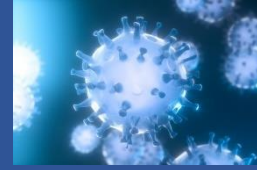


COVID-19

Sep 24 - 30, 2020



RESEARCH PUBLICATIONS

Publication Date: Sep 30, 2020

COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T-cell responses

Abstract

An effective vaccine is needed to halt the spread of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. Recently, safety, tolerability and antibody response data from an ongoing placebo-controlled, observer-blinded phase 1/2 coronavirus disease 2019 (COVID-19) vaccine trial was reported with BNT162b1, a lipid nanoparticle (LNP) formulated nucleoside-modified messenger RNA (mRNA) encoding the receptor binding domain (RBD) of the SARS-CoV-2 spike protein¹. Here we present antibody and T-cell responses after BNT162b1 vaccination from a second, non-randomized open-label phase 1/2 trial in healthy adults, 18-55 years of age. Two doses of 1 to 50 µg of BNT162b1 elicited robust CD4⁺ and CD8⁺ T-cell responses and strong antibody responses, with RBD-binding IgG concentrations clearly above those in a COVID-19 human convalescent sample (HCS) panel. Day 43 SARS-CoV-2 serum neutralising geometric mean titers were 0.7-fold (1 µg) to 3.5-fold (50 µg) those of the HCS panel. Immune sera broadly neutralised pseudoviruses with diverse SARS-CoV-2 spike variants. Most participants had T helper type 1 (TH1) skewed T cell immune responses with RBD-specific CD8⁺ and CD4⁺ T-cell expansion. Interferon (IFN) γ was produced by a high fraction of RBD-specific CD8⁺ and CD4⁺ T cells. The robust RBD-specific antibody, T-cell and favourable cytokine responses induced by the BNT162b1 mRNA vaccine suggest multiple beneficial mechanisms with potential to protect against COVID-19.

Reference

<https://www.nature.com/articles/s41586-020-2814-7>

Ultrastructural analysis of SARS-CoV-2 interactions with the host cell via high resolution scanning electron microscopy

Abstract

SARS-CoV-2 is the cause of the ongoing COVID-19 pandemic. Here, the interaction of this new coronavirus with Vero cells was investigated using high resolution scanning electron microscopy. Surface morphology, the interior of infected cells and the distribution of viral particles in both environments were observed 2 and 48 h after infection. We showed areas of viral processing, details of vacuole contents, and viral interactions with the cell surface. Intercellular connections were also approached, and viral particles were adhered to these extensions suggesting direct cell-to-cell transmission of SARS-CoV-2.

Reference

<https://www.nature.com/articles/s41598-020-73162-5>

The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

Abstract

A recent genetic association study identified a gene cluster on chromosome 3 as a risk locus for respiratory failure upon SARS-CoV-2 infection. A new study comprising 3,199 hospitalized COVID-19 patients and controls finds that this is the major genetic risk factor for severe SARS-CoV-2 infection and hospitalization (COVID-19 Host Genetics Initiative). Here, it is shown that the risk is conferred by a genomic segment of ~50 kb that is inherited from Neanderthals and is carried by ~50% of people in South Asia and ~16% of people in Europe today.

Reference

<https://www.nature.com/articles/s41586-020-2818-3>

SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition

Abstract

T cell immunity is central for the control of viral infections. To characterize T cell immunity, but also for the development of vaccines, identification of exact viral T cell epitopes is fundamental. Here we identify and characterize multiple dominant and subdominant SARS-CoV-2 HLA class I and HLA-DR peptides as potential T cell epitopes in COVID-19 convalescent and unexposed individuals. SARS-CoV-2-specific peptides enabled detection of post-infectious T cell immunity, even in seronegative convalescent individuals. Cross-reactive SARS-CoV-2 peptides revealed pre-existing T cell responses in 81% of unexposed individuals and validated similarity with common cold coronaviruses, providing a functional basis for heterologous immunity in SARS-CoV-2 infection. Diversity of SARS-CoV-2 T cell responses was associated with mild symptoms of COVID-19, providing evidence that immunity requires recognition of multiple epitopes. Together, the proposed SARS-CoV-2 T cell epitopes enable identification of heterologous and post-infectious T cell immunity and facilitate development of diagnostic, preventive and therapeutic measures for COVID-19.

Reference

<https://www.nature.com/articles/s41590-020-00808-x>

Novel hybrid antiviral VTRRT-13V2.1 against SARS-CoV2 main protease: Retro-combinatorial synthesis and molecular dynamics analysis

Abstract

The COVID-19 pandemic caused by SARS-CoV-2 has now emerged as a global health problem. The SARS-CoV-2 main protease (Mpro) emerged as a promising drug target because of its essential role in the processing of polyproteins, which is translated from viral RNA. The present study reporting a designed novel hybrid antiviral molecule (VTRRT-13.V2.1) against SARS-CoV2 main protease. A series of different combinations of hybrid antiviral was generated from nonspecific antiviral molecules currently used to control COVID-19. To enhance the specificity of the designed hybrid

antiviral molecule, the core pocket region of the active site of M^{pro} protein was targeted. In-silico screening, molecular mechanics, molecular dynamics simulation (MDS) analysis identified a hybrid VTRRT-13.V2 molecule. Retrosynthetic analysis and combinatorial synthesis generated 1000 analogs of VTRRT-13.V2 molecules. Docking, molecular mechanics, and MDS analysis selected VTRRT-13.V2.1 as a possible inhibitor for SARS-CoV2 main protease. Comparative analysis of all the results showed that VTRRT-13.V2.1 have the highest docking Glide score (-12.28 kcal/mol) and best binding energy (-52.23 kcal/mol) as compared to the other hybrid constructs *i.e.* VTRRT-13.V2 (-9.47 and -47.36 kcal/mol), VTRRT-13 (-5.08 and -30.30 kcal/mol), and current antiviral investigated. The mutational sensitivity screening showed the binding residues of M^{pro} are not present in mutation hotspots. It was also observed that VTRRT-13.V2.1 does not have any human off-targets. SARS-CoV2 main protease is essential for the survival of this virus; hence, a designed novel hybrid antiviral molecule (VT-RRT-13.V2.1) might be useful to control the infection of COVID-19 infection.

Reference

[https://www.cell.com/heliyon/fulltext/S2405-8440\(20\)31965-4](https://www.cell.com/heliyon/fulltext/S2405-8440(20)31965-4)

Epidemiology and transmission dynamics of COVID-19 in two Indian states

Abstract

Although most COVID-19 cases have occurred in low-resource countries, little is known about the epidemiology of the disease in such contexts. Data from the Indian states of Tamil Nadu and Andhra Pradesh provide a detailed view into SARS-CoV-2 transmission pathways and mortality in a high-incidence setting. Reported cases and deaths have been concentrated in younger cohorts than expected from observations in higher-income countries, even after accounting for demographic differences across settings. Among 575,071 individuals exposed to 84,965 confirmed cases, infection probabilities ranged from 4.7-10.7% for low-risk and high-risk contact types. Same-age contacts were associated with the greatest infection risk. Case-fatality ratios spanned 0.05% at ages 5-17 years to 16.6% at ages ≥ 85 years. Primary data are urgently needed from low-resource countries to guide control measures.

Reference

<https://science.sciencemag.org/content/early/2020/09/29/science.abd7672>

The community psychosocial burden during the COVID-19 pandemic in Indonesia

Abstract

Background: Restricting community mobility during COVID-19 can potentially trigger anxiety, depression and stress in the community. The study aims to analyze variables associated with the community psychosocial burden (anxiety level) during the co-19 pandemic in Indonesia.

Methods: This study collected data (n = 8,031) online. Psychosocial burden was measured based on the anxiety level which include 5 aspects, such as economic, religious, educational, employment, and social issues. Each question used a Likert scale. Six independent were examined, such as age, gender, religion, marital, education, and employment. In the final stage, a multivariate test was performed using a multinomial logistic regression.

Results: Someone older experienced less high anxiety. The age group of 20–29 years was 4,330 times likely to experience higher anxiety than the age group of ≥ 50 years. While, those in the age group of 40–49 years were 2,322 times more likely to have higher anxiety than those in the age group of ≥ 50 years. Male respondents had lower possibility of medium to high anxiety than females. Respondents with secondary and lower education had 3,117 times possibilities to experience higher anxiety than those with high education level.

Conclusion: Four variables affected the psychosocial burden i.e, anxiety level of community in Indonesia. These involved age, gender, education, and employment.

Reference

[https://www.cell.com/heliyon/fulltext/S2405-8440\(20\)31979-4](https://www.cell.com/heliyon/fulltext/S2405-8440(20)31979-4)

Broad host range of SARS-CoV-2 and the molecular basis for SARS-CoV-2 binding to cat ACE2

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the recent pandemic COVID-19, is reported to have originated from bats, with its intermediate host unknown to date. Here, 26 animal counterparts of the human ACE2 (hACE2) were screened, the receptor for SARS-CoV-2 and SARS-CoV, and found that the ACE2s from various species, including pets, domestic animals and multiple wild animals, could bind to SARS-CoV-2 receptor binding domain (RBD) and facilitate the transduction of SARS-CoV-2 pseudovirus. Comparing to SARS-CoV-2, SARS-CoV seems to have a slightly wider range in choosing its receptor. It is further resolved the cryo-electron microscopy (cryo-EM) structure of the cat ACE2 (cACE2) in complex with the SARS-CoV-2 RBD at a resolution of 3 Å, revealing similar binding mode as hACE2 to the SARS-CoV-2 RBD. These results shed light on pursuing the intermediate host of SARS-CoV-2 and highlight the necessity of monitoring susceptible hosts to prevent further outbreaks.

Reference

<https://www.nature.com/articles/s41421-020-00210-9>

Susceptibility of tree shrew to SARS-CoV-2 infection

Abstract

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became a pandemic event in the world, it has not only caused huge economic losses, but also a serious threat to global public health. Many scientific questions about SARS-CoV-2 and Coronavirus disease (COVID-19) were raised and urgently need to be answered, including the susceptibility of animals to SARS-CoV-2 infection. Here it is tested whether tree shrew, an emerging experimental animal domesticated from wild animal, is susceptible to SARS-CoV-2 infection. No clinical signs were observed in SARS-CoV-2

inoculated tree shrews during this experiment except the increasing body temperature particularly in female animals. Low levels of virus shedding and replication in tissues occurred in all three age groups. Notably, young tree shrews (6 months to 12 months) showed virus shedding at the earlier stage of infection than adult (2 years to 4 years) and old (5 years to 7 years) animals that had longer duration of virus shedding comparatively. Histopathological examine revealed that pulmonary abnormalities were the main changes but mild although slight lesions were also observed in other tissues. In summary, tree shrew is less susceptible to SARS-CoV-2 infection compared with the reported animal models and may not be a suitable animal for COVID-19 related researches. However, tree shrew may be a potential intermediate host of SARS-CoV-2 as an asymptomatic carrier.

Reference

<https://www.nature.com/articles/s41598-020-72563-w>

Viral epitope profiling of COVID-19 patients reveals cross-reactivity and correlates of severity

Abstract

Understanding humoral responses to SARS-CoV-2 is critical for improving diagnostics, therapeutics, and vaccines. Deep serological profiling of 232 COVID-19 patients and 190 pre-COVID-19 era controls using VirScan revealed over 800 epitopes in the SARS-CoV-2 proteome, including 10 epitopes likely recognized by neutralizing antibodies. Pre-existing antibodies in controls recognized SARS-CoV-2 ORF1, while only COVID-19 patients primarily recognized spike and nucleoprotein. A machine learning model trained on VirScan data predicted SARS-CoV-2 exposure history with 99% sensitivity and 98% specificity; a rapid Luminex-based diagnostic was developed from the most discriminatory SARS-CoV-2 peptides. Individuals with more severe COVID-19 exhibited stronger and broader SARS-CoV-2 responses, weaker antibody responses to prior infections, and higher incidence of CMV and HSV-1, possibly influenced by demographic covariates. Among hospitalized patients, males make greater SARS-CoV-2 antibody responses than females.

Reference

<https://science.sciencemag.org/content/early/2020/09/28/science.abd4250>

Clinical criteria for COVID-19-associated hyperinflammatory syndrome: A cohort study

Abstract

Background: A subset of patients with COVID-19 develops a hyperinflammatory syndrome that has similarities with other hyperinflammatory disorders. However, clinical criteria specifically to define COVID-19-associated hyperinflammatory syndrome (cHIS) have not been established. We aimed to develop and validate diagnostic criteria for cHIS in a cohort of inpatients with COVID-19.

Methods: Clinical research articles published between Jan 1, 1990, and Aug 20, 2020 was searched, on features and diagnostic criteria for secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, macrophage activation-like syndrome of sepsis, cytokine release syndrome, and COVID-19. Published clinical data for COVID-19 with clinical features of other hyperinflammatory or cytokine storm syndromes was compared. Based on a framework of conserved clinical characteristics, we developed a six-criterion additive scale for cHIS: fever, macrophage activation (hyperferritinaemia), haematological dysfunction (neutrophil to lymphocyte ratio), hepatic injury (lactate dehydrogenase or aspartate aminotransferase), coagulopathy (D-dimer), and cytokinaemia (C-reactive protein, interleukin-6, or triglycerides). We then validated the association of the cHIS scale with in-hospital mortality and need for mechanical ventilation in consecutive patients in the Intermountain Prospective Observational COVID-19 (IPOC) registry who were admitted to hospital with PCR-confirmed COVID-19. We used a multistate model to estimate the temporal implications of cHIS.

Findings: 299 patients admitted to hospital with COVID-19 between March 13 and May 5, 2020 were included, in analyses. Unadjusted discrimination of the maximum daily cHIS score was 0.81 (95% CI 0.74–0.88) for in-hospital mortality and 0.92 (0.88–0.96) for mechanical ventilation; these results remained significant in multivariable analysis (odds ratio 1.6 [95% CI 1.2–2.1], $p=0.0020$, for mortality and 4.3 [3.0–6.0], $p<0.0001$,

for mechanical ventilation). 161 (54%) of 299 patients met two or more cHIS criteria during their hospital admission; these patients had higher risk of mortality than patients with a score of less than 2 (24 [15%] of 138 vs one [1%] of 161) and for mechanical ventilation (73 [45%] vs three [2%]). In the multistate model, using daily cHIS score as a time-dependent variable, the cHIS hazard ratio for worsening from low to moderate oxygen requirement was 1.4 (95% CI 1.2–1.6), from moderate oxygen to high-flow oxygen 2.2 (1.1–4.4), and to mechanical ventilation 4.0 (1.9–8.2).

Interpretation: It was proposed and validated criteria for hyperinflammation in COVID-19. This hyperinflammatory state, cHIS, is commonly associated with progression to mechanical ventilation and death. External validation is needed. The cHIS scale might be helpful in defining target populations for trials and immunomodulatory therapies.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30343-X/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30343-X/fulltext)

Tackling COVID19 by exploiting pre-existing cross-reacting spike-specific immunity

Abstract

The pandemic of novel coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The lack of targeted molecular therapy for patients with SARS-CoV-2 infection has led to high mortality. The study of pre-existing cross-reacting immunity to pre- and post-pandemic coronaviruses provides direction for the development of targeted molecular therapy for members of this class of virus. Combining two or more anti-SARS-CoV-2 spike receptor binding domain (RBD) antibodies should strengthen SARS-CoV-2 neutralization and might restrict the generation of neutralization-evading mutants.

Reference

[https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016\(20\)30492-5](https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(20)30492-5)

Structural and functional modelling of SARS-CoV-2 entry in animal models

Abstract

SARS-CoV-2 is the novel coronavirus responsible for the outbreak of COVID-19, a disease that has spread to over 100 countries and, as of the 26th July 2020, has infected over 16 million people. Despite the urgent need to find effective therapeutics, research on SARS-CoV-2 has been affected by a lack of suitable animal models. To facilitate the development of medical approaches and novel treatments, we compared the ACE2 receptor, and TMPRSS2 and Furin proteases usage of the SARS-CoV-2 Spike glycoprotein in human and in a panel of animal models, i.e. guinea pig, dog, cat, rat, rabbit, ferret, mouse, hamster and macaque. Here we showed that ACE2, but not TMPRSS2 or Furin, has a higher level of sequence variability in the Spike protein interaction surface, which greatly influences Spike protein binding mode. Using molecular docking simulations we compared the SARS-CoV and SARS-CoV-2 Spike proteins in complex with the ACE2 receptor and showed that the SARS-CoV-2 Spike glycoprotein is compatible to bind the human ACE2 with high specificity. In contrast, TMPRSS2 and Furin are sufficiently similar in the considered hosts not to drive susceptibility differences. Computational analysis of binding modes and protein contacts indicates that macaque, ferrets and hamster are the most suitable models for the study of inhibitory antibodies and small molecules targeting the SARS-CoV-2 Spike protein interaction with ACE2. Since TMPRSS2 and Furin are similar across species, our data also suggest that transgenic animal models expressing human ACE2, such as the hACE2 transgenic mouse, are also likely to be useful models for studies investigating viral entry.

Reference

<https://www.nature.com/articles/s41598-020-72528-z>

Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses

Abstract

Development of effective preventative interventions against SARS-CoV-2, the etiologic agent of COVID-19 is urgently needed. The viral surface spike (S) protein of SARS-CoV-2 is a key target for prophylactic measures as it is critical for the viral replication cycle and the primary target of neutralizing antibodies. We evaluated design elements previously shown for other coronavirus S protein-based vaccines to be successful, e.g., prefusion-stabilizing substitutions and heterologous signal peptides, for selection of a S-based SARS-CoV-2 vaccine candidate. In vitro characterization demonstrated that the introduction of stabilizing substitutions (i.e., furin cleavage site mutations and two consecutive prolines in the hinge region of S2) increased the ratio of neutralizing versus non-neutralizing antibody binding, suggestive for a prefusion conformation of the S protein. Furthermore, the wild-type signal peptide was best suited for the correct cleavage needed for a natively folded protein. These observations translated into superior immunogenicity in mice where the Ad26 vector encoding for a membrane-bound stabilized S protein with a wild-type signal peptide elicited potent neutralizing humoral immunity and cellular immunity that was polarized towards Th1 IFN- γ . This optimized Ad26 vector-based vaccine for SARS-CoV-2, termed Ad26.COVS, is currently being evaluated in a phase I clinical trial (ClinicalTrials.gov Identifier: NCT04436276).

Reference

<https://www.nature.com/articles/s41541-020-00243-x>

Modeling lung perfusion abnormalities to explain early COVID-19 hypoxemia

Abstract

Early stages of the novel coronavirus disease (COVID-19) are associated with silent hypoxia and poor oxygenation despite relatively minor parenchymal involvement. Although speculated that such paradoxical findings may be explained by impaired hypoxic pulmonary vasoconstriction in infected lung regions, no studies have determined whether such extreme degrees of perfusion redistribution are physiologically

plausible, and increasing attention is directed towards thrombotic microembolism as the underlying cause of hypoxemia. Herein, a mathematical model demonstrates that the large amount of pulmonary venous admixture observed in patients with early COVID-19 can be reasonably explained by a combination of pulmonary embolism, ventilation-perfusion mismatching in the noninjured lung, and normal perfusion of the relatively small fraction of injured lung. Although underlying perfusion heterogeneity exacerbates existing shunt and ventilation-perfusion mismatch in the model, the reported hypoxemia severity in early COVID-19 patients is not replicated without either extensive perfusion defects, severe ventilation-perfusion mismatch, or hyperperfusion of nonoxygenated regions.

Reference

<https://www.nature.com/articles/s41467-020-18672-6>

Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): An exploratory, open-label, phase 2 randomised controlled trial

Abstract

Background: Severe COVID-19 is characterised by inflammation and coagulation in the presence of complement system activation. We aimed to explore the potential benefit and safety of selectively blocking the anaphylatoxin and complement protein C5a with the monoclonal antibody IFX-1 (vilobelimab), in patients with severe COVID-19.

Methods: We did an exploratory, open-label, randomised phase 2 trial (part of the adaptive phase 2/3 PANAMO trial) of intravenous IFX-1 in adults with severe COVID-19 at three academic hospitals in the Netherlands. Eligibility criteria were age 18 years or older; severe pneumonia with pulmonary infiltrates consistent with pneumonia, a clinical history of severe shortness of breath within the past 14 days, or a need for non-invasive or invasive ventilation; severe disease defined as a ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air ($\text{PaO}_2/\text{FiO}_2$) between 100 mm Hg and 250 mm Hg in the supine position; and severe acute respiratory syndrome coronavirus 2 infection confirmed by RT-PCR. Patients were randomly assigned 1:1 to receive IFX-1 (up to seven doses of 800 mg intravenously) plus best supportive care

(IFX-1 group) or best supportive care only (control group). The primary outcome was the percentage change in PaO₂/FiO₂ in the supine position between baseline and day 5. Mortality at 28 days and treatment-emergent and serious adverse events were key secondary outcomes. The primary analysis was done in the intention-to-treat population and safety analyses were done in all patients according to treatment received. This trial is registered at ClinicalTrials.gov (NCT04333420).

Findings: Between March 31 and April 24, 2020, 30 patients were enrolled and randomly assigned to the IFX-1 group (n=15) or the control group (n=15). During the study it became clear that several patients could not be assessed regularly in the supine position because of severe hypoxaemia. It was therefore decided to focus on all PaO₂/FiO₂ assessments (irrespective of position). At day 5 after randomisation, the mean PaO₂/FiO₂ (irrespective of position) was 158 mm Hg (SD 63; range 84–265) in the IFX-1 group and 189 mm Hg (89; 71–329) in the control group. Analyses of the least squares mean relative change in PaO₂/FiO₂ at day 5 showed no differences between treatment groups (17% change in the IFX-1 group vs 41% in the control group; difference -24% [95% CI -58 to 9], p=0·15. Kaplan-Meier estimates of mortality by 28 days were 13% (95% CI 0–31) for the IFX-1 group and 27% (4–49) for the control group (adjusted hazard ratio for death 0·65 [95% CI 0·10–4·14]). The frequency of serious adverse events were similar between groups (nine [60%] in the IFX-1 group vs seven [47%] in the control group) and no deaths were considered related to treatment assignment. However, a smaller proportion of patients had pulmonary embolisms classed as serious in the IFX-1 group (two [13%]) than in the control group (six [40%]). Infections classed as serious were reported in three (20%) patients in the IFX-1 group versus five (33%) patients in the control group.

Interpretation: In this small exploratory phase 2 part of the PANAMO trial, C5a inhibition with IFX-1 appears to be safe in patients with severe COVID-19. The secondary outcome results in favour of IFX-1 are preliminary because the study was not powered on these endpoints, but they support the investigation of C5a inhibition with IFX-1 in a phase 3 trial using 28-day mortality as the primary endpoint.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30341-6/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30341-6/fulltext)

An alternative binding mode of IGHV3-53 antibodies to the SARS-CoV-2 receptor binding domain

Abstract

IGHV3-53-encoded neutralizing antibodies are commonly elicited during SARS-CoV-2 infection and target the receptor-binding domain (RBD) of the spike (S) protein. Such IGHV3-53 antibodies generally have a short CDR H3 due to structural constraints in binding the RBD (mode A). However, a small subset of IGHV3-53 antibodies to the RBD contain a longer CDR H3. Crystal structures of two IGHV3-53 neutralizing antibodies here demonstrate that a longer CDR H3 can be accommodated in a different binding mode (mode B). These two classes of IGHV3-53 antibodies both target the ACE2 receptor binding site, but with very different angles of approach and molecular interactions. Overall, these findings emphasize the versatility of IGHV3-53 in this common antibody response to SARS-CoV-2, where conserved IGHV3-53 germline-encoded features can be combined with very different CDR H3 lengths and light chains for SARS-CoV-2 RBD recognition and virus neutralization.

Reference

Wu, Nicholas C., Meng Yuan, Hejun Liu, Chang-Chun D. Lee, Xueyong Zhu, Sandhya Bangaru, Jonathan L. Torres et al. "An alternative binding mode of IGHV3-53 antibodies to the SARS-CoV-2 receptor binding domain." *BioRxiv* (2020).

Publication Date: Sep 26, 2020

Reducing false negatives in COVID-19 testing by using microneedle-based oropharyngeal swabs

Abstract

Coronavirus disease 2019 (COVID-19) has become a severe threat to human health worldwide. Early etiological diagnosis plays a critical role in controlling COVID-19 pandemic. However, etiological diagnosis has been largely compromised by high "false negative" rates of viral nucleic acid testing, resulting from limited sampling efficiency using conventional oropharyngeal swabs. Herein, we engineer regular swabs by using a

microneedle (MN) patch to significantly improve the quality and quantity of virus collection. The combination of MNs with different crosslinking levels endows the patches with dual capability of mucus penetration and virus extraction. Moreover, the antibody (Ab) against viral spike protein was integrated into the patch, conferring MNs with an active virus capture potential. By taking advantage of the biological and engineered species, it is believed the designed MN/Ab swabs could serve as a promising tool to improve current sampling efficiency with less "false negatives", contributing to the containment of COVID-19 pandemic.

Reference

Chen, Wei, Bo Cai, Zhi Geng, Fenghua Chen, Zheng Wang, Lin Wang, and Xiaoyuan Chen. "Reducing false negatives in COVID-19 testing by using microneedle-based oropharyngeal swabs." *Matter*.

Publication Date: Sep 25, 2020

Quantification of SARS-CoV-2 neutralizing antibody by a pseudotyped virus-based assay

Abstract

Pseudotyped viruses are useful virological tools because of their safety and versatility. On the basis of a vesicular stomatitis virus (VSV) pseudotyped virus production system, we developed a pseudotyped virus-based neutralization assay against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in biosafety level 2 facilities. Compared with the binding antibody test, the neutralization assay could discriminate the protective agents from the antibody family. This protocol includes production and titration of the SARS-CoV-2 S pseudotyped virus and the neutralization assay based on it. Various types of samples targeting virus attachment and entry could be evaluated for their potency, including serum samples derived from animals and humans, monoclonal antibodies and fusion inhibitors (peptides or small molecules). If the pseudotyped virus stock has been prepared in advance, it will take 2 days to get the potency data for the candidate samples. Experience in handling cells is needed before implementing this protocol.

Reference

<https://www.nature.com/articles/s41596-020-0394-5>

Viral presence and immunopathology in patients with lethal COVID-19: A prospective autopsy cohort study

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) targets multiple organs and causes severe coagulopathy. Histopathological organ changes might not only be attributable to a direct virus-induced effect, but also the immune response. The aims of this study were to assess the duration of viral presence, identify the extent of inflammatory response, and investigate the underlying cause of coagulopathy.

Methods: This prospective autopsy cohort study was done at Amsterdam University Medical Centers (UMC), the Netherlands. With informed consent from relatives, full body autopsy was done on 21 patients with COVID-19 for whom autopsy was requested between March 9 and May 18, 2020. In addition to histopathological evaluation of organ damage, the presence of SARS-CoV-2 nucleocapsid protein and the composition of the immune infiltrate and thrombi were assessed, and all were linked to disease course.

Findings: Our cohort (n=21) included 16 (76%) men, and median age was 68 years (range 41–78). Median disease course (time from onset of symptoms to death) was 22 days (range 5–44 days). In 11 patients tested for SARS-CoV-2 tropism, SARS-CoV-2 infected cells were present in multiple organs, most abundantly in the lungs, but presence in the lungs became sporadic with increased disease course. Other SARS-CoV-2-positive organs included the upper respiratory tract, heart, kidneys, and gastrointestinal tract. In histological analyses of organs (sampled from nine to 21 patients per organ), an extensive inflammatory response was present in the lungs, heart, liver, kidneys, and brain. In the brain, extensive inflammation was seen in the olfactory bulbs and medulla oblongata. Thrombi and neutrophilic plugs were present in the lungs, heart, kidneys, liver, spleen, and brain and were most frequently observed late in the disease course (15 patients with thrombi, median disease course 22 days; ten patients with neutrophilic plugs, 21 days). Neutrophilic plugs were observed in two

forms: solely composed of neutrophils with neutrophil extracellular traps (NETs), or as aggregates of NETs and platelets.

Interpretation: In patients with lethal COVID-19, an extensive systemic inflammatory response was present, with a continued presence of neutrophils and NETs. However, SARS-CoV-2-infected cells were only sporadically present at late stages of COVID-19. This suggests a maladaptive immune response and substantiates the evidence for immunomodulation as a target in the treatment of severe COVID-19.

Reference

Schurink, Bernadette, Eva Roos, Teodora Radonic, Ellis Barbe, Catherine SC Bouman, Hans H. de Boer, Godelieve J. de Bree *et al.* "Viral presence and immunopathology in patients with lethal COVID-19: A prospective autopsy cohort study." *The Lancet Microbe* (2020).

Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: A cross-sectional study

Abstract

Background: Many patients receiving dialysis in the USA share the socioeconomic characteristics of underserved communities, and undergo routine monthly laboratory testing, facilitating a practical, unbiased, and repeatable assessment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroprevalence.

Methods: For this cross-sectional study, in partnership with a central laboratory that receives samples from approximately 1300 dialysis facilities across the USA, we tested the remainder plasma of 28 503 randomly selected adult patients receiving dialysis in July, 2020, using a spike protein receptor binding domain total antibody chemiluminescence assay (100% sensitivity, 99.8% specificity). We extracted data on age, sex, race and ethnicity, and residence and facility ZIP codes from the anonymised electronic health records, linking patient-level residence data with cumulative and daily cases and deaths per 100 000 population and with nasal swab test positivity rates. We standardised prevalence estimates according to the overall US dialysis and adult

population, and present estimates for four prespecified strata (age, sex, region, and race and ethnicity).

Findings: The sampled population had similar age, sex, and race and ethnicity distribution to the US dialysis population, with a higher proportion of older people, men, and people living in majority Black and Hispanic neighbourhoods than in the US adult population. Seroprevalence of SARS-CoV-2 was 8.0% (95% CI 7.7–8.4) in the sample, 8.3% (8.0–8.6) when standardised to the US dialysis population, and 9.3% (8.8–9.9) when standardised to the US adult population. When standardised to the US dialysis population, seroprevalence ranged from 3.5% (3.1–3.9) in the west to 27.2% (25.9–28.5) in the northeast. Comparing seroprevalent and case counts per 100 000 population, we found that 9.2% (8.7–9.8) of seropositive patients were diagnosed. When compared with other measures of SARS-CoV-2 spread, seroprevalence correlated best with deaths per 100 000 population (Spearman's $\rho=0.77$). Residents of non-Hispanic Black and Hispanic neighbourhoods experienced higher odds of seropositivity (odds ratio 3.9 [95% CI 3.4–4.6] and 2.3 [1.9–2.6], respectively) compared with residents of predominantly non-Hispanic white neighbourhoods. Residents of neighbourhoods in the highest population density quintile experienced increased odds of seropositivity (10.3 [8.7–12.2]) compared with residents of the lowest density quintile. County mobility restrictions that reduced workplace visits by at least 5% in early March, 2020, were associated with lower odds of seropositivity in July, 2020 (0.4 [0.3–0.5]) when compared with a reduction of less than 5%.

Interpretation: During the first wave of the COVID-19 pandemic, fewer than 10% of the US adult population formed antibodies against SARS-CoV-2, and fewer than 10% of those with antibodies were diagnosed. Public health efforts to limit SARS-CoV-2 spread need to especially target racial and ethnic minority and densely populated communities.

Reference

Anand, Shuchi, Maria Montez-Rath, Jialin Han, Julie Bozeman, Russell Kerschmann, Paul Beyer, Julie Parsonnet, and Glenn M. Chertow. "Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: A cross-sectional study." *The Lancet* (2020).

Sequence analysis of SARS-CoV-2 genome reveals features important for vaccine design

Abstract

As the SARS-CoV-2 pandemic is rapidly progressing, the need for the development of an effective vaccine is critical. A promising approach for vaccine development is to generate, through codon pair deoptimization, an attenuated virus. This approach carries the advantage that it only requires limited knowledge specific to the virus in question, other than its genome sequence. Therefore, it is well suited for emerging viruses, for which we may not have extensive data. We performed comprehensive in silico analyses of several features of SARS-CoV-2 genomic sequence (e.g., codon usage, codon pair usage, dinucleotide/junction dinucleotide usage, RNA structure around the frameshift region) in comparison with other members of the coronaviridae family of viruses, the overall human genome, and the transcriptome of specific human tissues such as lung, which are primarily targeted by the virus. Our analysis identified the spike (S) and nucleocapsid (N) proteins as promising targets for deoptimization and suggests a roadmap for SARS-CoV-2 vaccine development, which can be generalizable to other viruses.

Reference

Kames, Jacob, David D. Holcomb, Ofer Kimchi, Michael DiCuccio, Nobuko Hamasaki-Katagiri, Tony Wang, Anton A. Komar, Aikaterini Alexaki, and Chava Kimchi-Sarfaty. "Sequence analysis of SARS-CoV-2 genome reveals features important for vaccine design." *BioRxiv* (2020).

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Abstract

Clinical outcome upon infection with SARS-CoV-2 ranges from silent infection to lethal COVID-19. We have found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern TLR3- and IRF7-dependent type I interferon (IFN) immunity to influenza virus, in 659 patients with life-threatening COVID-

19 pneumonia, relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, we experimentally define LOF variants in 23 patients (3.5%), aged 17 to 77 years, underlying autosomal recessive or dominant deficiencies. We show that human fibroblasts with mutations affecting this pathway are vulnerable to SARS-CoV-2. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

Reference

Zhang, Qian, Paul Bastard, Zhiyong Liu, Jérémie Le Pen, Marcela Moncada-Velez, Jie Chen, Masato Ogishi et al. "Inborn errors of type I IFN immunity in patients with life-threatening COVID-19." *Science* (2020).

Ultrapotent human antibodies protect against SARS-CoV-2 challenge *via* multiple mechanisms

Abstract

Efficient therapeutic options are needed to control the spread of SARS-CoV-2 that has caused more than 922,000 fatalities as of September 13th, 2020. We report the isolation and characterization of two ultrapotent SARS-CoV-2 human neutralizing antibodies (S2E12 and S2M11) that protect hamsters against SARS-CoV-2 challenge. Cryo-electron microscopy structures show that S2E12 and S2M11 competitively block ACE2 attachment and that S2M11 also locks the spike in a closed conformation by recognition of a quaternary epitope spanning two adjacent receptor-binding domains. Cocktails including S2M11, S2E12 or the previously identified S309 antibody broadly neutralize a panel of circulating SARS-CoV-2 isolates and activate effector functions. Our results pave the way to implement antibody cocktails for prophylaxis or therapy, circumventing or limiting the emergence of viral escape mutants.

Reference

Tortorici, M. Alejandra, Martina Beltramello, Florian A. Lempp, Dora Pinto, Ha V. Dang, Laura E. Rosen, Matthew McCallum et al. "Ultrapotent human antibodies protect against SARS-CoV-2 challenge *via* multiple mechanisms." *Science* (2020).

Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

Abstract

Interindividual clinical variability in the course of SARS-CoV-2 infection is immense. We report that at least 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG auto-Abs against IFN- ω (13 patients), the 13 types of IFN- α (36), or both (52), at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1,227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 were men. A B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.

Reference

Bastard, Paul, Lindsey B. Rosen, Qian Zhang, Eleftherios Michailidis, Hans-Heinrich Hoffmann, Yu Zhang, Karim Dorgham et al. "Auto-antibodies against type I IFNs in patients with life-threatening COVID-19." *Science* (2020).

Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: An observational cohort study using the OpenSAFELY platform

Abstract

Background: Early descriptions of patients admitted to hospital during the COVID-19 pandemic showed a lower prevalence of asthma and chronic obstructive pulmonary disease (COPD) than would be expected for an acute respiratory disease like COVID-19, leading to speculation that inhaled corticosteroids (ICSs) might protect against infection with severe acute respiratory syndrome coronavirus 2 or the development of serious sequelae. We assessed the association between ICS and COVID-19-related death among people with COPD or asthma using linked electronic health records (EHRs) in England, UK.

Methods: In this observational study, we analysed patient-level data for people with COPD or asthma from primary care EHRs linked with death data from the Office of National Statistics using the OpenSAFELY platform. The index date (start of follow-up) for both cohorts was March 1, 2020; follow-up lasted until May 6, 2020. For the COPD cohort, individuals were eligible if they were aged 35 years or older, had COPD, were a current or former smoker, and were prescribed an ICS or long-acting β agonist plus long-acting muscarinic antagonist (LABA–LAMA) as combination therapy within the 4 months before the index date. For the asthma cohort, individuals were eligible if they were aged 18 years or older, had been diagnosed with asthma within 3 years of the index date, and were prescribed an ICS or short-acting β agonist (SABA) only within the 4 months before the index date. We compared the outcome of COVID-19-related death between people prescribed an ICS and those prescribed alternative respiratory medications: ICSs versus LABA–LAMA for the COPD cohort, and low-dose or medium-dose and high-dose ICSs versus SABAs only in the asthma cohort. We used Cox regression models to estimate hazard ratios (HRs) and 95% CIs for the association between exposure categories and the outcome in each population, adjusted for age, sex, and all other prespecified covariates. We calculated e-values to quantify the effect of unmeasured confounding on our results.

Findings: We identified 148 557 people with COPD and 818 490 people with asthma who were given relevant respiratory medications in the 4 months before the index date. People with COPD who were prescribed ICSs were at increased risk of COVID-19-related death compared with those prescribed LABA–LAMA combinations (adjusted HR 1.39 [95% CI 1.10–1.76]). Compared with those prescribed SABAs only, people with asthma who were prescribed high-dose ICS were at an increased risk of death (1.55 [1.10–2.18]), whereas those given a low or medium dose were not (1.14 [0.85–1.54]). Sensitivity analyses showed that the apparent harmful association we observed could be explained by relatively small health differences between people prescribed ICS and those not prescribed ICS that were not recorded in the database (e value lower 95% CI 1.43).

Interpretation: Our results do not support a major role for regular ICS use in protecting against COVID-19-related death among people with asthma or COPD. Observed

increased risks of COVID-19-related death can be plausibly explained by unmeasured confounding due to disease severity.

Reference

Comprehensive Schultze, Anna, Alex J. Walker, Brian MacKenna, Caroline E. Morton, Krishnan Bhaskaran, Jeremy P. Brown, Christopher T. Rentsch et al. "Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: An observational cohort study using the OpenSAFELY platform." *The Lancet Respiratory Medicine* (2020).

ReScan, a multiplex diagnostic pipeline, pans human sera for SARS-CoV-2 antigens

Abstract

Comprehensive understanding of the serological response to SARS-CoV-2 infection is important for both pathophysiologic insight and diagnostic development. Here, we generate a pan-human coronavirus programmable phage display assay to perform proteome-wide profiling of coronavirus antigens enriched by 98 COVID-19 patient sera. Next, we employ ReScan, a method to efficiently sequester phage expressing the most immunogenic peptides and print them onto paper-based microarrays using acoustic liquid handling, which isolates and identifies 9 candidate antigens, 8 of which are derived from the 2 proteins used for SARS-CoV-2 serologic assays: spike and nucleocapsid proteins. After deployment in a high-throughput assay amenable to clinical lab settings, these antigens show improved specificity over a whole protein panel. This proof-of-concept study demonstrates that ReScan will have broad applicability for other emerging infectious diseases or autoimmune diseases that lack a valid biomarker, enabling a seamless pipeline from antigen discovery to diagnostic using one recombinant protein source.

Reference

Zamecnik, Colin R., Jayant V. Rajan, Kevin A. Yamauchi, Sabrina A. Mann, Rita P. Loudermilk, Gavin M. Sowa, Kelsey C. Zorn et al. "ReScan, a multiplex diagnostic

pipeline, pans human sera for SARS-CoV-2 antigens." *Cell Reports Medicine* (2020): 100123.

PPAR γ cistrome repression during activation of lung monocyte-macrophages in severe COVID-19

Abstract

The molecular mechanisms of cytokine storm in patients with severe COVID-19 infections are poorly understood. To uncover these events, we performed transcriptome analyses of lung biopsies from COVID-19 patients, revealing a gene enrichment pattern similar to that of PPAR γ -knockout macrophages. Single-cell gene expression analysis of bronchoalveolar lavage fluids revealed a characteristic trajectory of PPAR γ -related disturbance in the CD14⁺/CD16⁺ cells. We identified a correlation with the disease severity and the reduced expression of several members of the PPAR γ complex such as EP300, RXRA, RARA, SUMO1, NR3C1, CCDC88A. CHIP-seq analyses confirmed repression of the PPAR γ -RXRA-NR3C1 cistrome in COVID-19 lung samples. Further analysis of protein-protein networks highlighted an interaction between the PPAR γ -associated protein SUMO1 and a nucleoprotein of the SARS virus. Overall, these results demonstrate for the first time, the involvement of the PPAR γ complex in severe COVID-19 lung disease and suggest strongly its role in the major monocyte / macrophage-mediated inflammatory storm.

Reference

Desterke, Christophe, Ali G. Turhan, Annelise Bennaceur-Griscelli, and Frank Griscelli. "PPAR γ cistrome repression during activation of lung monocyte-macrophages in severe COVID-19." *iScience* (2020): 101611.

NEWS LETTER

Publication Date: Sep 30, 2020

COVID has killed more than one million people. How many more will die?

Nine months into the coronavirus pandemic, the official global death toll has now exceeded one million people. But researchers warn that this figure probably vastly underestimates the actual number of people who have died from COVID-19. In reality, many deaths related to the coronavirus have gone unreported, particularly in countries where testing isn't widespread. The death toll will continue to rise as diagnostic capacity increases around the globe. One group of modellers suggests that the number of deaths could exceed 3 million people by January, if the virus is allowed to spread unchecked. For more details, read the link given below.

Reference

<https://www.nature.com/articles/d41586-020-02762-y>

CORRESPONDANCE

Publication Date: Sep 25, 2020

Genetic variants mimicking therapeutic inhibition of IL-6 receptor signaling and risk of COVID-19

Few effective therapeutic options are available for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. IL-6 receptor blockade has been proposed as one potential therapeutic strategy, and more than 40 clinical trials of anti-IL-6 receptor antibodies (including tocilizumab and sarilumab) in the setting of SARS-CoV-2 infection are underway. Early evidence from observational studies and open-label, uncontrolled trials has suggested that IL-6 receptor blockers might confer benefit, particularly in patients with severe COVID-19.

Human genetics enables the investigation of potential opportunities for drug repurposing. We leveraged large-scale human genetic data to investigate whether IL-6 receptor blockade might confer therapeutic benefit in COVID-19. A genetic instrument consisting of seven genetic variants in or close to *IL6R* (pairwise $r^2 \leq 0.1$) was recently shown to be associated with altered concentrations of C-reactive protein, fibrinogen, circulating IL-6, and soluble IL-6 receptor, concordant with known effects of pharmacological IL-6 receptor blockade. We investigated the effect of these *IL6R* variants on risk of hospitalisation for COVID-19 and other SARS-CoV-2-related outcomes using data from the COVID-19 Host Genetics Initiative.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30345-3/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30345-3/fulltext)

PERSPECTIVE

Publication Date: Sep 29, 2020

Mitochondria – in the crossfire of SARS-CoV-2 and immunity

The pathophysiology, immune reaction, differential vulnerability of different population groups and viral host immune system evasion strategies of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection are not yet well understood. Here, we reviewed the multitude of known strategies of coronaviruses and other viruses to usurp mitochondria-associated mechanisms involved in the host innate immune response and put them in context with the current knowledge on SARS-CoV-2. We argue that maintenance of mitochondrial integrity is essential for adequate innate immune system responses and to blunt mitochondrial modulation by SARS-CoV-2. Mitochondrial health thus may determine differential vulnerabilities to SARS-CoV-2 infection rendering markers of mitochondrial functions promising potential biomarkers for SARS-CoV-2 infection risk and severity of outcome. Current knowledge gaps on our understanding of mitochondrial involvement in SARS-CoV-2 infection, life-style and pharmacological strategies to improve mitochondrial integrity and potential reciprocal interactions with chronic and age-related diseases, e.g. Parkinson's Disease, are pointed out.

Reference

[https://www.cell.com/iscience/fulltext/S2589-0042\(20\)30823-3](https://www.cell.com/iscience/fulltext/S2589-0042(20)30823-3)

REPORT

Publication Date: Sep 29, 2020

Cross-sectional evaluation of humoral responses against SARS-CoV-2 Spike

The SARS-CoV-2 virus is responsible for the coronavirus disease 2019 (COVID-19) pandemic, infecting millions of people and causing hundreds of thousands of deaths. The Spike glycoproteins of SARS-CoV-2 mediates viral entry and is the main target for neutralizing antibodies. Understanding the antibody response directed against SARS-CoV-2 is crucial for the development of vaccine, therapeutic and public health interventions. Here we perform a cross-sectional study on 106 different SARS-CoV-2-infected individuals to evaluate humoral responses against SARS-CoV-2 Spike. The vast majority of infected individuals elicits anti-Spike antibodies within 2 weeks after the onset of symptoms. The levels of receptor-binding domain (RBD)-specific IgG persist overtime, while the levels of anti-RBD IgM decrease after symptoms resolution. While most of individuals develop neutralizing antibodies within two weeks of infection, the level of neutralizing activity is significantly decreased over time. Our results highlight the importance of studying the persistence of neutralizing activity upon natural SARS-CoV-2 infection.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(20\)30168-3](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30168-3)

COMMENT

Publication Date: Sep 29, 2020

Decarceration and community re-entry in the COVID-19 era

Jails and prisons are exceptionally susceptible to viral outbreaks, such as severe acute respiratory syndrome coronavirus 2. The USA has extremely high rates of incarceration and COVID-19 is causing an urgent health crisis in correctional facilities and detention centres. Epidemics happening in prisons are compounding the elevated risks that COVID-19 poses to people of colour, older people, and those with comorbidities. Intersectoral community re-entry efforts in the USA and other countries have shown that releasing people from correctional facilities as a pandemic-era public health intervention is safe and can support both public safety and community rebuilding. Therefore, substantial decarceration in the USA should be initiated. A point of focus for such efforts is that many people in prison are serving excessively long sentences and pose acceptable safety risks for release. Properly managed, correctional depopulation will prevent considerable COVID-19 morbidity and mortality and reduce prevailing socioeconomic and health inequities.

Reference

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30730-1/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30730-1/fulltext)

Publication Date: Sep 28, 2020

The opening salvo of anti-complement therapy against COVID-19

The COVID-19 pandemic remains unrelenting as the autumn of 2020 approaches. Despite many clinical trials underway to find effective treatments for COVID-19, few studies have yielded positive results. Increasing evidence shows diffuse activation of the complement pathway in severe COVID-19 infections, from increased serum levels to widespread deposition in autopsy specimens. Initial case reports and case series using complement inhibitors in COVID-19 have shown promising results. The complement pathway, a key effector of the innate immune system, has emerged as a

nidus of investigation in this pandemic. In brief, the complement cascade can be activated by three pathways (classical, lectin, and alternative), which converge on the terminal complement pathway at C3. The terminal pathway results in anaphylatoxins, C3a and C5a, and the membrane attack complex (MAC), C5b-9. The anaphylatoxins are potent activators of neutrophils and monocytes. The MAC disrupts pathogen cell membranes. The dysregulation of this pathway is hypothesised to underlie severe COVID-19 complications.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30353-2/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30353-2/fulltext)

Modelling the epidemic trend of the 2019 novel coronavirus outbreak in China

A new coronavirus disease (COVID-19) with infection of a novel coronavirus named as “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) has spread globally since December 2019. As of 22th September 2020, more than 200 countries worldwide have reported about 30 million confirmed cases and more than 950,000 deaths. China has reported a total of 85,307 (including 2,758 imported) cases and 4,634 deaths. To control the dispersal of COVID-19, the Chinese government initiated an unprecedented lockdown in Hubei province and raised national public health response to the highest state of emergency –level 1 of 4 levels of severity in the Chinese Emergency System in 23rd January 2020. People were encouraged to stay at home as much as possible, and all public events and gatherings were cancelled or delayed, which had significantly reduced the social contacts in the public space (e.g. public transportations, supermarkets, offices, etc.) but increase person to-person contacts in households. At the same time, the usage rate of the face mask is very high in public space (consistently >90% during the time of lockdown). The duration for detection and diagnosis of infected individuals were shortened, and consequently diagnosed individuals and those who were in close contact with them could be isolated timely. With strict social distancing and non-pharmaceutical interventions, China has contained the spread of COVID-19 and reopened its economy since early April. The successful experiences in China will provide important evidence and scientific insights to other countries that are amid the pandemic.

Reference

[https://www.cell.com/the-innovation/fulltext/S2666-6758\(20\)30051-5](https://www.cell.com/the-innovation/fulltext/S2666-6758(20)30051-5)

Publication Date: Sep 25, 2020

COVID-19 vaccination: Returning to WHO's health for all

The development and distribution of a COVID-19 vaccine has the potential to greatly change the course of the pandemic; however, ensuring equitable access will require countries, organisations, and corporations to place their trust in global health. The COVID-19 vaccine initiative (COVAX) shows how public–private partnerships can exacerbate existing chasms or allow organisations, such as WHO, to guide a realistic and adequate approach.

Development of vaccines that meet regulatory and licensing requirements involves high costs in terms of facilities, equipment, and human resources and is a lengthy process that often fails. The high cost restricts many countries from developing a vaccine, which causes low income and middle-income countries to rely on research and development from more powerful economies. Additionally, research highlights the challenges in reaching population-level effectiveness with a vaccine, regardless of production capacity, because of weak delivery infrastructures and barriers to access that determine uptake.

Reference

[https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30415-0/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30415-0/fulltext)

Characterizing COVID-19 maternal-fetal transmission and placental infection using comprehensive molecular pathology

Among the most worrisome consequences of a newly emergent viral disease is its potential effect on pregnant women. It is particularly important to determine whether a novel virus is transmissible from a mother to her infant, a process termed vertical infection, and if so, under what circumstances. There are three possible mechanisms for vertical infection – intrauterine infection (including transplacental and ascending infections), intrapartum transmission (during delivery), and postpartum infection.

Intrauterine transplacental transmission is an important cause of vertical infection of the foetus from viruses, having occurred in previous epidemics of emergent viral diseases such as HIV, Ebola, hepatitis E and Zika viruses. However, following the birth of a neonate that is subsequently found to have a viral infection, it can be challenging to determine exactly how and when the infant became infected. These details have important implications that can influence obstetrical management decisions, best practice delivery options, and neonatal care including viral testing strategies, skin-to-skin maternal contact, need for neonatal isolation and safety of breast feeding.

In previous epidemics of such pathogenic coronaviruses as SARS and MERS, as well as other RNA respiratory viruses, transplacental infections have either been absent or were rare. However, increasing reports of neonates testing positive for COVID-19 shortly after birth have focused attention on the possibility of intrauterine infection, and specifically on transplacental transmission. Until recently, it has not been possible to determine how newborn infants acquired their infection, leading investigators to speculate on when, how and from whom they acquired COVID-19.

Reference

[https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(20\)30359-5/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30359-5/fulltext)

Publication Date: Sep 24, 2020

Differential expression of ACE2 in the respiratory tracts and its relationship to COVID-19 pathogenesis

Since its initial outbreak in December 2019 in Wuhan, China, COVID-19 has quickly and firmly established itself as one of the most devastating global pandemics in history. Not only has it resulted in hundreds of thousands of lives lost worldwide, but it has also led to unprecedented damage to national economies and ways of life, which will take years to recover from. Medical and scientific communities have been racing to study the disease and find efficient strategies for cure and prevention. Enormous efforts and resources have been invested in the study of the disease, including the biology of the virus, as well as potential treatment options and vaccine development. Significant

progress has been made with new findings contributing to the scientific literature on a daily basis.

But much is still unknown about the pathogenesis of the virus. Lung biopsy and autopsy studies have revealed that in many early-phase and non-fatal cases of COVID-19, pulmonary pathology is characterized mainly by alveolar proteinaceous fluid exudation and the accumulation of macrophages. In severe or fatal cases, however, the core pathological change seems to be diffuse alveolar damage (DAD) with the formation of hyalinized membranes. In addition, endothelial cell damage, thrombosis of small blood vessels, and superimposed bronchopneumonia can be seen in a significant subset of these patients. From a demographic perspective, fatal SARS-CoV-2 infection has been seen in all groups of patients, but risks for increased disease severity and fatal outcome have been strongly correlated with advanced age, male gender, and underlying comorbidities. Elucidating the underlying mechanisms for this risk association may shed light on how to better treat patients to prevent death.

Reference

[https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(20\)30380-7/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30380-7/fulltext)