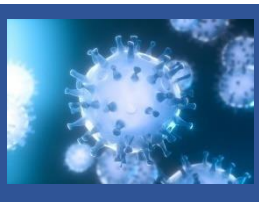
COVID-19

Nov 12 - 18, 2020



RESEARCH PUBLICATIONS

Publication Date: Nov 18, 2020

Actionable cytopathogenic host responses of human alveolar type 2 cells to SARS-CoV-2

Abstract

Human transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causative pathogen of the COVID-19 pandemic, exerts a massive health and socioeconomic crisis. The virus infects alveolar epithelial type 2 cells (AT2s), leading to lung injury and impaired gas exchange, but the mechanisms driving infection and pathology are unclear. We performed a quantitative phosphoproteomic survey of induced pluripotent stem cell-derived AT2s (iAT2s) infected with SARS-CoV-2 at air-liquid interface (ALI). Time course analysis revealed rapid remodeling of diverse host systems, including signaling, RNA processing, translation, metabolism, nuclear integrity, protein trafficking, and cytoskeletal-microtubule organization, leading to cell cycle arrest, genotoxic stress, and innate immunity. Comparison to analogous data from transformed cell lines revealed respiratory-specific processes hijacked by SARS-CoV-2, highlighting potential novel therapeutic avenues which were validated by a high hit rate in a targeted small molecule screen in our iAT2 ALI system.

Reference

https://www.cell.com/molecular-cell/fulltext/S1097-2765(20)30828-5

Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): A single-blind, randomised, controlled, phase 2/3 trial

Abstract

Background: Older adults (aged ≥70 years) are at increased risk of severe disease and death if they develop COVID-19 and are therefore a priority for immunisation should an efficacious vaccine be developed. Immunogenicity of vaccines is often worse in older adults as a result of immunosenescence. We have reported the immunogenicity of a novel chimpanzee adenovirus-vectored vaccine, ChAdOx1 nCoV-19, in young adults, and now describe the safety and immunogenicity of this vaccine in a wider range of participants, including adults aged 70 years and older.

Methods: In this report of the phase 2 component of a single-blind, randomised, controlled, phase 2/3 trial (COV002), healthy adults aged 18 years and older were enrolled at two UK clinical research facilities, in an age-escalation manner, into 18–55 years, 56–69 years, and 70 years and older immunogenicity subgroups. Participants were eligible if they did not have severe or uncontrolled medical comorbidities or a high frailty score (if aged ≥65 years). First, participants were recruited to a low-dose cohort, and within each age group, participants were randomly assigned to receive either intramuscular ChAdOx1 nCoV-19 (2·2 × 1010 virus particles) or a control vaccine, MenACWY, using block randomisation and stratified by age and dose group and study site, using the following ratios: in the 18–55 years group, 1:1 to either two doses of ChAdOx1 nCoV-19 or two doses of MenACWY; in the 56–69 years group, 3:1:3:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY; and in the 70 years and older, 5:1:5:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. Prime-booster regimens were given 28 days apart. Participants were then recruited to the standard-dose cohort (3·5–6·5 × 1010 virus particles of ChAdOx1 nCoV-19) and the same randomisation procedures were followed, except the 18–55 years group was assigned in a 5:1 ratio to two doses of ChAdOx1 nCoV-19 or two doses of MenACWY. Participants and investigators, but not staff administering the vaccine, were masked to vaccine allocation. The specific objectives of this report were

to assess the safety and humoral and cellular immunogenicity of a single-dose and two-dose schedule in adults older than 55 years. Humoral responses at baseline and after each vaccination until 1 year after the booster were assessed using an in-house standardised ELISA, a multiplex immunoassay, and a live severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) microneutralisation assay (MNA80). Cellular responses were assessed using an ex-vivo IFN-γ enzyme-linked immunospot assay. The coprimary outcomes of the trial were efficacy, as measured by the number of cases of symptomatic, virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were by group allocation in participants who received the vaccine. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. This study is ongoing and is registered with ClinicalTrials.gov, NCT04400838, and ISRCTN, 15281137.

Findings: Between May 30 and Aug 8, 2020, 560 participants were enrolled: 160 aged 18–55 years (100 assigned to ChAdOx1 nCoV-19, 60 assigned to MenACWY), 160 aged 56–69 years (120 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY), and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY). Seven participants did not receive the boost dose of their assigned two-dose regimen, one participant received the incorrect vaccine, and three were excluded from immunogenicity analyses due to incorrectly labelled samples. 280 (50%) of 552 analysable participants were female. Local and systemic reactions were more common in participants given ChAdOx1 nCoV-19 than in those given the control vaccine, and similar in nature to those previously reported (injection-site pain, feeling feverish, muscle ache, headache), but were less common in older adults (aged ≥56 years) than younger adults. In those receiving two standard doses of ChAdOx1 nCoV-19, after the prime vaccination local reactions were reported in 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 in the 56–69 years group, and 30 (61%) of 49 in the 70 years and older group, and systemic reactions in 42 (86%) participants in the 18–55 years group, 23 (77%) in the 56–69 years group, and 32 (65%) in the 70 years and older group. As of Oct 26, 2020, 13 serious adverse events occurred during the study period, none of which were considered to be related to either study vaccine. In participants who received two doses of vaccine, median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts

(standard-dose groups: 18–55 years, 20 713 arbitrary units [AU]/mL [IQR 13 898–33 550], n=39; 56–69 years, 16 170 AU/mL [10 233–40 353], n=26; and ≥70 years 17 561 AU/mL [9705–37 796], n=47; p=0·68). Neutralising antibody titres after a boost dose were similar across all age groups (median MNA80 at day 42 in the standard-dose groups: 18–55 years, 193 [IQR 113–238], n=39; 56–69 years, 144 [119–347], n=20; and ≥70 years, 161 [73–323], n=47; p=0·40). By 14 days after the boost dose, 208 (>99%) of 209 boosted participants had neutralising antibody responses. T-cell responses peaked at day 14 after a single standard dose of ChAdOx1 nCoV-19 (18–55 years: median 1187 spot-forming cells [SFCs] per million peripheral blood mononuclear cells [IQR 841–2428], n=24; 56–69 years: 797 SFCs [383–1817], n=29; and ≥70 years: 977 SFCs [458–1914], n=48).

Interpretation: ChAdOx1 nCoV-19 appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32466-1/fulltext

Crystallographic structure of wild-type SARS-CoV-2 main protease acyl-enzyme intermediate with physiological C-terminal autoprocessing site

Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen that causes the disease COVID-19, produces replicase polyproteins 1a and 1ab that contain, respectively, 11 or 16 nonstructural proteins (nsp). Nsp5 is the main protease (Mpro) responsible for cleavage at eleven positions along these polyproteins, including at its own N- and C-terminal boundaries, representing essential processing events for subsequent viral assembly and maturation. X-ray crystallographic structures of this cysteine protease has been determined in its wild-type free active site state at 1.8 Å resolution, in its acyl-enzyme intermediate state with the native C-terminal autocleavage sequence at 1.95 Å resolution and in its product bound state at 2.0 Å resolution by employing an active site mutation (C145A). It was characterized the stereochemical

features of the acyl-enzyme intermediate including critical hydrogen bonding distances underlying catalysis in the Cys/His dyad and oxyanion hole. It was also identified a highly ordered water molecule in a position compatible for a role as the deacylating nucleophile in the catalytic mechanism and characterize the binding groove conformational changes and dimerization interface that occur upon formation of the acyl-enzyme. Collectively, these crystallographic snapshots provide valuable mechanistic and structural insights for future antiviral therapeutic development including revised molecular docking strategies based on Mpro inhibition.

Reference

https://www.nature.com/articles/s41467-020-19662-4

Architecture of a SARS-CoV-2 mini replication and transcription complex

Abstract

Non-structural proteins (nsp) constitute the SARS-CoV-2 replication and transcription complex (RTC) to play a pivotal role in the virus life cycle. Here we determine the atomic structure of a SARS-CoV-2 mini RTC, assembled by viral RNA-dependent RNA polymerase (RdRp, nsp12) with a template-primer RNA, nsp7 and nsp8, and two helicase molecules (nsp13-1 and nsp13-2), by cryo-electron microscopy. Two groups of mini RTCs with different conformations of nsp13-1 are identified. In both of them, nsp13-1 stabilizes overall architecture of the mini RTC by contacting with nsp13-2, which anchors the 5′-extension of RNA template, as well as interacting with nsp7-nsp8-nsp12-RNA. Orientation shifts of nsp13-1 results in its variable interactions with other components in two forms of mini RTC. The mutations on nsp13-1:nsp12 and nsp13-1:nsp13-2 interfaces prohibit the enhancement of helicase activity achieved by mini RTCs. These results provide an insight into how helicase couples with polymerase to facilitate its function in virus replication and transcription.

Reference

https://www.nature.com/articles/s41467-020-19770-1

Serological follow-up of SARS-CoV-2 asymptomatic subjects

Abstract

SARS-CoV-2 symptoms are non-specific and can range from asymptomatic presentation to severe pneumonia. Asymptomatic subjects carrying SARS-CoV-2 often remain undiagnosed and it is still debated whether they develop immunoglobulins (Ig) and how long they persist. The aim of this study was to investigate the development and persistence of antibodies against SARS-CoV-2 in asymptomatic subjects infected by the virus. This follow-up study was performed on the 31 asymptomatic subjects who presented a positive nasal swab or serology against SARS-CoV-2 (Ig against Spike-RBD) in the first part of the UNICORN study (March 2020) aimed at attesting previous or current contacts with the virus in the personnel of the University of Milan. Eight weeks after the first Ig measure, these subjects were invited to donate a second blood sample for testing serum antibodies (IgM, IgG and total antibodies) and to fill-in a structured questionnaire. About 80% of asymptomatic subjects did not present circulating immunoglobulins against SARS-CoV-2 after 8 weeks from a positive nasal swab against the virus. Moreover, in more than 40% of these subjects, no Ig against SARS-CoV-2 were detected at any time. Finally, about two third of subjects with immunoglobulins at baseline did not present IgG against SARS-CoV-2 after 8 weeks. The majority of subjects who developed an asymptomatic SARS-CoV-2 infection do not present antibodies against the RBD-spike protein after 8 weeks of follow-up. These data should be taken into account for the interpretation of the serological evidences on SARS-CoV-2 that are emerging nowadays.

Reference

https://www.nature.com/articles/s41598-020-77125-8

Open resource of clinical data from patients with pneumonia for the prediction of COVID-19 outcomes via deep learning

Abstract

Data from patients with coronavirus disease 2019 (COVID-19) are essential for guiding clinical decision making, for furthering the understanding of this viral disease, and for

diagnostic modelling. Here, we describe an open resource containing data from 1,521 patients with pneumonia (including COVID-19 pneumonia) consisting of chest computed tomography (CT) images, 130 clinical features (from a range of biochemical and cellular analyses of blood and urine samples) and laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clinical status. We show the utility of the database for prediction of COVID-19 morbidity and mortality outcomes using a deep learning algorithm trained with data from 1,170 patients and 19,685 manually labelled CT slices. In an independent validation cohort of 351 patients, the algorithm discriminated between negative, mild and severe cases with areas under the receiver operating characteristic curve of 0.944, 0.860 and 0.884, respectively. The open database may have further uses in the diagnosis and management of patients with COVID-19.

Reference

https://www.nature.com/articles/s41551-020-00633-5

Macrophage expression and prognostic significance of the long pentraxin PTX3 in COVID-19

Abstract

Long pentraxin 3 (PTX3) is an essential component of humoral innate immunity, involved in resistance to selected pathogens and in the regulation of inflammation. The present study was designed to assess the presence and significance of PTX3 in Coronavirus Disease 2019 (COVID-19). RNA-sequencing analysis of peripheral blood mononuclear cells, single-cell bioinformatics analysis and immunohistochemistry of lung autopsy samples revealed that myelomonocytic cells and endothelial cells express high levels of PTX3 in patients with COVID-19. Increased plasma concentrations of PTX3 were detected in 96 patients with COVID-19. PTX3 emerged as a strong independent predictor of 28-d mortality in multivariable analysis, better than conventional markers of inflammation, in hospitalized patients with COVID-19. The prognostic significance of PTX3 abundance for mortality was confirmed in a second independent cohort (54 patients). Thus, circulating and lung myelomonocytic cells and endothelial cells are a

major source of PTX3, and PTX3 plasma concentration can serve as an independent strong prognostic indicator of short-term mortality in COVID-19.

Reference

https://www.nature.com/articles/s41590-020-00832-x

Open resource of clinical data from patients with pneumonia for the prediction of COVID-19 outcomes *via* deep learning

Abstract

Consumer wearable devices that continuously measure vital signs have been used to monitor the onset of infectious disease. Here, we show that data from consumer smartwatches can be used for the pre-symptomatic detection of coronavirus disease 2019 (COVID-19). It was analysed physiological and activity data from 32 individuals infected with COVID-19, identified from a cohort of nearly 5,300 participants, and found that 26 of them (81%) had alterations in their heart rate, number of daily steps or time asleep. Of the 25 cases of COVID-19 with detected physiological alterations for which we had symptom information, 22 were detected before (or at) symptom onset, with four cases detected at least nine days earlier. Using retrospective smartwatch data, we show that 63% of the COVID-19 cases could have been detected before symptom onset in real time via a two-tiered warning system based on the occurrence of extreme elevations in resting heart rate relative to the individual baseline. The findings suggest that activity tracking and health monitoring via consumer wearable devices may be used for the large-scale, real-time detection of respiratory infections, often pre-symptomatically.

Reference

https://www.nature.com/articles/s41598-020-76488-2

Investigating duration and intensity of Covid-19 social-distancing strategies

Abstract

The exponential character of the recent Covid-19 outbreak requires a change in strategy from containment to mitigation. Meanwhile, most countries apply social distancing with the objective to keep the number of critical cases below the capabilities of the health care system. Due to the novelty and rapid spread of the virus, an a priori assessment of this strategy was not possible. In this study, we present a model-based systems analysis to assess the effectiveness of social distancing measures in terms of intensity and duration of application. Results show a super-linear scaling between intensity (percent contact reduction) and required duration of application to have an added value (a lower number of fatalities). This holds true for an effective reproduction of R>1 and is reverted for R<1. If R is not reduced below 1, secondary effects of required long-term isolation are likely to unravel the added value of disease mitigation. If an extinction is not feasible, we recommend moderate social-distancing that is well balanced against capability limits of national health-care systems.

Reference

https://www.nature.com/articles/s41598-020-76392-9

Development of CpG-adjuvanted stable prefusion SARS-CoV-2 spike antigen as a subunit vaccine against COVID-19

Abstract

The COVID-19 pandemic is a worldwide health emergency which calls for an unprecedented race for vaccines and treatment. In developing a COVID-19 vaccine, we applied technology previously used for MERS-CoV to produce a prefusion-stabilized SARS-CoV-2 spike protein, S-2P. To enhance immunogenicity and mitigate the potential vaccine-induced immunopathology, CpG 1018, a Th1-biasing synthetic toll-like receptor 9 (TLR9) agonist was selected as an adjuvant candidate. S-2P in combination with CpG 1018 and aluminum hydroxide (alum) was found to be the most potent immunogen and induced high titer of neutralizing antibodies in sera of immunized mice against pseudotyped lentivirus reporter or live wild-type SARS-CoV-2. In addition, the

antibodies elicited were able to cross-neutralize pseudovirus containing the spike protein of the D614G variant, indicating the potential for broad spectrum protection. A marked Th1 dominant response was noted from cytokines secreted by splenocytes of mice immunized with CpG 1018 and alum. No vaccine-related serious adverse effects were found in the dose-ranging study in rats administered single- or two-dose regimens of S-2P combined with CpG 1018 alone or CpG 1018 with alum. These data support continued development of CHO-derived S-2P formulated with CpG 1018 and alum as a candidate vaccine to prevent COVID-19 disease.

Reference

https://www.nature.com/articles/s41598-020-77077-z

The spatiotemporal estimation of the risk and the international transmission of COVID-19: A global perspective

Abstract

An ongoing novel coronavirus outbreak (COVID-19) started in Wuhan, China, in December 2019. Currently, the spatiotemporal epidemic transmission, prediction, and risk are insufficient for COVID-19 but we urgently need relevant information globally. A novel two-stage simulation model was developed to simulate the spatiotemporal changes in the number of cases and estimate the future worldwide risk. Simulation results show that if there is no specific medicine for it, it will form a global pandemic. Taiwan, South Korea, Hong Kong, Japan, Thailand, and the United States are the most vulnerable. The relationship between each country's vulnerability and days before the first imported case occurred shows an exponential decrease. It was successfully predicted the outbreak of South Korea, Japan, and Italy in the early stages of the global pandemic based on the information before February 12, 2020. The development of the epidemic is now earlier than we expected. However, the trend of spread is similar to our estimation.

Reference

https://www.nature.com/articles/s41598-020-77242-4

Preparing for a future COVID-19 wave: Insights and limitations from a data-driven evaluation of non-pharmaceutical interventions in Germany

Abstract

To contain the COVID-19 pandemic, governments introduced strict Non-Pharmaceutical Interventions (NPI) that restricted movement, public gatherings, national and international travel, and shut down large parts of the economy. Yet, the impact of the enforcement and subsequent loosening of these policies on the spread of COVID-19 is not well understood. Accordingly, we measure the impact of NPIs on mitigating disease spread by exploiting the spatio-temporal variations in policy measures across the 16 states of Germany. While this quasi-experiment does not allow for causal identification, each policy's effect on reducing disease spread provides meaningful insights. We adapt the Susceptible–Exposed–Infected–Recovered model for disease propagation to include data on daily confirmed cases, interstate movement, and social distancing. By combining the model with measures of policy contributions on mobility reduction, we forecast scenarios for relaxing various types of NPIs. The model finds that in Germany policies that mandated contact restrictions (e.g., movement in public space limited to two persons or people co-living), closure of educational institutions (e.g., schools), and retail outlet closures are associated with the sharpest drops in movement within and across states. Contact restrictions appear to be most effective at lowering COVID-19 cases, while border closures appear to have only minimal effects at mitigating the spread of the disease, even though cross-border travel might have played a role in seeding the disease in the population. It was believed that a deeper understanding of the policy effects on mitigating the spread of COVID-19 allows a more accurate forecast of disease spread when NPIs are partially loosened and gives policymakers better data for making informed decisions.

Reference

https://www.nature.com/articles/s41598-020-76244-6

Androgen signaling regulates SARS-CoV-2 receptor levels and is associated with severe COVID-19 symptoms in men

Abstract

SARS-CoV-2 infection has led to a global health crisis, and yet our understanding of the disease and potential treatment options remains limited. The infection occurs through binding of the virus with angiotensin converting enzyme 2 (ACE2) on the cell membrane. Here, a screening strategy was established to identify drugs that reduce ACE2 levels in human embryonic stem cell (hESC)-derived cardiac cells and lung organoids. Target analysis of hit compounds revealed androgen signaling as a key modulator of ACE2 levels. Treatment with antiandrogenic drugs reduced ACE2 expression and protected hESC-derived lung organoids against SARS-CoV-2 infection. Finally, clinical data on COVID-19 patients demonstrated that prostate diseases, which are linked to elevated androgen, are significant risk factors and that genetic variants that increase androgen levels are associated with higher disease severity. These findings offer insights on the mechanism of disproportionate disease susceptibility in men and identify antiandrogenic drugs as candidate therapeutics for COVID-19.

Reference

https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(20)30547-6

Cryo-EM Structures of SARS-CoV-2 Spike without and with ACE2 Reveal a pH-Dependent Switch to Mediate Endosomal Positioning of Receptor-Binding Domains

Abstract

The SARS-CoV-2 spike employs mobile receptor-binding domains (RBDs) to engage the human ACE2 receptor and to facilitate virus entry, which can occur through low pH-endosomal pathways. To understand how ACE2 binding and low pH impact spike conformation, we determined cryo-EM structures –at serological and endosomal pH– delineating spike recognition of up to three ACE2 molecules. RBDs freely adopted ‘up’

conformations required for ACE2 interaction, primarily through RBD movement combined with smaller alterations in neighboring domains. In the absence of ACE2, cryo-EM structures revealed single-RBD-up conformations to dominate at pH 5.5, resolving into a solitary all-down conformation at lower pH. Notably, a pH-dependent refolding region (residues 824-858) at the spike-interdomain interface displayed dramatic structural rearrangements and mediated RBD positioning through coordinated movements of the entire trimer apex. These findings provide insight into how receptor interactions and endosomal pH alter RBD positioning and potentially facilitate immune evasion from RBD-up binding antibody.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30621-1

Integrative imaging reveals SARS-CoV-2 induced reshaping of subcellular morphologies

Abstract

Pathogenesis induced by SARS-CoV-2 is thought to result from both an inflammation dominated cytokine response and virus-induced cell perturbation causing cell death. Here, we employ an integrative imaging analysis to determine morphological organelle alterations induced in SARS-CoV-2 infected human lung epithelial cells. We report 3D electron microscopy reconstructions of whole-cells and subcellular compartments, revealing extensive fragmentation of the Golgi apparatus, alteration of the mitochondrial network and recruitment of peroxisomes to viral replication organelles formed by clusters of double-membrane vesicles (DMVs). These are tethered to the endoplasmic reticulum, providing insights into DMV biogenesis and spatial coordination of SARS-CoV-2 replication. Live cell imaging combined with an infection sensor reveals profound remodeling of cytoskeleton elements. Pharmacological inhibition of their dynamics suppresses SARS-CoV-2 replication. We thus report insights into virus-induced cytopathic effects, and provide alongside a comprehensive publicly available repository of 3D data-sets of SARS-CoV-2 infected cells for download and smooth online visualization.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30620-X

A machine learning-aided global diagnostic and comparative tool to assess effect of quarantine control in COVID-19 spread

Abstract

A globally applicable diagnostic COVID-19 model was developed by augmenting the classical SIR epidemiological model with a neural network module. The model does not rely upon previous epidemics like SARS/MERS and all parameters are optimized via machine learning algorithms used on publicly available COVID-19 data. The model decomposes the contributions to the infection time series to analyze and compare the role of quarantine control policies used in highly affected regions of Europe, North America, South America, and Asia in controlling the spread of the virus. For all continents considered, our results show a generally strong correlation between strengthening of the quarantine controls as learnt by the model and actions taken by the regions' respective governments. In addition, we have hosted our quarantine diagnosis results for the top 70 affected countries worldwide, on a public platform.

Reference

https://www.cell.com/patterns/fulltext/S2666-3899(20)30193-8

Phosphoregulation of phase separation by the SARS-CoV-2 N protein suggests a biophysical basis for its dual functions

Abstract

The nucleocapsid (N) protein of coronaviruses serves two major functions: compaction of the RNA genome in the virion and regulation of viral gene transcription. It is not clear how the N protein mediates such distinct functions. The N protein contains two RNA-binding domains surrounded by regions of intrinsic disorder. Phosphorylation of the central disordered region promotes the protein’s transcriptional function, but the underlying mechanism is not known. Here we show that the N protein of SARS-CoV-2, together with viral RNA, forms biomolecular condensates. Unmodified N protein forms partially ordered gel-like condensates and discrete 15-nm particles based on multivalent

RNA-protein and protein-protein interactions. Phosphorylation reduces these interactions, generating a more liquid-like droplet. We propose that distinct oligomeric states support the two functions of the N protein: unmodified protein forms a structured oligomer that is suited for nucleocapsid assembly, and phosphorylated protein forms a liquid-like compartment for viral genome processing.

Reference

https://www.cell.com/molecular-cell/fulltext/S1097-2765(20)30803-0

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: A randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

Abstract

Background: With the unprecedented morbidity and mortality associated with the COVID-19 pandemic, a vaccine against COVID-19 is urgently needed. We investigated CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated vaccine candidate against COVID-19, containing inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), for its safety, tolerability and immunogenicity.

Methods: In this randomised, double-blind, placebo-controlled, phase 1/2 clinical trial, healthy adults aged 18–59 years were recruited from the community in Suining County of Jiangsu province, China. Adults with SARS-CoV-2 exposure or infection history, with axillary temperature above 37·0°C, or an allergic reaction to any vaccine component were excluded. The experimental vaccine for the phase 1 trial was manufactured using a cell factory process (CellSTACK Cell Culture Chamber 10, Corning, Wujiang, China), whereas those for the phase 2 trial were produced through a bioreactor process (ReadyToProcess WAVE 25, GE, Umea, Sweden). The phase 1 trial was done in a dose-escalating manner. At screening, participants were initially separated (1:1), with no specific randomisation, into two vaccination schedule cohorts, the days 0 and 14 vaccination cohort and the days 0 and 28 vaccination cohort, and within each cohort the first 36 participants were assigned to block 1 (low dose CoronaVac [3 μg per 0·5 mL of aluminium hydroxide diluent per dose) then another 36 were assigned to block 2 (high-dose Coronavc [6 μg per 0·5 mL of aluminium hydroxide diluent per dse]). Within each

block, participants were randomly assigned (2:1), using block randomisation with a block size of six, to either two doses of CoronaVac or two doses of placebo. In the phase 2 trial, at screening, participants were initially separated (1:1), with no specific randomisation, into the days 0 and 14 vaccination cohort and the days 0 and 28 vaccination cohort, and participants were randomly assigned (2:2:1), using block randomisation with a block size of five, to receive two doses of either low-dose CoronaVac, high-dose CoronaVac, or placebo. Participants, investigators, and laboratory staff were masked to treatment allocation. The primary safety endpoint was adverse reactions within 28 days after injection in all participants who were given at least one dose of study drug (safety population). The primary immunogenic outcome was seroconversion rates of neutralising antibodies to live SARS-CoV-2 at day 14 after the last dose in the days 0 and 14 cohort, and at day 28 after the last dose in the days 0 and 28 cohort in participants who completed their allocated two-dose vaccination schedule (per-protocol population). This trial is registered with ClinicalTrials.gov, NCT04352608, and is closed to accrual.

Findings: Between April 16 and April 25, 2020, 144 participants were enrolled in the phase 1 trial, and between May 3 and May 5, 2020, 600 participants were enrolled in the phase 2 trial. 743 participants received at least one dose of investigational product (n=143 for phase 1 and n=600 for phase 2; safety population). In the phase 1 trial, the incidence of adverse reactions for the days 0 and 14 cohort was seven (29%) of 24 participants in the 3 ug group, nine (38%) of 24 in the 6 μg group, and two (8%) of 24 in the placebo group, and for the days 0 and 28 cohort was three (13%) of 24 in the 3 μg group, four (17%) of 24 in the 6 μg group, and three (13%) of 23 in the placebo group. The seroconversion of neutralising antibodies on day 14 after the days 0 and 14 vaccination schedule was seen in 11 (46%) of 24 participants in the 3 μg group, 12 (50%) of 24 in the 6 μg group, and none (0%) of 24 in the placebo group; whereas at day 28 after the days 0 and 28 vaccination schedule, seroconversion was seen in 20 (83%) of 24 in the 3 μg group, 19 (79%) of 24 in the 6 μg group, and one (4%) of 24 in the placebo group. In the phase 2 trial, the incidence of adverse reactions for the days 0 and 14 cohort was 40 (33%) of 120 participants in the 3 μg group, 42 (35%) of 120 in the 6 μg group, and 13 (22%) of 60 in the placebo group, and for the days 0 and 28 cohort was 23 (19%) of 120 in the 3 μg group, 23 (19%) of 120 in the 6 μg group, and

11 (18%) of 60 for the placebo group. Seroconversion of neutralising antibodies was seen for 109 (92%) of 118 participants in the 3 μg group, 117 (98%) of 119 in the 6 μg group, and two (3%) of 60 in the placebo group at day 14 after the days 0 and 14 schedule; whereas at day 28 after the days 0 and 28 schedule, seroconversion was seen in 114 (97%) of 117 in the 3 μg group, 118 (100%) of 118 in the 6 μg group, and none (0%) of 59 in the placebo group.

Interpretation: Taking safety, immunogenicity, and production capacity into account, the 3 μg dose of CoronaVac is the suggested dose for efficacy assessment in future phase 3 trials.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30843-4/fulltext

High-content screening of Thai medicinal plants reveals *Boesenbergia rotunda* extract and its component Panduratin A as anti-SARS-CoV-2 agents

Abstract

Since December 2019, the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused severe pneumonia, a disease named COVID-19, that became pandemic and created an acute threat to public health. The effective therapeutics are in urgent need. Here, we developed a high-content screening for the antiviral candidates using fluorescence-based SARS-CoV-2 nucleoprotein detection in Vero E6 cells coupled with plaque reduction assay. Among 122 Thai natural products, we found that Boesenbergia rotunda extract and its phytochemical compound, panduratin A, exhibited the potent anti-SARS-CoV-2 activity. Treatment with B. rotunda extract and panduratin A after viral infection drastically suppressed SARS-CoV-2 infectivity in Vero E6 cells with IC50 of 3.62 μg/mL (CC50 = 28.06 μg/mL) and 0.81 μM (CC50 = 14.71 μM), respectively. Also, the treatment of panduratin A at the pre-entry phase inhibited SARS-CoV-2 infection with IC50 of 5.30 μM (CC50 = 43.47 μM). Our study demonstrated, for the first time, that panduratin A exerts the inhibitory effect against SARS-CoV-2 infection at both pre-entry and post-infection phases. Apart from Vero E6 cells, treatment with this compound was able to suppress viral infectivity in human airway epithelial cells. This result confirmed the potential of panduratin A as the

anti-SARS-CoV-2 agent in the major target cells in human. Since B. rotunda is a culinary herb generally grown in China and Southeast Asia, its extract and the purified panduratin A may serve as the promising candidates for therapeutic purposes with economic advantage during COVID-19 situation.

Reference

https://www.nature.com/articles/s41598-020-77003-3

STAT2 signaling restricts viral dissemination but drives severe pneumonia in SARS-CoV-2 infected hamsters

Abstract

Emergence of SARS-CoV-2 causing COVID-19 has resulted in hundreds of thousands of deaths. In search for key targets of effective therapeutics, robust animal models mimicking COVID-19 in humans are urgently needed. Here, we show that Syrian hamsters, in contrast to mice, are highly permissive to SARS-CoV-2 and develop bronchopneumonia and strong inflammatory responses in the lungs with neutrophil infiltration and edema, further confirmed as consolidations visualized by micro-CT alike in clinical practice. Moreover, we identify an exuberant innate immune response as key player in pathogenesis, in which STAT2 signaling plays a dual role, driving severe lung injury on the one hand, yet restricting systemic virus dissemination on the other. Our results reveal the importance of STAT2-dependent interferon responses in the pathogenesis and virus control during SARS-CoV-2 infection and may help rationalizing new strategies for the treatment of COVID-19 patients.

Reference

https://www.nature.com/articles/s41467-020-19684-y

Upper airway gene expression reveals suppressed immune responses to SARS-CoV-2 compared with other respiratory viruses

Abstract

SARS-CoV-2 infection is characterized by peak viral load in the upper airway prior to or at the time of symptom onset, an unusual feature that has enabled widespread

transmission of the virus and precipitated a global pandemic. How SARS-CoV-2 is able to achieve high titer in the absence of symptoms remains unclear. Here, we examine the upper airway host transcriptional response in patients with COVID-19 (n = 93), other viral (n = 41) or non-viral (n = 100) acute respiratory illnesses (ARIs). Compared with other viral ARIs, COVID-19 is characterized by a pronounced interferon response but attenuated activation of other innate immune pathways, including toll-like receptor, interleukin and chemokine signaling. The IL-1 and NLRP3 inflammasome pathways are markedly less responsive to SARS-CoV-2, commensurate with a signature of diminished neutrophil and macrophage recruitment. This pattern resembles previously described distinctions between symptomatic and asymptomatic viral infections and may partly explain the propensity for pre-symptomatic transmission in COVID-19. We further use machine learning to build 27-, 10- and 3-gene classifiers that differentiate COVID-19 from other ARIs with AUROCs of 0.981, 0.954 and 0.885, respectively. Classifier performance is stable across a wide range of viral load, suggesting utility in mitigating false positive or false negative results of direct SARS-CoV-2 tests.

Reference

https://www.nature.com/articles/s41467-020-19587-y

Immune suppression in the early stage of COVID-19 disease

Abstract

The outbreak of COVID-19 has become a worldwide pandemic. The pathogenesis of this infectious disease and how it differs from other drivers of pneumonia is unclear. Here we analyze urine samples from COVID-19 infection cases, healthy donors and non-COVID-19 pneumonia cases using quantitative proteomics. The molecular changes suggest that immunosuppression and tight junction impairment occur in the early stage of COVID-19 infection. Further subgrouping of COVID-19 patients into moderate and severe types shows that an activated immune response emerges in severely affected patients. We propose a two-stage mechanism of pathogenesis for this unusual viral infection. Our data advance our understanding of the clinical features of COVID-19 infections and provide a resource for future mechanistic and therapeutics studies.

Reference

https://www.nature.com/articles/s41467-020-19706-9

Publication Date: Nov 16, 2020

Ultrasensitive and selective detection of SARS-CoV-2 using thermotropic liquid crystals and image-based machine learning

Abstract

Rapid, robust virus detection techniques with ultrahigh sensitivity and selectivity are required for the outbreak of the pandemic coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Here, it was reported that the femtomolar concentrations of single-stranded ribonucleic acid (ssRNA) of SARS-CoV-2 trigger ordering transitions in liquid crystal (LC) films decorated with cationic surfactant and complementary 15-mer single-stranded deoxyribonucleic acid (ssDNA) probe. More importantly, the sensitivity of the LC to the severe acute respiratory syndrome (SARS) ssRNA, with a 3 base pair-mismatch compared to the SARS-CoV-2 ssRNA, is measured to decrease by seven orders of magnitude, suggesting that the LC ordering transitions depend strongly on the targeted oligonucleotide sequence. Finally, it was designed a LC-based diagnostic kit and a smartphone-based application (App) to enable automatic detection of SARS-CoV-2 ssRNA, which could be used for reliable self-test of SARS-CoV-2 at home without the need for complex equipment or procedures.

Reference

https://www.cell.com/cell-reports-physical-science/fulltext/S2666-3864(20)30298-8

Real-time suicide mortality data from police reports in Queensland, Australia, during the COVID-19 pandemic: An interrupted time-series analysis

Abstract

Background: Deaths by suicide can increase during infectious disease outbreaks. This study analysed suspected suicide rates in 2020 relative to 2015–19 to assess any early effects of the COVID-19 pandemic in Queensland, Australia.

Methods: Data was analysed from the interim Queensland Suicide Register (iQSR), a state-wide real-time suicide surveillance system, using an interrupted time-series design. The data source for the iQSR is the Form 1 police report of a death to a coroner. Two QSR staff independently classed the probability of a death by suicide as possible, probable, or beyond reasonable doubt. The analysis included the probable or beyond reasonable doubt categories as suspected suicides. The primary outcome was the monthly suspected suicide rate. We applied Poisson and negative binomial regressions to assess whether Queensland's Public Health Emergency Declaration on Jan 29, 2020, affected suspected suicides from Feb 1 to Aug 31, 2020. Secondary outcomes included absolute or relative changes in police-reported motives of recent unemployment, financial problems, domestic violence, and relationship breakdown.

Findings: 3793 suspected suicides were recorded with an unadjusted monthly rate of 14·85 deaths per 100 000 people (from Jan 1, 2015, to Jan 1, 2020) before the declaration, and 443 suspected suicides were recorded with an unadjusted monthly rate of 14·07 deaths per 100 000 people (Feb 1, 2020, onwards) after the declaration. An interrupted time-series Poisson regression model unadjusted (rate ratio [RR] 0·94, 95% CI 0·82–1·06) and adjusted for overdispersion, seasonality, and pre-exposure trends (RR 1·02, 95% CI 0·83–1·25) indicated no evidence of a change in suspected suicide rates. We found no absolute or relative increases in the motives for suspected suicides, including recent unemployment, financial problems, relationship breakdown, or domestic violence from February to August, 2020, compared with the pre-exposure period.

Interpretation: There does not yet appear to be an overall change in the suspected suicide rate in the 7 months since Queensland declared a public health emergency. Despite this, COVID-19 has contributed to some suspected suicides in Queensland. Ongoing community spread and increasing death rates of COVID-19, and its impact on national economies and mental health, reinforces the need for governments to maintain the monitoring and reporting of suicide mortality in real time.

Reference

https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30435-1/fulltext

Eliciting B cell immunity against infectious diseases using nanovaccines

Abstract

Infectious diseases, including the coronavirus disease 2019 (COVID-19) pandemic that has brought the world to a standstill, are emerging at an unprecedented rate with a substantial impact on public health and global economies. For many life-threatening global infectious diseases, such as human immunodeficiency virus (HIV) infection, malaria and influenza, effective vaccinations are still lacking. There are numerous roadblocks to developing new vaccines, including a limited understanding of immune correlates of protection to these global infections. To induce a reproducible, strong immune response against difficult pathogens, sophisticated nanovaccine technologies are under investigation. In contrast to conventional vaccines, nanovaccines provide improved access to lymph nodes, optimal packing and presentation of antigens, and induction of a persistent immune response. This Review provides a perspective on the global trends in emerging nanoscale vaccines for infectious diseases and describes the biological, experimental and logistical problems associated with their development, and how immunoengineering can be leveraged to overcome these challenges.

Reference

https://www.nature.com/articles/s41565-020-00790-3

DeepLMS: A deep learning predictive model for supporting online learning in the Covid-19 era

Abstract

Coronavirus (Covid-19) pandemic has imposed a complete shut-down of face-to-face teaching to universities and schools, forcing a crash course for online learning plans and technology for students and faculty. In the midst of this unprecedented crisis, video conferencing platforms (e.g., Zoom, WebEx, MS Teams) and learning management systems (LMSs), like Moodle, Blackboard and Google Classroom, are being adopted and heavily used as online learning environments (OLEs). However, as such media solely provide the platform for e-interaction, effective methods that can be used to predict the learner's behavior in the OLEs, which should be available as supportive tools to educators and metacognitive triggers to learners. Here we show, for the first time,

that Deep Learning techniques can be used to handle LMS users' interaction data and form a novel predictive model, namely DeepLMS, that can forecast the quality of interaction (QoI) with LMS. Using Long Short-Term Memory (LSTM) networks, DeepLMS results in average testing Root Mean Square Error (RMSE) <0.009, and average correlation coefficient between ground truth and predicted QoI values r≥0.97 ($p<0.05$), when tested on QoI data from one database pre- and two ones during-Covid-19 pandemic. DeepLMS personalized QoI forecasting scaffolds user's online learning engagement and provides educators with an evaluation path, additionally to the content-related assessment, enriching the overall view on the learners' motivation and participation in the learning process.

Reference

https://www.nature.com/articles/s41598-020-76740-9

Detection of SARS-CoV-2 antibodies is insufficient for the diagnosis of active or cured COVID-19

Abstract

The performance of Abbott's SARS-CoV-2 IgG assay and the PanbioTM COVID-19 IgG/IgM rapid test device for the diagnosis of either active or cured COVID-19 was assessed. Three cohorts of patients were chosen. Cohort 1, patients (n = 65) who attended the emergency department on March 30, 2020 with clinical suspicion of active COVID-19 (n = 56 with proven/probable COVID-19). Cohort 2, hospital workers (n = 92) who had either been (n = 40) or not (n = 52) diagnosed with proven/probable COVID-19 and were asymptomatic at the time of the sampling. Cohort 3, patients (n = 38) cared at the hospital before the start of the COVID-19 pandemic. Detection of serum antibodies was done using Abbott´s SARS-CoV-2 IgG assay and the PanbioTM COVID-19 IgG/IgM device. Both methods showed 98% agreement for IgG detection. No antibodies were detected in the 38 samples from hospitalized pre-COVID subjects. The diagnostic performance of IgGs detected by Abbott´s SARS-CoV-2 assay in Cohorts 1/2 was: sensitivity (60.7%/75%) and specificity (100%/84.6%). The diagnostic performance of IgM by PanbioTM COVID-19 in Cohorts 1/2 was: sensitivity (16%/17.5%) and specificity

(100%/98.1%). It was shown that IgG detection alone is insufficient for the diagnosis of active or cured COVID-19. IgM detection has a limited diagnostic value.

Reference

https://www.nature.com/articles/s41598-020-76914-5

Spike-specific circulating T follicular helper cell and cross-neutralizing antibody responses in COVID-19-convalescent individuals

Abstract

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and individuals with COVID-19 have symptoms that can be asymptomatic, mild, moderate or severe. In the early phase of infection, T- and B-cell counts are substantially decreased; however, IgM and IgG are detectable within 14 d after symptom onset. In COVID-19-convalescent individuals, spike-specific neutralizing antibodies are variable. No specific drug or vaccine is available for COVID-19 at the time of writing; however, patients benefit from treatment with serum from COVID-19-convalescent individuals. Nevertheless, antibody responses and cross-reactivity with other coronaviruses in COVID-19-convalescent individuals are largely unknown. Here, we show that the majority of COVID-19-convalescent individuals maintained SARS-CoV-2 spike S1- and S2-specific antibodies with neutralizing activity against the SARS-CoV-2 pseudotyped virus, and that some of the antibodies cross-neutralized SARS-CoV, Middle East respiratory syndrome coronavirus or both pseudotyped viruses. Convalescent individuals who experienced severe COVID-19 showed higher neutralizing antibody titres, a faster increase in lymphocyte counts and a higher frequency of CXCR3+ T follicular help (TFH) cells compared with COVID-19-convalescent individuals who experienced non-severe disease. Circulating TFH cells were spike specific and functional, and the frequencies of CXCR3+ TFH cells were positively associated with neutralizing antibody titres in COVID-19-convalescent individuals. No individuals had detectable autoantibodies. These findings provide insights into neutralizing antibody responses in COVID-19-convalescent individuals and facilitate the treatment and vaccine development for SARS-CoV-2 infection.

Reference

https://www.nature.com/articles/s41564-020-00824-5

Similarities and differences between the 'cytokine storms' in acute dengue and COVID-19

Abstract

Severe pneumonia and multiorgan dysfunction in COVID-19 and dengue haemorrhagic fever (DHF) are two diseases that can associate with an altered immune response to the infecting virus. To determine the similarities and differences in the cytokine and chemokine responses in these two infections, we compared responses in patients with varying severity of COVID-19 and acute dengue at different time points of illness. During early disease, patients who proceeded to develop COVID-19 severe pneumonia (SP) and DHF had significantly higher levels of IL-6, IL-10 and MIP3α than those who developed mild illness. The lowest levels of IFNγ in early illness were seen in those who succumbed to their illness due to COVID-19. Levels of serum IL-10 ($p = 0.0001$), IL-6 ($p = 0.002$), MIP-3α ($p = 0.02$) and CD40-L levels ($p = 0.002$) significantly increased from 5 to 9 day of illness to 10–21 day of illness in patients with moderate-to-severe COVID-19, but not in those with mild illness. In contrast, these cytokine/chemokine levels remained unchanged in those with DHF or dengue fever (DF) during febrile and critical phases. Although IL-10 levels were significantly higher in COVID-19 patients with SP, patients with DHF had 25-fold higher levels, whereas IL-6 levels were 11-fold higher in those with COVID-19 SP. IL-10 and other cytokines were evaluated in a larger cohort of patients during early illness (≤ 4 days) who proceeded to develop DF ($n = 71$) or DHF ($n = 64$). Of the cytokines evaluated, IL-10 was significantly higher ($p < 0.0001$) in those who went on to develop DHF compared to DF. Low IFNγ response to the SARS-CoV2 and high levels of immunosuppressive IL-10 in both COVID-19 and dengue during early illness are indicators of an altered antiviral response potentially contributing to disease severity.

Reference

https://www.nature.com/articles/s41598-020-76836-2

Risk attitudes and human mobility during the COVID-19 pandemic

Abstract

Behavioural responses to pandemics are less shaped by actual mortality or hospitalisation risks than they are by risk attitudes. We explore human mobility patterns as a measure of behavioural responses during the COVID-19 pandemic. Our results indicate that risk-taking attitudes are a critical factor in predicting reductions in human mobility and social confinement around the globe. We find that the sharp decline in mobility after the WHO (World Health Organization) declared COVID-19 to be a pandemic can be attributed to risk attitudes. Our results suggest that regions with risk-averse attitudes are more likely to adjust their behavioural activity in response to the declaration of a pandemic even before official government lockdowns. Further understanding of the basis of responses to epidemics, e.g., precautionary behaviour, will help improve the containment of the spread of the virus.

Reference

https://www.nature.com/articles/s41598-020-76763-2

Publication Date: Nov 14, 2020

Cryo-EM structure of an extended SARS-CoV-2 replication and transcription complex reveals an intermediate state in cap synthesis

Abstract

Transcription of SARS-CoV-2 mRNA requires sequential reactions facilitated by the replication and transcription complex (RTC). Here, a structural snapshot of SARS-CoV-2 RTC was presented as it transitions toward cap structure synthesis. It was determined the atomic cryo-EM structure of an extended RTC assembled by nsp7-nsp82-nsp12-nsp132-RNA and a single RNA-binding protein, nsp9. Nsp9 binds tightly to nsp12 (RdRp) NiRAN, allowing nsp9 N terminus inserting into the catalytic center of nsp12 NiRAN, which then inhibits activity. It was also shown that nsp12 NiRAN possesses guanylyltransferase activity, catalyzing the formation of cap core structure (GpppA). The orientation of nsp13 that anchors the 5′ extension of template RNA shows a remarkable conformational shift, resulting in zinc finger 3 of its ZBD inserting into a minor groove of paired template-primer RNA. These results reason an intermediate state of RTC toward

mRNA synthesis, pave a way to understand the RTC architecture, and provide a target for antiviral development.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31533-6

Publication Date: Nov 13, 2020

Innate and adaptive immunity of murine neural stem cell-derived piRNA exosomes/microvesicles against pseudotyped SARS-CoV-2 and HIV-based lentivirus

Abstract

Through testing pseudotyped SARS-CoV-2 and HIV-based lentivirus, this study reports that exosomes/microvesicles (Ex/Mv) isolated from murine hypothalamic neural stem/progenitor cells (htNSC) or subtype htNSCPGHM as well as hippocampal NSC have innate immunity-like actions against these RNA viruses. These extracellular vesicles also have a cell-free innate antiviral action through attacking and degrading viruses. It was further generated the induced versions of Ex/Mv through prior viral exposure to NSCs and found that these induced Ex/Mv were stronger than basal Ex/Mv in reducing the infection of these viruses, suggesting the involvement of an adaptive immunity-like antiviral function. These NSC Ex/Mv were found to be characterized by producing large libraries of piRNAs against genomes of various viruses, and some of these piRNAs were enriched during the adaptive immunity-like reaction, possibly contributing to the antiviral effects of these Ex/Mv. In conclusion, NSC Ex/Mv have antiviral immunity and could potentially be developed to combat against various viruses.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(20)31003-8

Real-Time Conformational Dynamics of SARS-CoV-2 Spikes on Virus Particles

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) mediates viral entry into cells and is critical for vaccine development against coronavirus disease 2019 (COVID-19). Structural studies have revealed distinct conformations of S,

but real-time information that connects these structures, is lacking. Here, single-molecule fluorescence (Förster) resonance energy transfer (smFRET) imaging was applied to observe conformational dynamics of S on virus particles. Virus-associated S dynamically samples at least four distinct conformational states. In response to human receptor angiotensin-converting enzyme 2 (hACE2), S opens sequentially into the hACE2-bound S conformation through at least one on-path intermediate. Conformational preferences observed upon exposure to convalescent plasma or antibodies suggest mechanisms of neutralization involving either competition with hACE2 for binding to the receptor-binding domain (RBD) or allosteric interference with conformational changes required for entry. Our findings inform on mechanisms of S recognition and conformations for immunogen design.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30618-1

Expression of SARS-CoV-2 entry factors in the pancreas of normal organ donors and individuals with COVID-19

Abstract

Diabetes is associated with increased mortality from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Given literature suggesting a potential association between SARS-CoV-2 infection and diabetes induction, we examined pancreatic expression of angiotensin-converting enzyme 2 (ACE2), the key entry factor for SARS-CoV-2 infection. Specifically, we analyzed five public scRNA-seq pancreas datasets and performed fluorescence in situ hybridization, western blotting, and immunolocalization for ACE2 with extensive reagent validation on normal human pancreatic tissues across the lifespan, as well as those from coronavirus disease 2019 (COVID-19) cases. These in silico and ex vivo analyses demonstrated prominent expression of ACE2 in pancreatic ductal epithelium and microvasculature, but we found rare endocrine cell expression at the mRNA level. Pancreata from individuals with COVID-19 demonstrated multiple thrombotic lesions with SARS-CoV-2 nucleocapsid protein expression that was primarily limited to ducts. These results suggest SARS-CoV-2 infection of pancreatic endocrine cells, via ACE2, is an unlikely central pathogenic feature of COVID-19-related diabetes.

Reference

https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30600-8

SARS-CoV-2 epitopes are recognized by a public and diverse repertoire of human T cell receptors

Abstract

Understanding the hallmarks of the immune response to SARS-CoV-2 is critical for fighting the COVID-19 pandemic. We assessed antibody and T cell reactivity in convalescent COVID-19 patients and healthy donors sampled both prior to and during the pandemic. Healthy donors examined during the pandemic exhibited increased numbers of SARS-CoV-2-specific T cells, but no humoral response. Their probable exposure to the virus resulted in either asymptomatic infection without antibody secretion, or activation of pre-existing immunity. In convalescent patients, we observed a public and diverse T cell response to SARS-CoV-2 epitopes, revealing T cell receptor (TCR) motifs with germline-encoded features. Bulk CD4+ and CD8+ T cell responses to the spike glycoprotein were mediated by groups of homologous TCRs, some of them shared across multiple donors. Overall, our results demonstrate that the T cell response to SARS-CoV-2, including the identified set of TCRs, can serve as a useful biomarker for surveying antiviral immunity.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(20)30469-6

The human leukocyte antigen class II immunopeptidome of the SARS-CoV-2 spike glycoprotein

Abstract

Precise elucidation of the antigen sequences for T cell immunosurveillance greatly enhances our ability to understand and modulate humoral responses to viral infection or active immunization. Mass spectrometry is used to identify 526 unique sequences from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein extracellular domain in a complex with human leukocyte antigen class II molecules on antigen-presenting cells from a panel of healthy donors selected to represent a majority of allele usage from this highly polymorphic molecule. The identified sequences span

the entire spike protein, and several sequences are isolated from a majority of the sampled donors, indicating promiscuous binding. Importantly, many peptides derived from the receptor binding domain used for cell entry are identified. This work represents a precise and comprehensive immunopeptidomic investigation with the SARS-CoV-2 spike glycoprotein and allows detailed analysis of features that may aid vaccine development to end the current coronavirus disease 2019 (COVID-19) pandemic.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31443-1

SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β cells

Abstract

Isolated reports of new-onset diabetes in individuals with COVID-19 have led to the hypothesis that SARS-CoV-2 is directly cytotoxic to pancreatic islet β cells. This would require binding and entry of SARS-CoV-2 into β cells via co-expression of its canonical cell entry factors, angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2); however, their expression in human pancreas has not been clearly defined. We analyzed six transcriptional datasets of primary human islet cells and found that ACE2 and TMPRSS2 were not co-expressed in single β cells. In pancreatic sections, ACE2 and TMPRSS2 protein was not detected in β cells from donors with and without diabetes. Instead, ACE2 protein was expressed in islet and exocrine tissue microvasculature and in a subset of pancreatic ducts, whereas TMPRSS2 protein was restricted to ductal cells. These findings reduce the likelihood that SARS-CoV-2 directly infects β cells *in vivo* through ACE2 and TMPRSS2.

Reference

https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30601-X

The flexibility of ACE2 in the context of SARS-CoV-2 infection

Abstract

The COVID-19 pandemic has swept over the world in the past months, causing significant loss of life and consequences to human health. Although numerous drug and vaccine development efforts are underway, there are many outstanding questions on

the mechanism of SARS-CoV-2 viral association to angiotensin-converting enzyme 2 (ACE2), its main host receptor, and host cell entry. Structural and biophysical studies indicate some degree of flexibility in the viral extracellular spike glycoprotein and at the receptor binding domain-receptor interface, suggesting a role in infection. Here, we perform explicitly solvated all-atom molecular dynamics simulations of the glycosylated, full-length membrane-bound ACE2 receptor, in both an apo and spike receptor binding domain (RBD) bound state, in order to probe the intrinsic dynamics of the ACE2 receptor in the context of the cell surface. A large degree of fluctuation in the full length structure is observed, indicating hinge bending motions at the linker region connecting the head to the transmembrane helix, while still not disrupting the ACE2 homodimer or ACE2-RBD interfaces. This flexibility translates into an ensemble of ACE2 homodimer conformations that could sterically accommodate binding of the spike trimer to more than one ACE2 homodimer, and suggests a mechanical contribution of the host receptor towards the large spike conformational changes required for cell fusion. This work presents further structural and functional insights into the role of ACE2 in viral infection that can potentially be exploited for the rational design of effective SARS-CoV-2 therapeutics.

Reference

https://www.cell.com/biophysj/fulltext/S0006-3495(20)30862-6

Enhanced expression of immune checkpoint receptors during SARS-CoV-2 viral infection

Abstract

The immune system is tightly regulated by the activity of stimulatory and inhibitory immune receptors. This immune homeostasis is usually disturbed during chronic viral infection. Using publicly available transcriptomic datasets, we conducted an in-silico analyses to evaluate the expression pattern of 38 selected immunoinhibitory receptors (IRs) associated with different myeloid and lymphoid immune cells during COVID-19 infection. Our analyses revealed a pattern of overall upregulation of IRs mRNA during SARS-CoV-2 infection. A large number of IRs expressed on both lymphoid and myeloid cells were upregulated in nasopharyngeal swabs (NPs), while lymphoid associated IRs were specifically upregulated in autopsies, reflecting severe, terminal stage, COVID-19

disease. Eight genes (BTLA, LAG3, FCGR2B, PDCD1, CEACAM1, CTLA4, CD72, and SIGLEC7), shared by NPs and autopsies, were more expressed in autopsies and were directly correlated with viral levels. Single-cell data from blood and bronchioalveolar samples also reflected the observed association between IRs upregulation and disease severity. Moreover, compared to SARS-CoV-1, influenza and respiratory syncytial virus infections, the number and intensities of upregulated IRs were higher in SARS-CoV-2 infections. In conclusion, the immunopathology and severity of COVID-19 could be attributed to dysregulation of different immune inhibitors. Targeting one or more of these immune inhibitors could represent an effective therapeutic approach for the treatment of COVID-19 early and late immune dysregulations.

Reference

https://www.cell.com/molecular-therapy-family/methods/fulltext/S2329-0501(20)30229-1

COVID-19 and diabetes mellitus: from pathophysiology to clinical management

Abstract

Initial studies found increased severity of coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in patients with diabetes mellitus. Furthermore, COVID-19 might also predispose infected individuals to hyperglycaemia. Interacting with other risk factors, hyperglycaemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes. Angiotensin-converting enzyme 2 (ACE2), which is part of the renin–angiotensin–aldosterone system (RAAS), is the main entry receptor for SARS-CoV-2; although dipeptidyl peptidase 4 (DPP4) might also act as a binding target. Preliminary data, however, do not suggest a notable effect of glucose-lowering DPP4 inhibitors on SARS-CoV-2 susceptibility. Owing to their pharmacological characteristics, sodium–glucose cotransporter 2 (SGLT2) inhibitors might cause adverse effects in patients with COVID-19 and so cannot be recommended. Currently, insulin should be the main approach to the control of acute glycaemia. Most available evidence does not distinguish between the major types of diabetes mellitus and is related to type 2 diabetes mellitus owing to its high prevalence. However, some limited evidence is now available on type 1

diabetes mellitus and COVID-19. Most of these conclusions are preliminary, and further investigation of the optimal management in patients with diabetes mellitus is warranted.

Reference

https://www.nature.com/articles/s41574-020-00435-4

Clinical presentations, laboratory and radiological findings, and treatments for 11,028 COVID-19 patients: A systematic review and meta-analysis

Abstract

This systematic review and meta-analysis investigated the comorbidities, symptoms, clinical characteristics and treatment of COVID-19 patients. Epidemiological studies published in 2020 (from January–March) on the clinical presentation, laboratory findings and treatments of COVID-19 patients were identified from PubMed/MEDLINE and Embase databases. Studies published in English by 27th March, 2020 with original data were included. Primary outcomes included comorbidities of COVID-19 patients, their symptoms presented on hospital admission, laboratory results, radiological outcomes, and pharmacological and in-patient treatments. 76 studies were included in this meta-analysis, accounting for a total of 11,028 COVID-19 patients in multiple countries. A random-effects model was used to aggregate estimates across eligible studies and produce meta-analytic estimates. The most common comorbidities were hypertension (18.1%, 95% CI 15.4–20.8%). The most frequently identified symptoms were fever (72.4%, 95% CI 67.2–77.7%) and cough (55.5%, 95% CI 50.7–60.3%). For pharmacological treatment, 63.9% (95% CI 52.5–75.3%), 62.4% (95% CI 47.9–76.8%) and 29.7% (95% CI 21.8–37.6%) of patients were given antibiotics, antiviral, and corticosteroid, respectively. Notably, 62.6% (95% CI 39.9–85.4%) and 20.2% (95% CI 14.6–25.9%) of in-patients received oxygen therapy and non-invasive mechanical ventilation, respectively. This meta-analysis informed healthcare providers about the timely status of characteristics and treatments of COVID-19 patients across different countries.

Reference

https://www.nature.com/articles/s41598-020-74988-9

Development and validation of a clinical score to estimate progression to severe or critical state in COVID-19 pneumonia hospitalized patients

Abstract

The prognosis of a patient with COVID-19 pneumonia is uncertain. Our objective was to establish a predictive model of disease progression to facilitate early decision-making. A retrospective study was performed of patients admitted with COVID-19 pneumonia, classified as severe (admission to the intensive care unit, mechanic invasive ventilation, or death) or non-severe. A predictive model based on clinical, laboratory, and radiological parameters was built. The probability of progression to severe disease was estimated by logistic regression analysis. Calibration and discrimination (receiver operating characteristics curves and AUC) were assessed to determine model performance. During the study period 1152 patients presented with SARS-CoV-2 infection, of whom 229 (19.9%) were admitted for pneumonia. During hospitalization, 51 (22.3%) progressed to severe disease, of whom 26 required ICU care (11.4); 17 (7.4%) underwent invasive mechanical ventilation, and 32 (14%) died of any cause. Five predictors determined within 24 h of admission were identified: Diabetes, Age, Lymphocyte count, SaO2, and pH (DALSH score). The prediction model showed a good clinical performance, including discrimination (AUC 0.87 CI 0.81, 0.92) and calibration (Brier score = 0.11). In total, 0%, 12%, and 50% of patients with severity risk scores ≤ 5%, 6–25%, and > 25% exhibited disease progression, respectively. A risk score based on five factors predicts disease progression and facilitates early decision-making according to prognosis.

Reference

https://www.nature.com/articles/s41598-020-75651-z

Associations between blood type and COVID-19 infection, intubation, and death

Abstract

The rapid global spread of the novel coronavirus SARS-CoV-2 has strained healthcare and testing resources, making the identification and prioritization of individuals most at-risk a critical challenge. Recent evidence suggests blood type may affect risk of severe COVID-19. Here, observational healthcare data was used on 14,112 individuals tested

for SARS-CoV-2 with known blood type in the New York Presbyterian (NYP) hospital system to assess the association between ABO and Rh blood types and infection, intubation, and death. Increased infection prevalence was found among non-O types. Risk of intubation was decreased among A and increased among AB and B types, compared with type O, while risk of death was increased for type AB and decreased for types A and B. It was estimated that Rh-negative blood type to have a protective effect for all three outcomes. The results add to the growing body of evidence suggesting blood type may play a role in COVID-19.

Reference

https://www.nature.com/articles/s41467-020-19623-x

How did COVID-19 impact on dental antibiotic prescribing across England?

Abstract

Introduction: Antibiotic resistance is a global problem driven by unnecessary antibiotic use. Between 25 March-8 June 2020, COVID-19 restrictions severely reduced access to dentistry in England. Dental practices were instructed to manage patients remotely with advice, analgesics and antibiotics, where appropriate.

Aim: To describe the impact of the policy to restrict dental access on antibiotic prescribing.

Methods: NHS Business Services Authority 2018-2020 data for England were analysed to describe national and regional trends in dental antibiotic use.

Results: Antibiotic prescribing in April to July 2020 was 25% higher than April to July 2019, with a peak in June 2020. Some regions experienced greater increases and for longer periods than others. The increase was highest in London (60%) and lowest in the South West (10%). East of England had the highest rate of dental antibiotic prescriptions per 1,000 of the population every month over the study period (April to July 2020).

Conclusion: Restricted access to dental care due to COVID-19 resulted in greatly increased dental antibiotic prescribing, against an otherwise downward trend. As dental care adapts to the COVID-19 era, it is important to ensure access for all to high-quality

urgent dental care. Understanding the reasons for variation will help to optimise the use of antibiotics in the future.

Reference

https://www.nature.com/articles/s41415-020-2336-6

Characterization of neutralizing antibody with prophylactic and therapeutic efficacy against SARS-CoV-2 in rhesus monkeys

Abstract

Efficacious interventions are urgently needed for the treatment of COVID-19. Here, we report a monoclonal antibody (mAb), MW05, with SARS-CoV-2 neutralizing activity by disrupting the interaction of receptor binding domain (RBD) with angiotensin-converting enzyme 2 (ACE2) receptor. Crosslinking of Fc with FcγRIIB mediates antibody-dependent enhancement (ADE) activity by MW05. This activity is eliminated by introducing the LALA mutation to the Fc region (MW05/LALA). Potent prophylactic and therapeutic effects against SARS-CoV-2 are observed in rhesus monkeys. A single dose of MW05/LALA blocks infection of SARS-CoV-2 in prophylactic treatment and clears SARS-CoV-2 in three days in a therapeutic treatment setting. These results pave the way for the development of MW05/LALA as an antiviral strategy for COVID-19.

Reference

https://www.nature.com/articles/s41467-020-19568-1

Publication Date: Nov 12, 2020

Genetic influences on viral-induced cytokine responses in the lung

Abstract

Infection with respiratory viruses such as influenza, respiratory syncytial virus and coronavirus provides a difficult immunological challenge for the host, where a balance must be established between controlling viral replication and limiting damage to the delicate lung structure. Although the genetic architecture of host responses to respiratory viral infections is not yet understood, it is clear there is underlying heritability that influences pathogenesis. Immune control of virus replication is essential in

respiratory infections, but overt activation can enhance inflammation and disease severity. Cytokines initiate antiviral immune responses but are implicated in viral pathogenesis. Here, it was discussed that how host genetic variation may influence cytokine responses to respiratory viral infections and, based on our current understanding of the role that cytokines play in viral pathogenesis, how this may influence disease severity. It was also discussed that how induced pluripotent stem cells may be utilized to probe the mechanistic implications of allelic variation in genes in virus-induced inflammatory responses. Ultimately, this could help to design better immune modulators, stratify high risk patients and tailor anti-inflammatory treatments, potentially expanding the ability to treat respiratory virus outbreaks in the future.

Reference

https://www.nature.com/articles/s41385-020-00355-6

Molecular targeting of vulnerable RNA sequences in SARS CoV-2: Identifying clinical feasibility

Abstract

Covid-19 (SARS CoV-2) has become a deadly, world-wide pandemic. Although most who are infected survive, complications from the virus can be pronounced and long-lasting. To date, of all the respiratory viruses including influenza and coronaviruses, only influenza has had a drug (i.e., Tamiflu) specifically targeted to treat and prevent infection. As a result, additional agents that specifically target viral production and are clinically feasible are needed to alleviate respiratory viral infections. The idea of using a miRNA/siRNA molecular approach for treating various diseases was postulated over a decade ago; however, only within the past few years has it become feasible. One technological advancement has been the molecular linkage of lipophilic moieties to mi/siRNAs in order to bypass the need for enveloping these inhibitory RNAs in lipid-based transfection reagents, which could irritate the airway if inhaled. Here we show that siRNAs and miRNAs inhibit SARS CoV-2 spike protein production in a dose-dependent manner in both HEK293 cells and a primary human airway tracheal cell line. We also show that this inhibition is equally robust using a clinically relevant siRNA that does not need to be prepped with a transfection reagent.

Reference

https://www.nature.com/articles/s41434-020-00210-0

Predicting airborne coronavirus inactivation by far-UVC in populated rooms using a high-fidelity coupled radiation-CFD model

Abstract

There are increased risks of contracting COVID-19 in hospitals and long-term care facilities, particularly for vulnerable groups. In these environments aerosolised coronavirus released through breathing increases the chance of spreading the disease. To reduce aerosol transmissions, the use of low dose far-UVC lighting to disinfect in-room air has been proposed. Unlike typical UVC, which has been used to kill microorganisms for decades but is carcinogenic and cataractogenic, recent evidence has shown that far-UVC is safe to use around humans. A high-fidelity, fully-coupled radiation transport and fluid dynamics model has been developed to quantify disinfection rates within a typical ventilated room. The model shows that disinfection rates are increased by a further 50-85% when using far-UVC within currently recommended exposure levels compared to the room's ventilation alone. With these magnitudes of reduction, far-UVC lighting could be employed to mitigate SARS-CoV-2 transmission before the onset of future waves, or the start of winter when risks of infection are higher. This is particularly significant in poorly-ventilated spaces where other means of reduction are not practical, in addition social distancing can be reduced without increasing the risk.

Reference

https://www.nature.com/articles/s41598-020-76597-y

Collider bias undermines our understanding of COVID-19 disease risk and severity

Abstract

Numerous observational studies have attempted to identify risk factors for infection with SARS-CoV-2 and COVID-19 disease outcomes. Studies have used datasets sampled from patients admitted to hospital, people tested for active infection, or people who

volunteered to participate. Here, we highlight the challenge of interpreting observational evidence from such non-representative samples. Collider bias can induce associations between two or more variables which affect the likelihood of an individual being sampled, distorting associations between these variables in the sample. Analysing UK Biobank data, compared to the wider cohort the participants tested for COVID-19 were highly selected for a range of genetic, behavioural, cardiovascular, demographic, and anthropometric traits. We discuss the mechanisms inducing these problems, and approaches that could help mitigate them. While collider bias should be explored in existing studies, the optimal way to mitigate the problem is to use appropriate sampling strategies at the study design stage.

Reference

https://www.nature.com/articles/s41467-020-19478-2

Mathematical modelling of the dynamics and containment of COVID-19 in Ukraine

Abstract

COVID-19 disease caused by the novel SARS-CoV-2 coronavirus has already brought unprecedented challenges for public health and resulted in huge numbers of cases and deaths worldwide. In the absence of effective vaccine, different countries have employed various other types of non-pharmaceutical interventions to contain the spread of this disease, including quarantines and lockdowns, tracking, tracing and isolation of infected individuals, and social distancing measures. Effectiveness of these and other measures of disease containment and prevention to a large degree depends on good understanding of disease dynamics, and robust mathematical models play an important role in forecasting its future dynamics. In this paper we focus on Ukraine, one of Europe's largest countries, and develop a mathematical model of COVID-19 dynamics, using latest data on parameters characterising clinical features of disease. For improved accuracy, our model includes age-stratified disease parameters, as well as age- and location-specific contact matrices to represent contacts. It was shown that the model is able to provide an accurate short-term forecast for the numbers and age distribution of cases and deaths. It was also simulated different lockdown scenarios, and the results suggest that reducing work contacts is more efficient at reducing the disease burden than reducing school contacts, or implementing shielding for people over 60.

Reference

https://www.nature.com/articles/s41598-020-76710-1

The emerging role of neutrophil extracellular traps in severe acute respiratory syndrome coronavirus 2 (COVID-19)

Abstract

The novel coronavirus SARS-CoV-2 causes COVID-19, a highly pathogenic viral infection threatening millions. The majority of the individuals infected are asymptomatic or mildly symptomatic showing typical clinical signs of common cold. However, approximately 20% of the patients can progress to acute respiratory distress syndrome (ARDS), evolving to death in about 5% of cases. Recently, angiotensin-converting enzyme 2 (ACE2) has been shown to be a functional receptor for virus entry into host target cells. The upregulation of ACE2 in patients with comorbidities may represent a propensity for increased viral load and spreading of infection to extrapulmonary tissues. This systemic infection is associated with higher neutrophil to lymphocyte ratio in infected tissues and high levels of pro-inflammatory cytokines leading to an extensive microthrombus formation with multiorgan failure. Herein we investigated whether SARS-CoV-2 can stimulate extracellular neutrophils traps (NETs) in a process called NETosis. We demonstrated for the first time that SARS-CoV-2 in fact is able to activate NETosis in human neutrophils. Our findings indicated that this process is associated with increased levels of intracellular Reactive Oxygen Species (ROS) in neutrophils. The ROS-NET pathway plays a role in thrombosis formation and our study suggest the importance of this target for therapy approaches against disease.

Reference

https://www.nature.com/articles/s41598-020-76781-0

Temporal lung changes on thin-section CT in patients with COVID-19 pneumonia

Abstract

It was examined that characteristics of chest CT across different time periods for patients with COVID-19 pneumonia in Huizhou, China. This study included 56 COVID-19 patients with abnormal CT acquired between January 22 and March 3, 2020. The

141 scans of 56 patients were classified into four groups (Groups 1–4) based on dates on which scans were obtained at the 1st, 2nd, 3rd week or longer than three weeks after illness onset. Forty-five patients with follow-up scans were categorized into four groups (Groups A–D) according to extent that lesions reduced (≥ 75%, 50–75%, 25–50% and < 25%). Ground-glass opacities (GGO) was prevalent in Groups 1–4 (58.1–82.6%), while percentages of consolidation ranged between 9.7% in Group 4 and 26.2% in Group 2. The highest frequency of fibrous stripes occurred in Group 3 (46.7%). Total CT scores were on average higher in Groups 2–3. Among 45 follow-up patients, 11 (24.4%) of them recovered with lesions reducing ≥ 75%, with the lowest median age and total CT scores on admission. There are temporal patterns of lung abnormalities in COVID-19 patients, with higher extent of lesion involvement occurring in the 2nd and 3rd week. Persisting lung changes indicate some patients may need isolation after discharge from hospital.

Reference

https://www.nature.com/articles/s41598-020-76776-x

Low SARS-CoV-2 seroprevalence in blood donors in the early COVID-19 epidemic in the Netherlands

Abstract

The world is combating an ongoing COVID-19 pandemic with health-care systems, society and economies impacted in an unprecedented way. It is unclear how many people have contracted the causative coronavirus (SARS-CoV-2) unknowingly and are asymptomatic. Therefore, reported COVID-19 cases do not reflect the true scale of outbreak. Here we present the prevalence and distribution of antibodies to SARS-CoV-2 in a healthy adult population of the Netherlands, which is a highly affected country, using a high-performance immunoassay. Our results indicate that one month into the outbreak (i) the seroprevalence in the Netherlands was 2.7% with substantial regional variation, (ii) the hardest-hit areas showed a seroprevalence of up to 9.5%, (iii) the seroprevalence was sex-independent throughout age groups (18–72 years), and (iv) antibodies were significantly more often present in younger people (18–30 years). Our study provides vital information on the extent of exposure to SARS-CoV-2 in a country where social distancing is in place.

Reference

https://www.nature.com/articles/s41467-020-19481-7

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REPORT

Publication Date: Nov 18, 2020

The Roborovski dwarf hamster – a highly susceptible model for a rapid and fatal course of SARS-CoV-2 infection

The COVID-19 pandemic caused by SARS-CoV-2 has precipitated an unprecedented and yet unresolved health crisis worldwide. Different mammals are susceptible to SARS-CoV-2; however, few species examined so far develop robust clinical disease that mirrors severe human cases or allows testing of vaccines and drugs under conditions of severe disease. Here, we compare the susceptibilities of three dwarf hamster species (Phodopus spp.) to SARS-CoV-2 and introduce the Roborovski dwarf hamster (P. roborovskii) as a highly susceptible COVID-19 model with consistent and fulminant clinical signs. Particularly, only this species shows SARS-CoV-2-induced severe acute diffuse alveolar damage and hyaline microthrombi in the lungs, changes described in patients who succumbed to the infection, but not reproduced in any experimentally infected animal. Based on our findings, we propose the Roborovski dwarf hamster as a valuable model to examine the efficacy and safety of vaccine candidates and therapeutics, particularly for use in highly susceptible individuals.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31477-7

Publication Date: Nov 17, 2020

Direct exposure to SARS-CoV-2 and cigarette smoke increases infection severity and alters the stem cell-derived airway repair response

Current smoking is associated with increased risk of severe COVID-19, but it is not clear how cigarette smoke (CS) exposure affects SARS-CoV-2 airway cell infection. We directly exposed air-liquid interface (ALI) cultures derived from primary human nonsmoker airway basal stem cells (ABSCs) to short term CS and then infected them

with SARS-CoV-2. It was found an increase in the number of infected airway cells after CS exposure with a lack of ABSC proliferation. Single-cell profiling of the cultures showed that the normal interferon response was reduced after CS exposure with infection. Treatment of CS-exposed ALI cultures with interferon β-1 abrogated the viral infection, suggesting one potential mechanism for more severe viral infection. Our data show that acute CS exposure allows for more severe airway epithelial disease from SARS-CoV-2 by reducing the innate immune response and ABSC proliferation and has implications for disease spread and severity in people exposed to CS.

Reference

https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(20)30548-8

Publication Date: Nov 12, 2020

SARS-CoV-2 D614G variant exhibits efficient replication *ex vivo* and transmission *in vivo*

The spike D614G substitution is prevalent in global SARS-CoV-2 strains, but its effects on viral pathogenesis and transmissibility remain unclear. We engineered a SARS-CoV-2 variant containing this substitution. The variant exhibits more efficient infection, replication, and competitive fitness in primary human airway epithelial cells, but maintains similar morphology and in vitro neutralization properties, compared with the ancestral wild-type virus. Infection of human angiotensin-converting enzyme 2 (ACE2) transgenic mice and Syrian hamsters with both viruses resulted in similar viral titers in respiratory tissues and pulmonary disease. However, the D614G variant transmits significantly faster and displayed increased competitive fitness than the wild-type virus in hamsters. These data show that the D614G substitution enhances SARS-CoV-2 infectivity, competitive fitness, and transmission in primary human cells and animal models.

Reference

https://science.sciencemag.org/content/early/2020/11/11/science.abe8499

COMMENT

Publication Date: Nov 17, 2020

Expecting the unexpected with COVID-19 vaccines

Global efforts for development of a COVID-19 vaccine are yielding multiple results including some new and as yet unlicensed technologies. Reception of these vaccine candidates by a skeptical public will challenge wide acceptance of new vaccines. Regulatory safety thresholds are a minimum bar that a product must pass to attain regulatory approval, but for the general public, cumulative safety experience will be important. Trust is earned with time, and with repeated experience. Vaccines have a long safety history, but COVID-19 vaccines are new. In this context, Yanjun Zhang and colleagues' report of their phase 1/2 trial of a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in *The Lancet Infectious Diseases* is instructive. In their randomised, placebo-controlled trial, Zhang and colleagues assessed two concentrations of the vaccine CoronaVac (Sinovac Life Sciences, Beijing, China), 3 μg and 6 μg per 0·5 mL diluent, in a two-dose regimen, using both 14 and 28 day intervals. The phase 1 trial was done in a dose-escalation manner to ensure the safety of dosing in the phase 2 trial. Their rationale for this study design was that extended intervals between doses might result in more durable responses, whereas regimens with shorter intervals between doses might be of use in early outbreak containment. Primary safety results were reported up to day 28 after each dose of study drug, while neutralising immunogenicity data were assessed at 14 days after the second dose for the day 0 and 14 vaccination cohort, and 28 days after the second dose for the days 0 and 28 vaccination cohort. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30870-7/fulltext

Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis

Abstract

Background: Patients from ethnic minority groups are disproportionately affected by Coronavirus disease (COVID-19). We performed a systematic review and meta-analysis to explore the relationship between ethnicity and clinical outcomes in COVID-19.

Methods: Databases (MEDLINE, EMBASE, PROSPERO, Cochrane library and MedRxiv) were searched up to 31st August 2020, for studies reporting COVID-19 data disaggregated by ethnicity. Outcomes were: risk of infection; intensive therapy unit (ITU) admission and death.

Findings: 18,728,893 patients from 50 studies were included; 26 were peer-reviewed; 42 were from the United States of America and 8 from the United Kingdom. Individuals from Black and Asian ethnicities had a higher risk of COVID-19 infection compared to White individuals. This was consistent in both the main analysis (pooled adjusted RR for Black: 2.02, 95% CI 1.67–2.44; pooled adjusted RR for Asian: 1.50, 95% CI 1.24–1.83) and sensitivity analyses examining peer-reviewed studies only (pooled adjusted RR for Black: 1.85, 95%CI: 1.46–2.35; pooled adjusted RR for Asian: 1.51, 95% CI 1.22–1.88). Individuals of Asian ethnicity may also be at higher risk of ITU admission (pooled adjusted RR 1.97 95% CI 1.34–2.89) (but no studies had yet been peer-reviewed) and death (pooled adjusted RR/HR 1.22 [0.99–1.50]).

Interpretation: Individuals of Black and Asian ethnicity are at increased risk of COVID-19 infection compared to White individuals; Asians may be at higher risk of ITU admission and death. These findings are of critical public health importance in informing interventions to reduce morbidity and mortality amongst ethnic minority groups.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30374-6/fulltext

Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: A randomised, double-blind, placebo-controlled, phase 2 trial

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection carries a substantial risk of severe and prolonged illness; treatment options are currently limited. We assessed the efficacy and safety of inhaled nebulised interferon beta-1a (SNG001) for the treatment of patients admitted to hospital with COVID-19.

Methods: We did a randomised, double-blind, placebo-controlled, phase 2 pilot trial at nine UK sites. Adults aged 18 years or older and admitted to hospital with COVID-19 symptoms, with a positive RT-PCR or point-of-care test, or both, were randomly assigned (1:1) to receive SNG001 (6 MIU) or placebo by inhalation via a mouthpiece daily for 14 days. The primary outcome was the change in clinical condition on the WHO Ordinal Scale for Clinical Improvement (OSCI) during the dosing period in the intention-to-treat population (all randomised patients who received at least one dose of the study drug). The OSCI is a 9-point scale, where 0 corresponds to no infection and 8 corresponds to death. Multiple analyses were done to identify the most suitable statistical method for future clinical trials. Safety was assessed by monitoring adverse events for 28 days. This trial is registered with Clinicaltrialsregister.eu (2020-001023-14) and ClinicalTrials.gov (NCT04385095); the pilot trial of inpatients with COVID-19 is now completed.

Findings: Between March 30 and May 30, 2020, 101 patients were randomly assigned to SNG001 (n=50) or placebo (n=51). 48 received SNG001 and 50 received placebo and were included in the intention-to-treat population. 66 (67%) patients required oxygen supplementation at baseline: 29 in the placebo group and 37 in the SNG001 group. Patients receiving SNG001 had greater odds of improvement on the OSCI scale (odds ratio 2·32 [95% CI 1·07–5·04]; p=0·033) on day 15 or 16 and were more likely than those receiving placebo to recover to an OSCI score of 1 (no limitation of activities) during treatment (hazard ratio 2·19 [95% CI 1·03–4·69]; p=0·043). SNG001 was well tolerated. The most frequently reported treatment-emergent adverse event was

headache (seven [15%] patients in the SNG001 group and five [10%] in the placebo group). There were three deaths in the placebo group and none in the SNG001 group.

Interpretation: Patients who received SNG001 had greater odds of improvement and recovered more rapidly from SARS-CoV-2 infection than patients who received placebo, providing a strong rationale for further trials.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30511-7/fulltext

Nebulised interferon beta-1a for patients with COVID-19

Abstract

The *Lancet Respiratory Medicine*, Phillip Monk and colleagues report the results of a randomised, double-blind, placebo-controlled phase 2 pilot trial of nebulised interferon beta-1a in 101 adults admitted to hospital with COVID-19. The authors found that patients who received nebulised interferon beta-1a had significantly greater odds of clinical improvement across the WHO Ordinal Scale for Clinical Improvement than those who received placebo, both on day 15/16 (odds ratio [OR] 2·32 [95% CI 1·07–5·04]; p=0·033) and on day 28 (3·15 [1·39–7·14]; p=0·006). However, there was no significant difference between treatment groups in the odds of hospital discharge by day 28: 39 (81%) of 48 patients had been discharged in the nebulised interferon beta-1a group compared with 36 (75%) of 48 in the placebo group (OR 1·84 [95% CI 0·64–5·29]; p=0·26).

Type 1 interferons are among the first cytokines produced during a viral infection and promote both innate and adaptive immunity. Interferon beta has shown an antiviral effect against coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in in-vitro studies and animal models. A recently published randomised clinical trial found that a combination of recombinant interferon beta-1b and lopinavir–ritonavir decreased mortality in patients with MERS-CoV infection. Clinical studies of SARS-CoV-2 found that a proportion of patients with severe COVID-19 had impaired type I interferon activity, potentially linked to autoantibodies against type I interferon. However,

preliminary results from the SOLIDARITY/DisCoVeRy randomised clinical trial in more than 2000 patients showed no efficacy of subcutaneous interferon alone or with lopinavir–ritonavir. The results of the present pilot study, in contrast to the results of the SOLIDARITY trial, corroborate findings from in-vitro studies and animal models showing that the interferon pathway is crucial in controlling SARS-CoV-2 infection. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30523-3/fulltext

A framework for research linking weather, climate and COVID-19

Early studies of weather, seasonality, and environmental influences on COVID-19 have yielded inconsistent and confusing results. To provide policy-makers and the public with meaningful and actionable environmentally-informed COVID-19 risk estimates, the research community must meet robust methodological and communication standards. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41467-020-19546-7

NEWSLETTER

Publication Date: Nov 16, 2020

COVID vaccine excitement builds as Moderna reports third positive result

Preliminary data show that the immunization is 94% effective and seems to prevent severe infections. Today, biotech company Moderna in Cambridge, Massachusetts, reported that its RNA-based vaccine is more than 94% effective at preventing COVID-19, on the basis of an analysis of 95 cases in its ongoing phase III efficacy trial. Scientists say that the press-released results share a few more details than last week's positive announcements from Pfizer and BioNTech, which are together working on a rival RNA vaccine, and from the Russian developers behind the controversial 'Sputnik V' vaccine. Moderna released figures suggesting that its vaccine is likely to prevent severe COVID-19 infections, something that was not clear from the other developers' announcements. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-020-03248-7

Publication Date: Nov 17, 2020

Repurposing fostamatinib to combat SARS-CoV-2-induced acute lung injury

A screen by Kost-Alimova *et al.* suggests that the FDA-approved SYK inhibitor fostamatinib inhibits MUC1 in the respiratory tract and has the potential to treat serious outcomes of coronavirus COVID-19, including acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). For more details, read the link given below.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30189-0