and/or convalescent time points, up to 102 days after symptom onset, quantifying 184 immunological parameters. Acute COVID-19 presented with high levels of IL-6, IL-18, and IL-10 and broad activation marked by the upregulation of CD38 on innate and adaptive lymphocytes and myeloid cells. Importantly, activated CXCR3+cTFH1 cells in acute COVID-19 significantly correlate with and predict antibody levels and their avidity at convalescence as well as acute neutralization activity. Strikingly, intensive care unit (ICU) patients with severe COVID-19 display higher levels of soluble IL-6, IL-6R, and IL-18, and hyperactivation of innate, adaptive, and myeloid compartments than patients with moderate disease. Our analyses provide a comprehensive map of longitudinal immunological responses in COVID-19 patients and integrate key cellular pathways of complex immune networks underpinning severe COVID-19, providing important insights into potential biomarkers and immunotherapies.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00019-7](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00019-7)

PERSPECTIVE

Publication Date: Feb 08, 2021

COVID-19 and metabolic diseases: A heightened awareness of health inequities and a renewed focus for research priorities

Chronic metabolic disorders such as diabetes and obesity are major public health issues in the United States. However, significant disparities in their prevalence and incidence place a greater burden on US racial and ethnic minority groups, contributing to worse COVID-19 outcomes in many. Improving treatment and prevention of diabetes and obesity is critical to the NIDDK. In this Perspective, we will review the burden of metabolic diseases in the United States, the observed disparities for metabolic diseases in relation to COVID-19, and research opportunities to address underlying causes of metabolic diseases, their associated health disparities, and COVID-19.

Reference

[https://www.cell.com/cell-metabolism/fulltext/S1550-4131\(21\)00062-0](https://www.cell.com/cell-metabolism/fulltext/S1550-4131(21)00062-0)

Publication Date: Feb 05, 2021

Superspreading genomes

Superspreading gained attention during the 2002–2004 SARS epidemic, and mathematical models highlighted its contrasting effects, by which the phenomenon is predicted to increase the probability that an outbreak will go extinct by chance but also to fuel the growth of outbreaks that evade extinction. Superspreading could also be involved in the adaptation of emerging infectious diseases to new hosts. Such events have since been identified in measles, Middle East respiratory syndrome, and Ebola outbreaks. Their presence can be detected from cluster sizes or spatial incidence data, but they appear most clearly in contact tracing data. However, studies to generate these data are expensive, invasive, and time consuming. Their quality is also limited because many people are unreliable respondents and list no or multiple potential sources of infection. Digital tracking could increase data quality but comes with substantial privacy risks. Most of these limitations are minimal for virus genome analyses. A common

motivation to monitor the diversity of circulating viral strains is that some genetic variations may threaten treatment or long-term vaccine efficiencies. But genetic evolution can also be harnessed to track infections as they spread, informing public health decisions. Assuming a constant mutation rate, viruses originating from infections that are close in the transmission chain should be more alike, from a genetic standpoint, than viruses from infections that are temporally or geographically distant. Using sequence data, it is possible to infer phylogenetic trees, which bear many similarities with dated genealogies of infections.

The evolutionary rate of SARS-CoV-2 has, so far, been relatively slow, making multiple sources of data particularly complementary. The ease with which virus genomes can now be generated and the importance of monitoring virus evolution are opportunities for phylodynamics to become a routine tool in outbreak management. For more details, read the link given below.

Reference

<https://science.sciencemag.org/content/371/6529/574>

COMMENT

Publication Date: Feb 03, 2021

Inactivated COVID-19 vaccines to make a global impact

Many inactivated vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being tested at various clinical stages. Most of these vaccines are formulated with aluminium hydroxide, and one, VLA-2001, has two adjuvants, CpG oligodeoxynucleotides and aluminium hydroxide. Because of the ease of production and scale-up and relatively low cost, inactivated vaccines can capture a sizeable portion of the SARS-CoV-2 vaccine landscape. Inactivated vaccines are well established and can provide advantages in a variety of distinct populations, including those with degrees of immune senescence. Given that the risk of more severe COVID-19 increases with age, the clinical evaluation of the responses of older adults to vaccines is essential. In *The Lancet Infectious Diseases*, Zhiwei Wu and colleagues report the results of a randomised, double-blind, placebo-controlled phase 1/2 clinical trial evaluating an inactivated COVID-19 vaccine, CoronaVac, in healthy adults aged 60 years and older (72 in phase 1 and 350 in phase 2). The aluminium hydroxide-adjuvanted vaccine was given as two injections (days 0 and 28), and three different doses were tested (1.5 µg, 3 µg, and 6 µg per injection). The vaccine showed good safety and tolerability; adverse reactions, the most frequent being injection site pain (39 [9%] of 421 participants), were all mild or moderate in severity and no serious adverse events related to vaccination were recorded. Neutralising antibody titres were measured for all doses 28 days after the second injection. Because similar responses were seen with doses of 3 µg (seroconversion rate 98.0% [95% CI 92.8–99.8]) and 6 µg (99.0% [94.5–100.0]) in phase 2, and these doses elicited better responses than did the 1.5 µg dose, the authors proposed the use of a 3 µg dose in the phase 3 trial. This report is a companion to an earlier report of the safety and immunogenicity of CoronaVac in adults aged 18–59 years. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00020-7/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00020-7/fulltext)

REPORT

Publication Date: Feb 10, 2021

Major role of IgM in the neutralizing activity of convalescent plasma against SARS-CoV-2

Characterization of the humoral response to SARS-CoV-2, the etiological agent of COVID-19, is essential to help control the infection. The neutralization activity of plasma from patients with COVID-19 decreases rapidly during the first weeks after recovery. However, the specific role of each immunoglobulin isotype in the overall neutralizing capacity is still not well understood. In this study, we select plasma from a cohort of convalescent patients with COVID-19 and selectively deplete immunoglobulin A, M, or G before testing the remaining neutralizing capacity of the depleted plasma. We find that depletion of immunoglobulin M is associated with the most substantial loss of virus neutralization, followed by immunoglobulin G. This observation may help design efficient antibody-based COVID-19 therapies and may also explain the increased susceptibility to SARS-CoV-2 of autoimmune patients receiving therapies that impair the production of immunoglobulin M (IgM).

Reference

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(21\)00104-2](https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00104-2)

Publication Date: Feb 04, 2021

Human erythroid progenitors are directly infected by SARS-CoV-2: Implications for emerging erythropoiesis in severe COVID-19 patients

It was documented here that intensive care COVID-19 patients suffer a profound decline in hemoglobin levels but show an increase of circulating nucleated red cells, suggesting that SARS-CoV-2 infection either directly or indirectly induces stress erythropoiesis. It was shown that ACE2 expression peaks during erythropoiesis and renders erythroid progenitors vulnerable to infection by SARS-CoV-2. Early erythroid progenitors, defined as CD34⁻CD117⁺CD71⁺CD235a⁻, show the highest levels of ACE2 and constitute the primary target cell to be infected during erythropoiesis. SARS-

CoV-2 causes the expansion of colony formation by erythroid progenitors and can be detected in these cells after 2 weeks of the initial infection. The findings constitute the first report of SARS-CoV-2 infectivity in erythroid progenitor cells and can contribute to understanding both the clinical symptoms of severe COVID-19 patients and how the virus can spread through the circulation to produce local inflammation in tissues, including the bone marrow.

Reference

[https://www.cell.com/stem-cell-reports/fulltext/S2213-6711\(21\)00052-7](https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(21)00052-7)