RESEARCH PUBLICATIONS

A hydrated 2,3-diaminophenazinium chloride as a promising building block against SARS-CoV-2

Abstract

Phenazine scaffolds are the versatile secondary metabolites of bacterial origin. It functions in the biological control of plant pathogens and contributes to the producing strains ecological fitness and pathogenicity. In the light of the excellent therapeutic properties of phenazine, a hydrated 2,3-diaminophenazinium chloride ($DAPH^+Cl^-\cdot 3H_2O$) was synthesized through direct catalytic oxidation of *o*-phenylenediamine with an iron(III) complex, $[Fe(1,10\text{-phenanthroline})_2Cl_2]NO_3$ in ethanol under aerobic condition. The crystal structure, molecular complexity and supramolecular aspects of $DAPH^+Cl^-$ were confirmed and elucidated with different spectroscopic methods and single crystal X-ray structural analysis. Crystal engineering study on $DAPH^+Cl^-$ exhibits a fascinating formation of $(H_2O)_2\ldots Cl^-\ldots(H_2O)$ cluster and energy framework analysis of defines the role of chloride ions in the stabilization of $DAPH^+Cl^-$. The bactericidal efficiency of the compound has been testified against few clinical bacteria like *Streptococcus pneumoniae, Escherichia coli*, *K. pneumoniae* using the disc diffusion method and the results of high inhibition zone suggest its excellent antibacterial properties. The phenazinium chloride exhibits a significant percentage of cell viability and a considerable inhibition property against SARS-CoV-2 at non-cytotoxic concentration compared to remdesivir. Molecular docking studies estimate a good binding propensity of $DAPH^+Cl^-$ with non-structural proteins (nsp2 and nsp7-nsp-8) and the main protease (M^{pro}) of SARS-CoV-2. The molecular dynamics simulation studies attribute the conformationally stable structures of the $DAPH^+Cl^-$ bound M^{pro} and nsp2,

nsp7-nsp8 complexes as evident from the considerable binding energy values, − 19.2 ± 0.3, − 25.7 ± 0.1, and − 24.5 ± 0.7 kcal/mol, respectively.

Reference

https://www.nature.com/articles/s41598-021-02280-5

Template switching and duplications in SARS-CoV-2 genomes give rise to insertion variants that merit monitoring

Abstract

The appearance of multiple new SARS-CoV-2 variants during the COVID-19 pandemic is a matter of grave concern. Some of these variants, such as B.1.617.2, B.1.1.7, and B.1.351, manifest higher infectivity and virulence than the earlier SARS-CoV-2 variants, with potential dramatic effects on the course of the pandemic. So far, analysis of new SARS-CoV-2 variants focused primarily on nucleotide substitutions and short deletions that are readily identifiable by comparison to consensus genome sequences. In contrast, insertions have largely escaped the attention of researchers although the furin site insert in the Spike (S) protein is thought to be a determinant of SARS-CoV-2 virulence. Here, we identify 346 unique inserts of different lengths in SARS-CoV-2 genomes and present evidence that these inserts reflect actual virus variance rather than sequencing artifacts. Two principal mechanisms appear to account for the inserts in the SARS-CoV-2 genomes, polymerase slippage and template switch that might be associated with the synthesis of subgenomic RNAs. At least three inserts in the N-terminal domain of the S protein are predicted to lead to escape from neutralizing antibodies, whereas other inserts might result in escape from T-cell immunity. Thus, inserts in the S protein can affect its antigenic properties and merit monitoring.

Reference

https://www.nature.com/articles/s42003-021-02858-9

Molecular insights into receptor binding energetics and neutralization of SARS-CoV-2 variants

Abstract

Despite an unprecedented global gain in knowledge since the emergence of SARS-CoV-2, almost all mechanistic knowledge related to the molecular and cellular details of viral replication, pathology and virulence has been generated using early prototypic isolates of SARS-CoV-2. Here, using atomic force microscopy and molecular dynamics, we investigated how these mutations quantitatively affected the kinetic, thermodynamic and structural properties of RBD—ACE2 complex formation. A significant increase in the RBD—ACE2 complex stability for several variants of concern, was observed. While the N501Y and E484Q mutations are particularly important for the greater stability, the N501Y mutation is unlikely to significantly affect antibody neutralization. This work provides unprecedented atomistic detail on the binding of SARS-CoV-2 variants and provides insight into the impact of viral mutations on infection-induced immunity.

Reference

BNT162b2 vaccine induces divergent B cell responses to SARS-CoV-2 S1 and S2

Abstract

The first ever US Food and Drug Administration-approved messenger RNA vaccines are highly protective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, the contribution of each dose to the generation of antibodies against SARS-CoV-2 spike (S) protein and the degree of protection against novel variants warrant further study. Here, we investigated the B cell response to the BNT162b2 vaccine by integrating B cell repertoire analysis with single-cell transcriptomics pre- and post-vaccination. The first vaccine dose elicits a recall response of IgA+ plasmablasts targeting the S subunit S2. Three weeks after the first dose, we observed an influx of minimally mutated IgG+ memory B cells that targeted the receptor binding domain on the S subunit S1 and likely developed from the naive B cell pool. This response was strongly boosted by the second dose and delivers potently neutralizing antibodies against SARS-CoV-2 and several of its variants.

Reference

https://www.nature.com/articles/s41590-021-01088-9

Drug repurposing for COVID-19 using graph neural network and harmonizing multiple evidence

Abstract

Since the 2019 novel coronavirus disease (COVID-19) outbreak in 2019 and the pandemic continues for more than one year, a vast amount of drug research has been conducted and few of them got FDA approval. The objective is to prioritize repurposable drugs using a pipeline that systematically integrates the interaction between COVID-19 and drugs, deep graph neural networks, and in vitro/population-based validations. We first collected all available drugs (n = 3635) related to COVID-19 patient treatment through CTDbase. We built a COVID-19 knowledge graph based on the interactions among virus baits, host genes, pathways, drugs, and phenotypes. A deep graph neural network approach was used to derive the candidate drug's representation based on the biological interactions. We prioritized the candidate drugs using clinical trial history, and then validated them with their genetic profiles, *in vitro* experimental efficacy, and population-based treatment effect. The top 22 drugs were highlighted including azithromycin, atorvastatin, aspirin, acetaminophen, and albuterol. Drug combinations were further pinpointed that may synergistically target COVID-19. In summary, it was demonstrated that the integration of extensive interactions, deep neural networks, and multiple evidence can facilitate the rapid identification of candidate drugs for COVID-19 treatment.

Reference

https://www.nature.com/articles/s41598-021-02353-5

A single dose, BCG-adjuvanted COVID-19 vaccine provides sterilising immunity against SARS-CoV-2 infection

Abstract

Global control of COVID-19 requires broadly accessible vaccines that are effective against SARS-CoV-2 variants. In this report, we exploit the immunostimulatory properties of bacille Calmette-Guérin (BCG), the existing tuberculosis vaccine, to deliver

a vaccination regimen with potent SARS-CoV-2-specific protective immunity. Combination of BCG with a stabilised, trimeric form of SARS-CoV-2 spike antigen promoted rapid development of virus-specific IgG antibodies in the blood of vaccinated mice, that was further augmented by the addition of alum. This vaccine formulation, BCG:CoVac, induced high-titre SARS-CoV-2 neutralising antibodies (NAbs) and Th1-biased cytokine release by vaccine-specific T cells, which correlated with the early emergence of T follicular helper cells in local lymph nodes and heightened levels of antigen-specific plasma B cells after vaccination. Vaccination of K18-hACE2 mice with a single dose of BCG:CoVac almost completely abrogated disease after SARS-CoV-2 challenge, with minimal inflammation and no detectable virus in the lungs of infected animals. Boosting BCG:CoVac-primed mice with a heterologous vaccine further increased SARS-CoV-2-specific antibody responses, which effectively neutralised B.1.1.7 and B.1.351 SARS-CoV-2 variants of concern. These findings demonstrate the potential for BCG-based vaccination to protect against major SARS-CoV-2 variants circulating globally.

Reference

https://www.nature.com/articles/s41541-021-00406-4

Socioeconomic inequality in mental well-being associated with COVID-19 containment measures in a low-incidence Asian globalized city

Abstract

The COVID-19 pandemic exposes and amplifies pre-existing inequalities even in places with relatively well-controlled outbreaks such as Hong Kong. This study aimed to explore whether the socioeconomically disadvantaged fare worse via various types of worry in terms of their mental health and well-being. Between September and October 2020, 1067 adults in Hong Kong were recruited via a cross-sectional population-wide telephone survey. The inter-relationship between deprivation, types of worry, mental health disorders, and subjective well-being was assessed using structural equation modelling. Results showed significant total effects of deprivation on worries about being infected ($p = 0.002$), economic activities and livelihood ($p < 0.001$), and personal savings ($p < 0.001$), as well as mental health disorders ($p < 0.001$) and subjective well-being ($p < 0.001$). Specifically, worry about economic activities and livelihood partly mediated

the total effect of deprivation on mental health disorders (p = 0.004), whereas worry about personal savings and worry about economic activities and livelihood partially mediated the total effect of deprivation on subjective well-being (p = 0.007 and 0.002, respectively). Socioeconomic inequality, particularly in mental health and well-being, could be exacerbated via people's economic concerns during the pandemic, which was largely induced by the COVID-19 containment measures rather than the pandemic per se given the relatively low COVID-19 incidence in Hong Kong.

Reference

https://www.nature.com/articles/s41598-021-02342-8

An interpretable machine learning model based on a quick pre-screening system enables accurate deterioration risk prediction for COVID-19

Abstract

A high-performing interpretable model is proposed to predict the risk of deterioration in coronavirus disease 2019 (COVID-19) patients. The model was developed using a cohort of 3028 patients diagnosed with COVID-19 and exhibiting common clinical symptoms that were internally verified (AUC 0.8517, 95% CI 0.8433, 0.8601). A total of 15 high risk factors for deterioration and their approximate warning ranges were identified. This included prothrombin time (PT), prothrombin activity, lactate dehydrogenase, international normalized ratio, heart rate, body-mass index (BMI), D-dimer, creatine kinase, hematocrit, urine specific gravity, magnesium, globulin, activated partial thromboplastin time, lymphocyte count (L%), and platelet count. Four of these indicators (PT, heart rate, BMI, HCT) and comorbidities were selected for a streamlined combination of indicators to produce faster results. The resulting model showed good predictive performance (AUC 0.7941 95% CI 0.7926, 0.8151). A website for quick pre-screening online was also developed as part of the study.

Reference

https://www.nature.com/articles/s41598-021-02370-4

Understanding the role of nACE2 in neurogenic hypertension among COVID-19 patients

Abstract

Currently, the third and fourth waves of the coronavirus disease-19 (COVID-19) pandemic are creating havoc in many parts of the world. Although vaccination programs have been launched in most countries, emerging new strains of the virus along with geographical variations are leading to varying success rates of the available vaccines. The presence of comorbidities such as diabetes, cardiovascular diseases and hypertension is responsible for increasing the severity of COVID-19 and, thus, the COVID-19 mortality rate. Angiotensin-converting enzyme 2 (ACE2), which is utilized by SARS-CoV-2 for entry into host cells, is widely expressed in the lungs, kidneys, testes, gut, adipose tissue, and brain. Infection within host cells mediates RAS overactivation, which leads to a decrease in the ACE2/ACE ratio, AT2R/AT1R ratio, and MasR/AT1R ratio. Such imbalances lead to the development of heightened inflammatory responses, such as cytokine storms, leading to post-COVID-19 complications and mortality. As the association of SARS-CoV-2 infection and hypertension remains unclear, this report provides an overview of the effects of SARS-CoV-2 infection on patients with hypertension. We discuss here the interaction of ACE2 with SARS-CoV-2, focusing on neuronal ACE2 (nACE2), and further shed light on the possible involvement of nACE2 in hypertension. SARS-CoV-2 enters the brain through neuronal ACE2 and spreads in various regions of the brain. The effect of viral binding to neuronal ACE2 in areas of the brain that regulate salt/water balance and blood pressure is also discussed in light of the neural regulation of hypertension in COVID-19.

Reference

https://www.nature.com/articles/s41440-021-00800-4

Heterogeneity of human anti-viral immunity shaped by virus, tissue, age, and sex

Abstract

The persistence of anti-viral immunity is essential for protection and exhibits profound heterogeneity across individuals. Here, the factors were elucidated that shape maintenance and function of anti-viral T cell immunity in the body by comprehensive

profiling of virus-specific T cells across blood, lymphoid organs, and mucosal tissues of organ donors. Flow cytometry was used, T cell receptor sequencing, single-cell transcriptomics, and cytokine analysis to profile virus-specific CD8+ T cells recognizing the ubiquitous pathogens influenza and cytomegalovirus. Our results reveal that virus specificity determines overall magnitude, tissue distribution, differentiation, and clonal repertoire of virus-specific T cells. Age and sex influence T cell differentiation and dissemination in tissues, while T cell tissue residence and functionality are highly correlated with the site. Together, our results demonstrate how the covariates of virus, tissue, age, and sex impact the anti-viral immune response, which is important for targeting, monitoring, and predicting immune responses to existing and emerging viruses.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01557-6

Protective activity of mRNA vaccines against ancestral and variant SARS-CoV-2 strains

Abstract

Although mRNA vaccines encoding the spike protein of SARS-CoV-2 prevent COVID-19, the emergence of new viral variants jeopardize their efficacy. Here, the immunogenicity and protective activity of historical (mRNA-1273, designed for Wuhan-1 spike protein) or modified (mRNA-1273.351, designed for B.1.351 spike protein) Moderna mRNA vaccines were assessed in 129S2 and K18-hACE2 mice. Mice were immunized with either high-dose or low-dose formulations of the mRNA vaccines, where low-dose vaccination modeled suboptimal immune responses. Immunization with formulations at either dose induced neutralizing antibodies in serum against ancestral SARS-CoV-2 WA1/2020 and several virus variants, although serum titers were lower against the B.1.617.2 (Delta) virus. Protection against weight loss and lung pathology was observed with all high-dose vaccines against all viruses. However, low-dose formulations of the vaccines, which produced lower magnitude antibody and T cell responses, showed breakthrough lung infections with B.1.617.2 and development of pneumonia in K18-hACE2 mice. Thus, in individuals with reduced immunity following

mRNA vaccination, breakthrough infection and disease may occur with some SARS-CoV-2 variants.

Reference

https://www.science.org/doi/10.1126/scitranslmed.abm3302

Changes in notifiable infectious disease incidence in China during the COVID-19 pandemic

Abstract

Nationwide nonpharmaceutical interventions (NPIs) have been effective at mitigating the spread of the novel coronavirus disease (COVID-19), but their broad impact on other diseases remains under-investigated. Here an ecological analysis was reported comparing the incidence of 31 major notifiable infectious diseases in China in 2020 to the average level during 2014-2019, controlling for temporal phases defined by NPI intensity levels. Respiratory diseases and gastrointestinal or enteroviral diseases declined more than sexually transmitted or bloodborne diseases and vector-borne or zoonotic diseases. Early pandemic phases with more stringent NPIs were associated with greater reductions in disease incidence. Non-respiratory diseases, such as hand, foot and mouth disease, rebounded substantially towards the end of the year 2020 as the NPIs were relaxed. Statistical modeling analyses confirm that strong NPIs were associated with a broad mitigation effect on communicable diseases, but resurgence of non-respiratory diseases should be expected when the NPIs, especially restrictions of human movement and gathering, become less stringent.

Reference

https://www.nature.com/articles/s41467-021-27292-7

Mucosal vaccination induces protection against SARS-CoV-2 in the absence of detectable neutralizing antibodies

Abstract

A candidate multigenic SARS-CoV-2 vaccine based on an MVA vector expressing both viral N and S proteins (MVA-S + N) was immunogenic, and induced T-cell responses and binding antibodies to both antigens but in the absence of detectable neutralizing antibodies. Intranasal immunization with the vaccine diminished viral loads and lung inflammation in mice after SARS-CoV-2 challenge, which correlated with the T-cell response induced by the vaccine in the lung, indicating that T-cell immunity is also likely critical for protection against SARS-CoV-2 infection in addition to neutralizing antibodies.

Reference

https://www.nature.com/articles/s41541-021-00405-5

A 3D structural SARS-CoV-2–human interactome to explore genetic and drug perturbations

Abstract

Emergence of new viral agents is driven by evolution of interactions between viral proteins and host targets. For instance, increased infectivity of SARS-CoV-2 compared to SARS-CoV-1 arose in part through rapid evolution along the interface between the spike protein and its human receptor ACE2, leading to increased binding affinity. To facilitate broader exploration of how pathogen–host interactions might impact transmission and virulence in the ongoing COVID-19 pandemic, state-of-the-art interface prediction was performed followed by molecular docking to construct a three-dimensional structural interactome between SARS-CoV-2 and human. We additionally carried out downstream meta-analyses to investigate enrichment of sequence divergence between SARS-CoV-1 and SARS-CoV-2 or human population variants along viral–human protein-interaction interfaces, predict changes in binding affinity by these mutations/variants and further prioritize drug repurposing candidates predicted to competitively bind human targets. This resource (http://3D-SARS2.yulab.org) was

believed to aid in development and testing of informed hypotheses for SARS-CoV-2 etiology and treatments.

Reference

https://www.nature.com/articles/s41592-021-01318-w

SARS-CoV-2 ORF10 suppresses the antiviral innate immune response by degrading MAVS through mitophagy

Abstract

The global coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused severe morbidity and mortality in humans. It is urgent to understand the function of viral genes. However, the function of open reading frame 10 (ORF10), which is uniquely expressed by SARS-CoV-2, remains unclear. In this study, it was shown that overexpression of ORF10 markedly suppressed the expression of type I interferon (IFN-I) genes and IFN-stimulated genes. Then, mitochondrial antiviral signaling protein (MAVS) was identified as the target via which ORF10 suppresses the IFN-I signaling pathway, and MAVS was found to be degraded through the ORF10-induced autophagy pathway. Furthermore, overexpression of ORF10 promoted the accumulation of LC3 in mitochondria and induced mitophagy. Mechanistically, ORF10 was translocated to mitochondria by interacting with the mitophagy receptor Nip3-like protein X (NIX) and induced mitophagy through its interaction with both NIX and LC3B. Moreover, knockdown of NIX expression blocked mitophagy activation, MAVS degradation, and IFN-I signaling pathway inhibition by ORF10. Consistent with our observations, in the context of SARS-CoV-2 infection, ORF10 inhibited MAVS expression and facilitated viral replication. In brief, our results reveal a novel mechanism by which SARS-CoV-2 inhibits the innate immune response; that is, ORF10 induces mitophagy-mediated MAVS degradation by binding to NIX.

Reference

https://www.nature.com/articles/s41423-021-00807-4

Immune response against SARS-CoV-2 variants: The role of neutralization assays

Abstract

Since the emergence of the novel coronavirus SARS-CoV-2 in late 2019, the COVID-19 pandemic has hindered social life and global economic activity. As of July 2021, SARS-CoV-2 has caused over four million deaths. The rapid spread and high mortality of the disease demanded the international scientific community to develop effective vaccines in a matter of months. However, unease about vaccine efficacy has arisen with the spread of the SARS-CoV-2 variants of concern (VOCs). Time- and cost-efficient in vitro neutralization assays are widely used to measure neutralizing antibody responses against VOCs. However, the extent to which in vitro neutralization reflects protection from infection remains unclear. Here, common neutralization assays were described based on infectious and pseudotyped viruses and evaluate their role in testing neutralizing responses against new SARS-CoV-2 variants. Additionally, the recent findings were briefly reviewed on the immune response elicited by available vaccines against major SARS-CoV-2 variants, including Alpha, Beta, Gamma, and Delta.

Reference

https://www.nature.com/articles/s41541-021-00404-6

Optimising health and economic impacts of COVID-19 vaccine prioritisation strategies in the WHO European Region: A mathematical modelling study

Abstract

Background: Countries in the World Health Organization (WHO) European Region differ in terms of the COVID-19 vaccine supply conditions. The health and economic impact of different age-based vaccine prioritization strategies were evaluated across this demographically and socio-economically diverse region.

Methods: Age-specific compartmental models were fitted to the reported daily COVID-19 mortality in 2020 to inform the immunity level before vaccine roll-out. Models capture country-specific differences in population structures, contact patterns, epidemic history, life expectancy, and GDP per capita.

Four strategies were examined that prioritise: all adults (V+), younger (20-59 year-olds) followed by older adults (60+) (V20), older followed by younger adults (V60), and the

oldest adults (75+) (V75) followed by incrementally younger age groups. We explored four roll-out scenarios (R1-4) — the slowest scenario (R1) reached 30% coverage by December 2022 and the fastest (R4) 80% by December 2021. Five decision-making metrics were summarised over 2021-22: mortality, morbidity, and losses in comorbidity-adjusted life expectancy, comorbidity- and quality-adjusted life years, and human capital. Six vaccine profiles were tested — the highest performing vaccine has 95% efficacy against both infection and disease, and the lowest 50% against diseases and 0% against infection.

Findings: Of the 20 decision-making metrics and roll-out scenario combinations, the same optimal strategy applied to all countries in only one combination; V60 was more or similarly desirable than V75 in 19 combinations. Of the 38 countries with fitted models, 11-37 countries had variable optimal strategies by decision-making metrics or roll-out scenarios. There are greater benefits in prioritising older adults when roll-out is slow and when vaccine profiles are less favourable.

Interpretation: The optimal age-based vaccine prioritisation strategies were sensitive to country characteristics, decision-making metrics, and roll-out speeds. A prioritisation strategy involving more age-based stages (V75) does not necessarily lead to better health and economic outcomes than targeting broad age groups (V60). Countries expecting a slow vaccine roll-out may particularly benefit from prioritising older adults.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00253-2/fulltext

Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial

Abstract

Background: Patients with immunocompromised disorders have mainly been excluded from clinical trials of vaccination against COVID-19. Thus, the aim of this prospective clinical trial was to investigate safety and efficacy of BNT162b2 mRNA vaccination in five selected groups of immunocompromised patients and healthy controls.

Methods: 539 Study subjects (449 patients and 90 controls) were included. The patients had either primary (n=90), or secondary immunodeficiency disorders due to human immunodeficiency virus infection (n=90), allogeneic hematopoietic stem cell transplantation/CAR T cell therapy (n=90), solid organ transplantation (SOT) (n=89), or chronic lymphocytic leukemia (CLL) (n=90). The primary endpoint was seroconversion rate two weeks after the second dose. The secondary endpoints were safety and documented SARS-CoV-2 infection.

Findings: Adverse events were generally mild, but one case of fatal suspected unexpected serious adverse reaction occurred. 72.2% of the immunocompromised patients seroconverted compared to 100% of the controls (p=0.004). Lowest seroconversion rates were found in the SOT (43.4%) and CLL (63.3%) patient groups with observed negative impact of treatment with mycophenolate mofetil and ibrutinib, respectively.

Interpretation: The results showed that the mRNA BNT162b2 vaccine was safe in immunocompromised patients. Rate of seroconversion was substantially lower than in healthy controls, with a wide range of rates and antibody titres among predefined patient groups and subgroups. This clinical trial highlights the need for additional vaccine doses in certain immunocompromised patient groups to improve immunity.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00499-0/fulltext

Relative ratios of human seasonal coronavirus antibodies predict the efficiency of cross-neutralization of SARS-CoV-2 spike binding to ACE2

Abstract

Background: Antibodies raised against human seasonal coronaviruses (sCoVs), which are responsible for the common cold, are known to cross-react with SARS-CoV-2 antigens. This prompts questions about their protective role against SARS-CoV-2 infections and COVID-19 severity. However, the relationship between sCoVs exposure and SARS-CoV-2 correlates of protection are not clearly identified.

Methods: A cross-sectional analysis of cross-reactivity and cross-neutralization to SARS-CoV-2 antigens (S-RBD, S-trimer, N) was performed using pre-pandemic sera

from four different groups: pediatrics and adolescents, individuals 21 to 70 years of age, older than 70 years of age, and individuals living with HCV or HIV. Data was then further analysed using machine learning to identify predictive patterns of neutralization based on sCoVs serology.

Findings: Antibody cross-reactivity to SARS-CoV-2 antigens varied between 1.6% and 15.3% depending on the cohort and the isotype-antigen pair analyzed. A range of neutralizing activity (0-45%) was shown with median inhibition ranging from 17.6 % to 23.3 % in serum that interferes with SARS-CoV-2 spike attachment to ACE2 independently of age group. While the abundance of sCoV antibodies did not directly correlate with neutralization, we show that neutralizing activity is rather dependent on relative ratios of IgGs in sera directed to all four sCoV spike proteins. More specifically, we identified antibodies to NL63 and OC43 as being the most important predictors of neutralization.

Interpretation: The data support the concept that exposure to sCoVs triggers antibody responses that influence the efficiency of SARS-CoV-2 spike binding to ACE2, which may potentially impact COVID-19 disease severity through other latent variables.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00494-1/fulltext

Publication Date: Nov 28, 2021

Effectiveness of BNT162b2 mRNA COVID-19 vaccine against SARS-CoV-2 variant Beta (B.1.351) among persons identified through contact tracing in Israel: A prospective cohort study

Abstract

Background: SARS-CoV-2 variant Beta (B.1.351) was designated as a Variant of Concern (VoC) after becoming the dominant strain in South Africa and spreading internationally. BNT162b2 showed lower levels of neutralizing antibodies against Beta than against other strains raising concerns about effectiveness of vaccines against infections caused by Beta. BNT162b2 vaccine effectiveness (VE) was estimated against Beta infections in Israel, a country with high vaccine uptake.

Methods: The Ministry of Health (MoH) identified Beta cases through mandatory reporting of SARS-CoV-2 cases and whole genome sequencing (WGS) of specimens from vaccination-breakthrough infections, reinfections, arriving international travelers, and a selection of other infected persons. A cohort analysis was conducted of exposure events of contacts of primary Beta cases. WGS was conducted on available PCR-positive specimens collected from contacts. VE estimates with 95% confidence intervals (CIs) against confirmed and probable Beta infections were determined by comparing infection risk between unvaccinated and fully-vaccinated (≥7 days after the second dose) contacts, and between unvaccinated and partially-vaccinated (<7 days after the second dose) contacts.

Findings: MoH identified 310 Beta cases through Jun 27, 2021. During the study period (Dec 11, 2020 – Mar 25, 2021), 164 non-institutionalized primary Beta cases, with 552 contacts aged ≥16 years, were identified. 343/552 (62%) contacts were interviewed and tested. 71/343 (21%) contacts were PCR-positive. WGS was performed on 7/71 (10%) PCR-positive specimens; all were Beta. Among SARS-CoV-2-infected contacts, 48/71 (68%) were symptomatic, 10/71 (14%) hospitalized, and 2/71 (3%) died. Fully-vaccinated VE against confirmed or probable Beta infections was 72% (95% CI -5 – 97%; p=0·04) and against symptomatic confirmed or probable Beta infections was 100% (95% CI 19 – 100%; p=0·01). There was no evidence of protection in partially-vaccinated contacts.

Interpretation: In a prospective observational study, two doses of BNT162b2 were effective against confirmed and probable Beta infections. Through the end of June 2021, introductions of Beta did not interrupt control of the pandemic in Israel.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00471-5/fulltext

Host parameters and mode of infection influence outcome in SARS-CoV-2 infected hamsters

Abstract

The golden hamster model of SARS-CoV-2 infection recapitulates key characteristics of COVID-19. In this work we examined the influence of the route of exposure, sex, and age on SARS-CoV-2 pathogenesis in hamsters. It was reported that delivery of SARS-CoV-2 by a low versus high volume intranasal or intragastric route results in comparable viral titers in the lung and viral shedding. However, low-volume intranasal exposure results in milder weight loss while intragastric exposure leads to a diminished capacity to regain body weight. Male hamsters, and particularly older male hamsters, display an impaired capacity to recover from illness and delayed viral clearance. These factors were found to influence the nature of the host inflammatory cytokine response, but had a minimal effect on the quality and durability of the humoral immune response and susceptibility to re-infection. These data further elucidate key factors that impact pre-clinical challenge studies carried out in the hamster model of COVID-19.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)01501-7

Structural, energetic and lipophilic analysis of SARS-CoV-2 non-structural protein 9 (NSP9)

Abstract

In SARS-CoV-2 replication complex, the Non-structural protein 9 (Nsp9) is an important RNA binding subunit in the RNA-synthesizing machinery. The dimeric forms of coronavirus Nsp9 increase their nucleic acid binding affinity and the *N*-finger motif appears to play a critical role in dimerization. Here, a structural, lipophilic and energetic study was presented about the Nsp9 dimer of SARS-CoV-2 through computational methods that complement hydrophobicity scales of amino acids with molecular dynamics simulations. Additionally, a virtual *N*-finger mutation was presented to

investigate whether this motif contributes to dimer stability. The results reveal for the native dimer that the *N*-finger contributes favorably through hydrogen bond interactions and two amino acids bellowing to the hydrophobic region, Leu45 and Leu106, are crucial in the formation of the cavity for potential drug binding. On the other hand, Gly100 and Gly104, are responsible for stabilizing the α-helices and making the dimer interface remain stable in both, native and mutant (without *N*-finger motif) systems. Besides, clustering results for the native dimer showed accessible cavities to drugs. In addition, the energetic and lipophilic analysis reveal that the higher binding energy in the native dimer can be deduced since it is more lipophilic than the mutant one, increasing non-polar interactions, which is in line with the result of MM-GBSA and SIE approaches where the van der Waals energy term has the greatest weight in the stability of the native dimer. Overall, a detailed study was provided on the Nsp9 dimer of SARS-CoV-2 that may aid in the development of new strategies for the treatment and prevention of COVID-19.

Reference

https://www.nature.com/articles/s41598-021-02366-0

Prevention of SARS-CoV-2 transmission during a large, live, indoor gathering (SPRING): A non-inferiority, randomised, controlled trial

Abstract

Background: Mass indoor gatherings were banned in early 2020 to prevent the spread of SARS-CoV-2. It was aimed to assess, under controlled conditions, whether infection rates among attendees at a large, indoor gathering event would be similar to those in non-attendees, given implementation of a comprehensive prevention strategy including antigen-screening within 3 days, medical mask wearing, and optimised ventilation.

Methods: The non-inferiority, prospective, open-label, randomised, controlled SPRING trial was done on attendees at a live indoor concert held in the Accor Arena on May 29, 2021 in Paris, France. Participants, aged 18–45 years, recruited via a dedicated website, had no comorbidities, COVID-19 symptoms, or recent case contact, and had had a negative rapid antigen diagnostic test within 3 days before the concert. Participants were randomly allocated in a 2:1 ratio to the experimental group (attendees) or to the control group (non-attendees). The allocation sequence was

computer-generated by means of permuted blocks of sizes three, six, or nine, with no stratification. The primary outcome measure was the number of patients who were SARS-CoV-2-positive by RT-PCR test on self-collected saliva 7 days post-gathering in the per-protocol population (non-inferiority margin <0·35%). This trial is registered with ClinicalTrials.gov, NCT04872075.

Findings: Between May 11 and 25, 2021, 18 845 individuals registered on the dedicated website, and 10 953 were randomly selected for a pre-enrolment on-site visit. Among 6968 who kept the appointment and were screened, 6678 participants were randomly assigned (4451 were assigned to be attendees and 2227 to be non-attendees; median age 28 years; 59% women); 88% (3917) of attendees and 87% (1947) of non-attendees complied with follow-up requirements. The day 7 RT-PCR was positive for eight of the 3917 attendees (observed incidence, 0·20%; 95% CI 0·09–0·40) and three of the 1947 non-attendees (0·15%; 0·03–0·45; absolute difference, 95% CI −0·26% to 0·28%), findings that met the non-inferiority criterion for the primary endpoint.

Interpretation: Participation in a large, indoor, live gathering without physical distancing was not associated with increased SARS-CoV-2–transmission risk, provided a comprehensive preventive intervention was implemented.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00673-3/fulltext

Next generation plasma proteome profiling of COVID-19 patients with mild to moderate symptoms

Abstract

Background: COVID-19 has caused millions of deaths globally, yet the cellular mechanisms underlying the various effects of the disease remain poorly understood. Recently, a new analytical platform for comprehensive analysis of plasma protein profiles using proximity extension assays combined with next generation sequencing has been developed, which allows for multiple proteins to be analyzed simultaneously without sacrifice on accuracy or sensitivity.

Methods: It was analyzed the plasma protein profiles of COVID-19 patients (n = 50) with mild and moderate symptoms by comparing the protein levels in newly diagnosed patients with the protein levels in the same individuals after 14 days.

Findings: The study has identified more than 200 proteins that are significantly elevated during infection and many of these are related to cytokine response and other immune-related functions. In addition, several other proteins are shown to be elevated, including SCARB2, a host cell receptor protein involved in virus entry. A comparison with the plasma protein response in patients with severe symptoms shows a highly similar pattern, but with some interesting differences.

Interpretation: The study presented here demonstrates the usefulness of "next generation plasma protein profiling" to identify molecular signatures of importance for disease progression and to allow monitoring of disease during recovery from the infection. The results will facilitate further studies to understand the molecular mechanism of the immune-related response of the SARS-CoV-2 virus.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00517-X/fulltext

SARS-CoV-2 infection triggers profibrotic macrophage responses and lung fibrosis

Abstract

COVID-19-induced 'acute respiratory distress syndrome' (ARDS) is associated with prolonged respiratory failure and high mortality, but the mechanistic basis of lung injury remains incompletely understood. Here, pulmonary immune responses and lung pathology were analyzed in two cohorts of patients with COVID-19 ARDS using functional single cell genomics, immunohistology and electron microscopy. We describe an accumulation of CD163-expressing monocyte-derived macrophages that acquired a profibrotic transcriptional phenotype during COVID-19 ARDS. Gene set enrichment and computational data integration revealed a significant similarity between COVID-19-associated macrophages and profibrotic macrophage populations identified in idiopathic pulmonary fibrosis. COVID-19 ARDS was associated with clinical, radiographic, histopathological, and ultrastructural hallmarks of pulmonary fibrosis. Exposure of

human monocytes to SARS-CoV-2, but not Influenza A virus or viral RNA analogs, was sufficient to induce a similar profibrotic phenotype *in vitro*. In conclusion, it was demonstrated that SARS-CoV-2 triggers profibrotic macrophage responses and pronounced fibroproliferative ARDS.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)01383-0

The antibody response to SARS-CoV-2 Beta underscores the antigenic distance to other variants

Abstract

Alpha-B.1.1.7, Beta-B.1.351, Gamma-P.1 and Delta-B.1.617.2 variants of SARS-CoV-2 express multiple mutations in the spike protein (S). These may alter the antigenic structure of S, causing escape from natural or vaccine-induced immunity. Beta is particularly difficult to neutralize using serum induced by early pandemic SARS-CoV-2 strains and is most antigenically separated from Delta. To understand this, we generated 674 mAbs from Beta infected individuals and performed a detailed structure-function analysis of the 27 most potent mAbs: one binding the spike N-terminal domain (NTD), the rest the receptor binding domain (RBD). Two of these RBD-binding mAbs recognise a neutralizing epitope conserved between SARS-CoV-1 and -2, whilst 18 target mutated residues in Beta: K417N, E484K, and N501Y. There is a major response to N501Y including a public IgVH4-39 sequence, with E484K and K417N also targeted. Recognition of these key residues underscores why serum from Beta cases poorly neutralizes early pandemic and Delta viruses.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00519-9

SARS-CoV-2 at the human-animal interphase: A review

Abstract

Since its emergence in China in December 2019, COVID-19 remains the recent leading disease of concern drawing the public health attention globally. The disease is known of viral origin and zoonotic nature originating from animals. However, to date neither the

source of the spillover nor the intermediate hosts are identified. Moreover, the public health situation is intermittently aggravated by identification of new animals susceptible to the SARS-CoV-2 infection, potentially replicating the virus and maintaining intra and interspecies spread of the disease. Although the role of a given animal and/or its produce is important to map the disease pattern, continuous efforts should be undertaken to further understand the epidemiology of SARS-CoV-2, a vital step to establish effective disease prevention and control strategy. This manuscript attempted to review updates regarding SARS-CoV-2 infection at the human-animal interface with consideration to postulations on the genetic relatedness and origin of the different SARS-CoV-2 variants isolated from different animal species. Also, the review addresses the possible role of different animal species and their produce in transmission of the disease. Also, the manuscript discussed the contamination potentiality of the virus and its environmental stability. Finally, we reviewed the currently instituted measures to prevent and manage the spread of SARS-CoV-2 infection. The manuscript suggested the One Health based control measures that could prove of value for the near future.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)02599-8

A Deep learning approach for predicting severity of COVID-19 patients using a parsimonious set of laboratory markers

Abstract

The SARS-CoV-2 virus has caused tremendous healthcare burden worldwide. Our focus was to develop a practical and easy to deploy system to predict the severe manifestation of disease in COVID-19 patients with an aim to assist clinicians in triage and treatment decisions. The proposed predictive algorithm is a trained artificial intelligence-based network using 8,427 COVID-19 patient records from four healthcare systems. The model provides a severity risk score along with likelihoods of various clinical outcomes, namely ventilator use and mortality. The trained model using patient age and nine laboratory markers has the prediction accuracy with an area under the curve (AUC) of 0·78 95% CI: 0·77-0·82, and the negative predictive value NPV of 0·86 95% CI: 0·84-0·88 for the need to use a ventilator and has an accuracy with AUC of

0·85 95% CI: 0·84-0·86, and the NPV of 0·94 95% CI: 0·92-0·96 for predicting in-hospital 30-day mortality.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)01494-2

Epidemiological associations with genomic variation in SARS-CoV-2

Abstract

SARS-CoV-2 (CoV) is the etiological agent of the COVID-19 pandemic and evolves to evade both host immune systems and intervention strategies. The CoV genome was divided into 29 constituent regions and applied novel analytical approaches to identify associations between CoV genomic features and epidemiological metadata. The results show that nonstructural protein 3 (nsp3) and Spike protein (S) have the highest variation and greatest correlation with the viral whole-genome variation. S protein variation is correlated with nsp3, nsp6, and 3′-to-5′ exonuclease variation. Country of origin and time since the start of the pandemic were the most influential metadata associated with genomic variation, while host sex and age were the least influential. We define a novel statistic—coherence—and show its utility in identifying geographic regions (populations) with unusually high (many new variants) or low (isolated) viral phylogenetic diversity. Interestingly, at both global and regional scales, geographic locations with high coherence neighboring regions of low coherence were identified; this emphasizes the utility of this metric to inform public health measures for disease spread. The results provide a direction to prioritize genes associated with outcome predictors (e.g., health, therapeutic, and vaccine outcomes) and to improve DNA tests for predicting disease status.

Reference

https://www.nature.com/articles/s41598-021-02548-w

Protective mucosal immunity against SARS-CoV-2 after heterologous systemic prime-mucosal boost immunization

Abstract

Several effective SARS-CoV-2 vaccines are currently in use, but effective boosters are needed to maintain or increase immunity due to waning responses and the emergence of novel variants. Here it was reported that intranasal vaccinations with adenovirus 5 and 19a vectored vaccines following a systemic plasmid DNA or mRNA priming result in systemic and mucosal immunity in mice. In contrast to two intramuscular applications of an mRNA vaccine, intranasal boosts with adenoviral vectors induce high levels of mucosal IgA and lung-resident memory T cells (TRM); mucosal neutralization of virus variants of concern is also enhanced. The mRNA prime provokes a comprehensive T cell response consisting of circulating and lung TRM after the boost, while the plasmid DNA prime induces mostly mucosal T cells. Concomitantly, the intranasal boost strategies lead to complete protection against a SARS-CoV-2 infection in mice. The data thus suggest that mucosal booster immunizations after mRNA priming is a promising approach to establish mucosal immunity in addition to systemic responses.

Reference

https://www.nature.com/articles/s41467-021-27063-4

A SARS-CoV-2 antigen rapid diagnostic test for resource limited settings

Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19 disease. RT-qPCR has been the primary method of diagnosis; however, the required infrastructure is lacking in many developing countries and the virus has remained a global challenge. More inexpensive and immediate test methods are required to facilitate local, regional, and national management strategies to re-open world economies. Here a SARS-CoV-2 antigen test was developed in an inexpensive lateral flow format to generate a chromatographic result identifying the presence of the SARS-CoV-2 antigen, and thus an active infection, within a patient anterior nares swab sample. Our 15-min test requires no equipment or laboratory infrastructure to administer with a limit of detection of 2.0×10^2 TCID50/mL and 87.5% sensitivity, 100% specificity

when tested against 40 known positive and 40 known negative patient samples established by a validated RT-qPCR test.

Reference

https://www.nature.com/articles/s41598-021-02128-y

A new p65 isoform that bind the glucocorticoid hormone and is expressed in inflammation liver diseases and COVID-19

Abstract

Inflammation is a physiological process whose deregulation causes some diseases including cancer. Nuclear Factor kB (NF-kB) is a family of ubiquitous and inducible transcription factors, in which the p65/p50 heterodimer is the most abundant complex, that play critical roles mainly in inflammation. Glucocorticoid Receptor (GR) is a ligand-activated transcription factor and acts as an anti-inflammatory agent and immunosuppressant. Thus, NF-kB and GR are physiological antagonists in the inflammation process. Here we show that in mice and humans there is a spliced variant of p65, named p65 iso5, which binds the corticosteroid hormone dexamethasone amplifying the effect of the glucocorticoid receptor and is expressed in the liver of patients with hepatic cirrhosis and hepatocellular carcinoma (HCC). Furthermore, the gene expression level of p65 and p65 iso5 was quantified in the PBMC of patients affected by SARS-CoV-2 disease. The results showed that in these patients the p65 and p65 iso5 mRNA levels are higher than in healthy subjects. The ability of p65 iso5 to bind dexamethasone and the regulation of the glucocorticoid (GC) response in the opposite way of the wild type improves our knowledge and understanding of the anti-inflammatory response and identifies it as a new therapeutic target to control inflammation and related diseases.

Reference

https://www.nature.com/articles/s41598-021-02119-z

Functional convalescent plasma antibodies and pre-infusion titers shape the early severe COVID-19 immune response

Abstract

Transfer of convalescent plasma (CP) had been proposed early during the SARS-CoV-2 pandemic as an accessible therapy, yet trial results worldwide have been mixed, potentially due to the heterogeneous nature of CP. Here deep profiling of SARS-CoV-2-specific antibody titer, Fc-receptor binding, and Fc-mediated functional assays in CP units, as well as in plasma were performed from hospitalized COVID-19 patients before and after CP administration. The profiling results show that, although all recipients exhibit expanded SARS-CoV-2-specific humoral immune responses, CP units contain more functional antibodies than recipient plasma. Meanwhile, CP functional profiles influence the evolution of recipient humoral immunity in conjuncture with the recipient's pre-existing SARS-CoV2-specific antibody titers: CP-derived SARS-CoV-2 nucleocapsid-specific antibody functions are associated with muted humoral immune evolution in patients with high titer anti-spike IgG. The data thus provide insights into the unexpected impact of CP-derived functional anti-spike and anti-nucleocapsid antibodies on the evolution of SARS-CoV-2-specific response following severe infection.

Reference

https://www.nature.com/articles/s41467-021-27201-y

Spike residue 403 affects binding of coronavirus spikes to human ACE2

Abstract

The bat sarbecovirus RaTG13 is a close relative of SARS-CoV-2, the cause of the COVID-19 pandemic. However, this bat virus was most likely unable to directly infect humans since its Spike (S) protein does not interact efficiently with the human ACE2 receptor. Here, it was shown that a single T403R mutation increases binding of RaTG13 S to human ACE2 and allows VSV pseudoparticle infection of human lung cells and intestinal organoids. Conversely, mutation of R403T in the SARS-CoV-2 S reduces pseudoparticle infection and viral replication. The T403R RaTG13 S is neutralized by sera from individuals vaccinated against COVID-19 indicating that vaccination might protect against future zoonoses. The data suggest that a positively charged amino acid

at position 403 in the S protein is critical for efficient utilization of human ACE2 by S proteins of bat coronaviruses. This finding could help to better predict the zoonotic potential of animal coronaviruses.

Reference

https://www.nature.com/articles/s41467-021-27180-0

A new p65 isoform that bind the glucocorticoid hormone and is expressed in inflammation liver diseases and COVID-19

Abstract

Inflammation is a physiological process whose deregulation causes some diseases including cancer. Nuclear Factor kB (NF-kB) is a family of ubiquitous and inducible transcription factors, in which the p65/p50 heterodimer is the most abundant complex, that play critical roles mainly in inflammation. Glucocorticoid Receptor (GR) is a ligand-activated transcription factor and acts as an anti-inflammatory agent and immunosuppressant. Thus, NF-kB and GR are physiological antagonists in the inflammation process. Here we show that in mice and humans there is a spliced variant of p65, named p65 iso5, which binds the corticosteroid hormone dexamethasone amplifying the effect of the glucocorticoid receptor and is expressed in the liver of patients with hepatic cirrhosis and hepatocellular carcinoma (HCC). Furthermore, we have quantified the gene expression level of p65 and p65 iso5 in the PBMC of patients affected by SARS-CoV-2 disease. The results showed that in these patients the p65 and p65 iso5 mRNA levels are higher than in healthy subjects. The ability of p65 iso5 to bind dexamethasone and the regulation of the glucocorticoid (GC) response in the opposite way of the wild type improves our knowledge and understanding of the anti-inflammatory response and identifies it as a new therapeutic target to control inflammation and related diseases.

Reference

https://www.nature.com/articles/s41598-021-02119-z

Upregulated type I interferon responses in asymptomatic COVID-19 infection are associated with improved clinical outcome

Abstract

Understanding key host protective mechanisms against SARS-CoV-2 infection can help improve treatment modalities for COVID-19. We used a blood transcriptome approach to study biomarkers associated with differing severity of COVID-19, comparing severe and mild Symptomatic disease with Asymptomatic COVID-19 and uninfected Controls. There was suppression of antigen presentation but upregulation of inflammatory and viral mRNA translation associated pathways in Symptomatic as compared with Asymptomatic cases. In severe COVID-19, CD177 a neutrophil marker, was upregulated while interferon stimulated genes (ISGs) were downregulated. Asymptomatic COVID-19 cases displayed upregulation of ISGs and humoral response genes with downregulation of ICAM3 and TLR8. Compared across the COVID-19 disease spectrum, we found type I interferon (IFN) responses to be significantly upregulated (IFNAR2, IRF2BP1, IRF4, MAVS, SAMHD1, TRIM1), or downregulated (SOCS3, IRF2BP2, IRF2BPL) in Asymptomatic as compared with mild and severe COVID-19, with the dysregulation of an increasing number of ISGs associated with progressive disease. These data suggest that initial early responses against SARS-CoV-2 may be effectively controlled by ISGs. Therefore, we hypothesize that treatment with type I interferons in the early stage of COVID-19 may limit disease progression by limiting SARS-CoV-2 in the host.

Reference

https://www.nature.com/articles/s41598-021-02489-4

Targeting conserved *N*-glycosylation blocks SARS-CoV-2 variant infection *in vitro*

Abstract

Background: Despite clinical success with anti-spike vaccines, the effectiveness of neutralizing antibodies and vaccines has been compromised by rapidly spreading SARS-CoV-2 variants. Viruses can hijack the glycosylation machinery of host cells to shield themselves from the host's immune response and attenuate antibody efficiency.

However, it remains unclear if targeting glycosylation on viral spike protein can impair infectivity of SARS-CoV-2 and its variants.

Methods: Flow cytometry, ELISA, and BioLayer interferometry approaches were adopted to assess binding of glycosylated or deglycosylated spike with ACE2. Viral entry was determined by luciferase, immunoblotting, and immunofluorescence assays. Genome-wide association study (GWAS) revealed a significant relationship between STT3A and COVID-19 severity. NF-κB/STT3A-regulated *N*-glycosylation was investigated by gene knockdown, chromatin immunoprecipitation, and promoter assay. We developed an antibody-drug conjugate (ADC) that couples non-neutralization anti-spike antibody with NGI-1 (4G10-ADC) to specifically target SARS-CoV-2-infected cells.

Findings: The receptor binding domain and three distinct SARS-CoV-2 surface *N*-glycosylation sites among 57,311 spike proteins retrieved from the NCBI-Virus-database are highly evolutionarily conserved (99.67%) and are involved in ACE2 interaction. STT3A is a key glycosyltransferase catalyzing spike glycosylation and is positively correlated with COVID-19 severity. It was found that inhibiting STT3A using N-linked glycosylation inhibitor-1 (NGI-1) impaired SARS-CoV-2 infectivity and that of its variants [Alpha (B.1.1.7) and Beta (B.1.351)]. Most importantly, 4G10-ADC enters SARS-CoV-2-infected cells and NGI-1 is subsequently released to deglycosylate spike protein, thereby reinforcing the neutralizing abilities of antibodies, vaccines, or convalescent sera and reducing SARS-CoV-2 variant infectivity.

Interpretation: The results indicated that targeting evolutionarily-conserved STT3A-mediated glycosylation via an ADC can exert profound impacts on SARS-CoV-2 variant infectivity. Thus, a novel deglycosylation method was identified suitable for eradicating SARS-CoV-2 variant infection *in vitro*.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00506-5/fulltext

Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study

Abstract

Background: Phase 3 trials found mRNA-1273 was highly effective in preventing COVID-19. We conducted a prospective cohort study at Kaiser Permanente Southern California (KPSC) to determine the real-world vaccine effectiveness (VE) of mRNA-1273 in preventing COVID-19 infection and severe disease.

Methods: For this planned interim analysis, individuals aged ≥18 years receiving 2 doses of mRNA-1273 ≥24 days apart (18/12/2020-31/03/2021) were 1:1 matched to randomly selected unvaccinated individuals by age, sex, and race/ethnicity, with follow-up through 30/06/2021. Outcomes were COVID-19 infection (SARS-CoV-2 positive molecular test or COVID-19 diagnosis code) or severe disease (COVID-19 hospitalization and COVID-19 hospital death). Adjusted hazard ratios (aHR) and confidence intervals (CI) for COVID-19 outcomes comparing vaccinated and unvaccinated individuals were estimated by Cox proportional hazards models accounting for multiple comparisons. Adjusted VE was calculated as (1-aHR)x100. Whole genome sequencing was performed on SARS-CoV-2 positive specimens from the KPSC population.

Findings: This analysis included 352,878 recipients of 2 doses of mRNA-1273 matched to 352,878 unvaccinated individuals. VE (99·3% CI) against COVID-19 infection was 87·4% (84·8–89·6%). VE against COVID-19 hospitalization and hospital death was 95·8% (90·7–98·1%) and 97·9% (66·9-99·9%), respectively. VE was higher against symptomatic (88·3% [98·3% CI: 86·1–90·2%]) than asymptomatic COVID-19 (72·7% [53·4–84·0%]), but was generally similar across age, sex, and racial/ethnic subgroups. VE among individuals with history of COVID-19 ranged from 8·2–33·6%. The most prevalent variants were Alpha (41·6%), Epsilon (17·5%), Delta (11·5%), and Gamma (9·1%), with Delta increasing to 54·0% of variants by June 2021.

Interpretation: These interim results provide reassuring evidence of the VE of 2 doses of mRNA-1273 across age, sex, and racial/ethnic subgroups, and against asymptomatic and symptomatic COVID-19, and severe COVID-19 outcomes. Among individuals with history of COVID-19, mRNA-1273 vaccination may offer added protection beyond

immunity acquired from prior infection. Longer follow-up is needed to fully evaluate VE of mRNA-1273 against emerging SARS-CoV-2 variants.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00130-7/fulltext

Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: Results from a nationwide case-control study in France

Abstract

Background: It was aimed to assess the settings and activities associated with SARS-CoV-2 infection in the context of B.1.617.2 (Delta) variant circulation in France, as well as the protection against symptomatic Delta infection.

Methods: In this nationwide case-control study, cases were SARS-CoV-2 infected adults recruited between 23 May and 13 August 2021. Controls were non-infected adults from a national representative panel matched to cases by age, sex, region, population density and calendar week. Participants completed an online questionnaire and multivariable logistic regression analysis was used to determine the association between acute SARS-CoV-2 infection and recent activity-related exposures, past history of SARS-CoV-2 infection, and COVID-19 vaccination.

Findings: Differences were not found in the settings and activities associated with Delta versus non-Delta infections and grouped them for subsequent analyses. In multivariable analysis involving 12634 cases (8644 Delta and 3990 non-Delta) and 5560 controls, we found individuals under 40 years and attending bars (aOR:1.9; 95%CI:1.6-2.2) or parties (aOR:3.4; 95%CI:2.8-4.2) to be at increased risk of infection. In those aged 40 years and older, having children attend daycare (aOR:1.9; 95%CI:1.1-3.3), kindergarten (aOR:1.6; 95%CI:1.2-2.1), primary school (aOR:1.4; 95%CI:1.2-1.6) or middle school (aOR:1.3; 95%CI:1.2-1.6) were associated with increased risk of infection. We found strong protection against symptomatic Delta infection for those with prior infection whether it was recent (2-6 months) (95%; 95%CI:90-97) or associated with one dose (85%; 95%CI:78-90) or two doses of mRNA vaccine (96%; 95%CI:87-99). For those without past infection, protection was lower with two doses of mRNA vaccine (67%; 95%CI:63-71).

Interpretation: In line with other observational studies, reduced vaccine effectiveness was found against symptomatic Delta infections. The settings and activities at increased risk of infection indicate where efforts to reinforce individual and public health measures need to be concentrated.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00264-7/fulltext

[Effectiveness of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection during the delta (B.1.617.2) variant surge in India: A test-negative, case-control study and a mechanistic study of post-vaccination immune responses](#)

Abstract

Background: SARS-CoV-2 variants of concern (VOCs) have threatened COVID-19 vaccine effectiveness. It was aimed to assess the effectiveness of the ChAdOx1 nCoV-19 vaccine, predominantly against the delta (B.1.617.2) variant, in addition to the cellular immune response to vaccination.

Methods: A test-negative, case-control study was done at two medical research centres in Faridabad, India. All individuals who had a positive RT-PCR test for SARS-CoV-2 infection between April 1, 2021, and May 31, 2021, were included as cases and individuals who had a negative RT-PCR test were included as controls after matching with cases on calendar week of RT-PCR test. The primary outcome was effectiveness of complete vaccination with the ChAdOx1 nCoV-19 vaccine against laboratory-confirmed SARS-CoV-2 infection. The secondary outcomes were effectiveness of a single dose against SARS-CoV-2 infection and effectiveness of a single dose and complete vaccination against moderate-to-severe disease among infected individuals. Additionally, *in-vitro* live-virus neutralization and T-cell immune responses were tested to the spike protein of the wild-type SARS-CoV-2 and VOCs among healthy (anti-nucleocapsid antibody negative) recipients of the ChAdOx1 nCoV-19 vaccine.

Findings: Of 2379 cases of confirmed SARS-CoV-2 infection, 85 (3·6%) were fully vaccinated compared with 168 (8·5%) of 1981 controls (adjusted OR [aOR] 0·37 [95% CI 0·28–0·48]), giving a vaccine effectiveness against SARS-CoV-2 infection of 63·1% (95% CI 51·5–72·1). 157 (6·4%) of 2451 of cases and 181 (9·1%) of 1994) controls had

received a single dose of the ChAdOx1 nCoV-19 vaccine (aOR 0·54 [95% CI 0·42–0·68]), thus vaccine effectiveness of a single dose against SARS-CoV-2 infection was 46·2% (95% CI 31·6–57·7). One of 84 cases with moderate-to-severe COVID-19 was fully vaccinated compared with 84 of 2295 cases with mild COVID-19 (aOR 0·19 [95% CI 0·01–0·90]), giving a vaccine effectiveness of complete vaccination against moderate-to-severe disease of 81·5% (95% CI 9·9–99·0). The effectiveness of a single dose against moderate-to-severe disease was 79·2% (95% CI 46·1–94·0); four of 87 individuals with moderate-to-severe COVID-19 had received a single dose compared with 153 of 2364 participants with mild disease (aOR 0·20 [95% CI 0·06–0·54]). Among 49 healthy, fully vaccinated individuals, neutralising antibody responses were lower against the alpha (B.1.1.7; geometric mean titre 244·7 [95% CI 151·8–394·4]), beta (B.1.351; 97·6 [61·2–155·8]), kappa (B.1.617.1; 112·8 [72·7–175·0]), and delta (88·4 [61·2–127·8]) variants than against wild-type SARS-CoV-2 (599·4 [376·9–953·2]). However, the antigen-specific CD4 and CD8 T-cell responses were conserved against both the delta variant and wild-type SARS-CoV-2.

Interpretation: The ChAdOx1 nCoV-19 vaccine remained effective against moderate-to-severe COVID-19, even during a surge that was dominated by the highly transmissible delta variant of SARS-CoV-2. Spike-specific T-cell responses were maintained against the delta variant. Such cellular immune protection might compensate for waning humoral immunity.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00680-0/fulltext

Model-based assessment of SARS-CoV-2 Delta variant transmission dynamics within partially vaccinated K-12 school populations

Abstract

Background: School reopening policies were examined amidst ongoing transmission of the highly transmissible Delta variant, accounting for vaccination among individuals ≥12 years.

Methods: Data was collected on social contacts among school-aged children in the California Bay Area and developed an individual-based transmission model to simulate

transmission of the Delta variant of SARS-CoV-2 in schools. We evaluated the additional infections in students and teachers/staff resulting over a 128-day semester from in-school instruction compared to remote instruction when various NPIs (mask use, cohorts, and weekly testing of students/teachers) were implemented, across various community-wide vaccination coverages (50%, 60%, 70%), and student (≥12 years) and teacher/staff vaccination coverages (50% - 95%).

Findings: At 70% vaccination coverage, universal masking reduced infections by >57% among students. Masking plus 70% vaccination coverage enabled achievement of <50 excess cases per 1,000 students/teachers, but stricter risk tolerances, such as <25 excess infections per 1,000 students/teachers, required a cohort approach in elementary and middle school populations. In the absence of NPIs, increasing the vaccination coverage of community members from 50% to 70% or elementary teachers from 70% to 95% reduced the excess rate of infection among elementary school students attributable to school transmission by 24% and 37%, respectively.

Interpretations: Amidst Delta variant circulation, we found that schools are not inherently low risk, yet can be made so with high community vaccination coverages and masking. Vaccination of adults protects unvaccinated children.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00129-0/fulltext

NEWSLETTER

Heavily mutated Omicron variant puts scientists on alert

Researchers in South Africa are racing to track the concerning rise of a new variant of the SARS-CoV-2 coronavirus that causes COVID-19. The variant harbours a large number of the mutations found in other variants, including Delta, and it seems to be spreading quickly across South Africa.

A top priority is to follow the variant more closely as it spreads: it was first identified in Botswana earlier this month and has since turned up in a traveler arriving in Hong Kong from South Africa. Scientists are also trying to understand the variant's properties, such as whether it can evade immune responses triggered by vaccines and whether it causes more or less severe disease than other variants do. For more details read the link given below.

Reference

https://www.nature.com/articles/d41586-021-03552-w

PERSPECTIVE

Implications of testicular ACE2 and the renin–angiotensin system for SARS-CoV-2 on testis function

Although many studies have focused on SARS-CoV-2 infection in the lungs, comparatively little is known about the potential effects of the virus on male fertility. SARS-CoV-2 infection of target cells requires the presence of furin, angiotensin-converting enzyme 2 (ACE2) receptors, and transmembrane protease serine 2 (TMPRSS2). Thus, cells in the body that express these proteins might be highly susceptible to viral entry and downstream effects. Currently, reports regarding the expression of the viral entry proteins in the testes are conflicting; however, other members of the SARS-CoV family of viruses — such as SARS-CoV — have been suspected to cause testicular dysfunction and/or orchitis. SARS-CoV-2, which displays many similarities to SARS-CoV, could potentially cause similar adverse effects. Commonalities between SARS family members, taken in combination with sparse reports of testicular discomfort and altered hormone levels in patients with SARS-CoV-2, might indicate possible testicular dysfunction. Thus, SARS-CoV-2 infection has the potential for effects on testis somatic and germline cells and experimental approaches might be required to help identify potential short-term and long-term effects of SARS-CoV-2 on male fertility.

Reference

https://www.nature.com/articles/s41585-021-00542-5

Immune dysregulation and immunopathology induced by SARS-CoV-2 and related coronaviruses — are we our own worst enemy?

Human coronaviruses cause a wide spectrum of disease, ranging from mild common colds to acute respiratory distress syndrome and death. Three highly pathogenic human coronaviruses — severe acute respiratory syndrome coronavirus (SARS-CoV), Middle

East respiratory syndrome coronavirus and SARS-CoV-2 — have illustrated the epidemic and pandemic potential of human coronaviruses, and a better understanding of their disease-causing mechanisms is urgently needed for the rational design of therapeutics. Analyses of patients have revealed marked dysregulation of the immune system in severe cases of human coronavirus infection, and there is ample evidence that aberrant immune responses to human coronaviruses are typified by impaired induction of interferons, exuberant inflammatory responses and delayed adaptive immune responses. In addition, various viral proteins have been shown to impair interferon induction and signalling and to induce inflammasome activation. This suggests that severe disease associated with human coronaviruses is mediated by both dysregulated host immune responses and active viral interference. Here it was discussed that current understanding of the mechanisms involved in each of these scenarios.

Reference

https://www.nature.com/articles/s41577-021-00656-2

Receptome profiling identifies KREMEN1 and ASGR1 as alternative functional receptors of SARS-CoV-2

Host cellular receptors play key roles in the determination of virus tropism and pathogenesis. However, little is known about SARS-CoV-2 host receptors with the exception of ACE2. Furthermore, ACE2 alone cannot explain the multi-organ tropism of SARS-CoV-2 nor the clinical differences between SARS-CoV-2 and SARS-CoV, suggesting the involvement of other receptor(s). Here, we performed genomic receptor profiling to screen 5054 human membrane proteins individually for interaction with the SARS-CoV-2 capsid spike (S) protein. Twelve proteins, including ACE2, ASGR1, and KREMEN1, were identified with diverse S-binding affinities and patterns. ASGR1 or KREMEN1 is sufficient for the entry of SARS-CoV-2 but not SARS-CoV *in vitro* and *in vivo*. SARS-CoV-2 utilizes distinct ACE2/ASGR1/KREMEN1 (ASK) receptor combinations to enter different cell types, and the expression of ASK together displays a markedly stronger correlation with virus susceptibility than that of any individual receptor at both the cell and tissue levels. The cocktail of ASK-related neutralizing antibodies provides the most substantial blockage of SARS-CoV-2 infection in human lung

organoids when compared to individual antibodies. The study revealed an interacting host receptome of SARS-CoV-2, and identified ASGR1 and KREMEN1 as alternative functional receptors that play essential roles in ACE2-independent virus entry, providing insight into SARS-CoV-2 tropism and pathogenesis, as well as a community resource and potential therapeutic strategies for further COVID-19 investigations.

Reference

https://www.nature.com/articles/s41422-021-00595-6

Dual electrochemical sensing of spiked virus and SARS-CoV-2 using natural bed-receptor (MV-gal1)

It has been necessary to use methods that can detect the specificity of a virus during virus screening. In this study, a dual platform was used to identify any spiked virus and specific SARS-CoV-2 antigen, sequentially. A natural bed-receptor surface was introduced as Microparticle Vesicle-Galactins1 (MV-gal1) with the ability of glycan binding to screen every spiked virus. MV are the native vesicles which may have the gal-1 receptor. Gal-1 is the one of lectin receptor which can bind to glycan. After dropping the MV-gal1 on the SCPE/GNP, the sensor is turned on due to the increased electrochemical exchange with $[Fe(CN)6]−3/−4$ probe. Dropping the viral particles of SARS-CoV-2 cause to turn off the sensor with covering the sugar bond (early screening). Then, with the addition of Au/Antibody-SARS-CoV-2 on the MV-gal1@SARS-CoV-2 Antigen, the sensor is turned on again due to the electrochemical amplifier of AuNP (specific detection).For the first time, our sensor has the capacity of screening of any spike virus, and the specific detection of COVID-19 (LOD: 4.57×10^2 copies/mL) by using the natural bed-receptor and a specific antibody in the point of care test.

Reference

https://www.nature.com/articles/s41598-021-02029-0

COMMENTARY

Narrating the natural history of live infection by SARS CoV-2 VOC in animal models

The requirement for rapid answers during the COVID-19 pandemic has stress-tested the resources of 21st century immunology, virology and vaccinology research, with life-and-death need for meaningful answers. Unsurprisingly, given the scale and features of the disease, many of the answers have come out of analysing the sadly abundant supply of infected people at different stages of disease severity. Such studies, from vaccine trials to characterisation of neutralising antibody epitopes, have yielded a huge body of knowledge that within less than 2-years has eclipsed the datasets for many or most other infectious diseases. However, such is the arms race against SARS-CoV-2 and its emerging variants of concern (VOC) that the questions keep coming and keep changing. Some are not of the type easily answered by sampling human cells or sera following real-life, natural exposure. For example, because a study of the earliest events following acute infection requires knowledge of viral isolate sequence, challenge dose and timing, or because of the need to understand the details of viral infection, inflammation and pathogenesis in the lungs or other target organs. For many of these research questions, the answers need to come either from human challenge studies or from animal infection models. Human challenge studies are now well underway but have to encompass several safety and ethical constraints, including virus isolates and dose and invasiveness of tissue sampling. That leaves a gap to be filled by animal studies. However, delivering pathologically and immunologically pertinent and illuminating animal models of human infectious diseases has been notoriously difficult. Even if the hurdle of species-specific receptors is overcome by sequence conservation or transgenesis, there is the common problem that specific patterns of multi-system pathology may be poorly reiterated. In the case of COVID-19, animal model studies have encompassed K18-ACE2 transgenic mice, Syrian hamsters, ferrets and non-human primate (especially macaque) studies. As in all animal models of human disease pathology, there are trade-offs between maintenance costs and therefore group sizes, the pertinence of pathology and disease course and, importantly, availability of

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appropriate reagent sets and cellular markers such as required for flow cytometry, tissue staining or cell separation. Macaque infection has been the gold standard, illuminating key questions such as the elucidation of vaccine efficacy, correlates of protection and immune response patterns after infection by VOC. However, studies are limited by constraints with respect to high cost, small group sizes, the small number of appropriately equipped research facilities and, in many countries, ethical hurdles. Work in the ferret model offers upper respiratory tract viral RNA replication and relatively pertinent lung pathology. ACE2 transgenic mice have been invaluable, especially for mechanistic questions of protective immunity, though the requirement to express ACE2 using a tissue-specific promoter such as K18 imposes a filter on cell-types susceptible to viral entry which is unlike the human pattern of infection and therefore, of multi-organ disease.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00498-9/fulltext