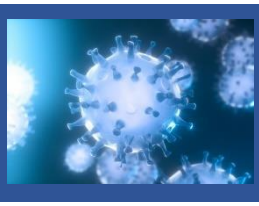

RESEARCH PUBLICATIONS

Publication Date: Oct 14, 2020

Modelling COVID 19 in the Basque Country from introduction to control measure response

Abstract

In March 2020, a multidisciplinary task force (so-called Basque Modelling Task Force, BMTF) was created to assist the Basque health managers and Government during the COVID-19 responses. BMTF is a modelling team, working on different approaches, including stochastic processes, statistical methods and artificial intelligence. Here we describe the efforts and challenges to develop a flexible modeling framework able to describe the dynamics observed for the tested positive cases, including the modelling development steps. The results obtained by a new stochastic SHARUCD model framework are presented. Our models differentiate mild and asymptomatic from severe infections prone to be hospitalized and were able to predict the course of the epidemic, providing important projections on the national health system's necessities during the increased population demand on hospital admissions. Short and longer-term predictions were tested with good results adjusted to the available epidemiological data. We have shown that the partial lockdown measures were effective and enough to slow down disease transmission in the Basque Country. The growth rate λ was calculated from the model and from the data and the implications for the reproduction ratio are shown. The analysis of the growth rates from the data led to improved model versions describing after the exponential phase also the new information obtained during the phase of response to the control measures. This framework is now being used to monitor disease transmission while the country lockdown was gradually lifted, with insights to specific programs for a general policy of "social distancing" and home quarantining.

Reference

https://www.nature.com/articles/s41598-020-74386-1

A materials-science perspective on tackling COVID-19

Abstract

The ongoing SARS-CoV-2 pandemic highlights the importance of materials science in providing tools and technologies for antiviral research and treatment development. In this Review, we discuss previous efforts in materials science in developing imaging systems and microfluidic devices for the in-depth and real-time investigation of viral structures and transmission, as well as material platforms for the detection of viruses and the delivery of antiviral drugs and vaccines. It highlighted the contribution of materials science to the manufacturing of personal protective equipment and to the design of simple, accurate and low-cost virus-detection devices. We then investigate future possibilities of materials science in antiviral research and treatment development, examining the role of materials in antiviral-drug design, including the importance of synthetic material platforms for organoids and organs-on-a-chip, in drug delivery and vaccination, and for the production of medical equipment. Materials-science-based technologies not only contribute to the ongoing SARS-CoV-2 research efforts but can also provide platforms and tools for the understanding, protection, detection and treatment of future viral diseases.

Reference

https://www.nature.com/articles/s41578-020-00247-y

Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness

Abstract

In response to the COVID-19 pandemic, many governments have taken drastic measures to avoid an overflow of intensive care units. Accurate metrics of disease spread are critical for the reopening strategies. Here, It was shown that self-reports of smell/taste changes are more closely associated with hospital overload and are earlier

markers of the spread of infection of SARS-CoV-2 than current governmental indicators. We also report a decrease in self-reports of new onset smell/taste changes as early as 5 days after lockdown enforcement. Cross-country comparisons demonstrate that countries that adopted the most stringent lockdown measures had faster declines in new reports of smell/taste changes following lockdown than a country that adopted less stringent lockdown measures. It was proposed that an increase in the incidence of sudden smell and taste change in the general population may be used as an indicator of COVID-19 spread in the population.

Reference

https://www.nature.com/articles/s41467-020-18963-y

Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries

Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic has changed many social, economic, environmental and healthcare determinants of health. An ensemble of 16 Bayesian models was applied to vital statistics data to estimate the all-cause mortality effect of the pandemic for 21 industrialized countries. From mid-February through May 2020, 206,000 (95% credible interval, 178,100–231,000) more people died in these countries than would have had the pandemic not occurred. The number of excess deaths, excess deaths per 100,000 people and relative increase in deaths were similar between men and women in most countries. England and Wales and Spain experienced the largest effect: ~100 excess deaths per 100,000 people, equivalent to a 37% (30–44%) relative increase in England and Wales and 38% (31–45%) in Spain. Bulgaria, New Zealand, Slovakia, Australia, Czechia, Hungary, Poland, Norway, Denmark and Finland experienced mortality changes that ranged from possible small declines to increases of 5% or less in either sex. The heterogeneous mortality effects of the COVID-19 pandemic reflect differences in how well countries have managed the pandemic and the resilience and preparedness of the health and social care system.

Reference

https://www.nature.com/articles/s41591-020-1112-0

Considerations for diagnostic COVID-19 tests

Abstract

During the early phase of the coronavirus disease 2019 (COVID-19) pandemic, design, development, validation, verification and implementation of diagnostic tests were actively addressed by a large number of diagnostic test manufacturers. Hundreds of molecular tests and immunoassays were rapidly developed, albeit many still await clinical validation and formal approval. In this Review, we summarize the crucial role of diagnostic tests during the first global wave of COVID-19. The technical and implementation problems were encountered during this early phase in the pandemic, and try to define future directions for the progressive and better use of (syndromic) diagnostics during a possible resurgence of COVID-19 in future global waves or regional outbreaks. Continuous global improvement in diagnostic test preparedness is essential for more rapid detection of patients, possibly at the point of care, and for optimized prevention and treatment, in both industrialized countries and low-resource settings.

Reference

https://www.nature.com/articles/s41579-020-00461-z

Coronavirus disease 2019 (COVID-19) in Italy: Features on chest computed tomography using a structured report system

Abstract

To assess the use of a structured report in the Chest Computed Tomography (CT) reporting of patients with suspicious viral pneumonia by COVID-19 and the evaluation of the main CT patterns. This study included 134 patients (43 women and 91 men; 68.8 years of mean age, range 29–93 years) with suspicious COVID-19 viral infection evaluated by reverse transcription real-time fluorescence polymerase chain reaction (RT-PCR) test. All patients underwent CT examinations at the time of admission. CT

images were reviewed by two radiologists who identified COVID-19 CT patterns using a structured reports. Temporal difference mean value between RT-PCRs and CT scan was 0.18 days ± 2.0 days. CT findings were positive for viral pneumonia in 94.0% patients while COVID-19 was diagnosed at RT-PCR in 77.6% patients. Time mean value to complete the structured report by radiologist was 8.5 min ± 2.4 min. The disease on chest CT predominantly affected multiple lobes and the main CT feature was ground glass opacity (GGO) with or without consolidation (96.8%). GGO was predominantly bilateral (89.3%), peripheral (80.3%), multifocal/patching (70.5%). Consolidation disease was predominantly bilateral (83.9%) with prevalent peripheral (87.1%) and segmental (47.3%) distribution. Additional CT signs were the crazy-paving pattern in 75.4% of patients, the septal thickening in 37.3% of patients, the air bronchogram sign in 39.7% and the “reversed halo” sign in 23.8%. Less frequent characteristics at CT regard discrete pulmonary nodules, increased trunk diameter of the pulmonary artery, pleural effusion and pericardium effusion (7.9%, 6.3%, 14.3% and 16.7%, respectively). Barotrauma sign was absent in all the patients. High percentage (54.8%) of the patients had mediastinal lymphadenopathy. Using a Chest CT structured report, with a standardized language, we identified that the cardinal hallmarks of COVID-19 infection were bilateral, peripheral and multifocal/patching GGO and bilateral consolidation with peripheral and segmental distribution.

Reference

https://www.nature.com/articles/s41598-020-73788-5

The architecture of inactivated SARS-CoV-2 with postfusion spikes revealed by Cryo-EM and Cryo-ET

Abstract

The ongoing global pandemic of coronavirus disease 2019 (COVID-19) resulted from the outbreak of SARS-CoV-2 in December 2019. Currently, multiple efforts are being made to rapidly develop vaccines and treatments to fight COVID-19. Current vaccine candidates use inactivated SARS-CoV-2 viruses; therefore, it is important to understand the architecture of inactivated SARS-CoV-2. β-Propiolactone-inactivated viruses were genetically and structurally characterized from a propagated and purified clinical strain

of SARS-CoV-2. We observed that the virus particles are roughly spherical or moderately pleiomorphic. Although a small fraction of prefusion spikes are found, most spikes appear nail shaped, thus resembling a postfusion state, where the S1 protein of the spike has disassociated from S2. Cryoelectron tomography and subtomogram averaging of these spikes yielded a density map that closely matches the overall structure of the SARS-CoV postfusion spike and its corresponding glycosylation site. Our findings have major implications for SARS-CoV-2 vaccine design, especially those using inactivated viruses.

Reference

https://www.cell.com/structure/fulltext/S0969-2126(20)30372-5

Publication Date: Oct 13, 2020

A systematic review of SARS-CoV-2 vaccine candidates

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging virus that is highly pathogenic and has caused the recent worldwide pandemic officially named coronavirus disease (COVID-19). Currently, considerable efforts have been put into developing effective and safe drugs and vaccines against SARS-CoV-2. Vaccines, such as inactivated vaccines, nucleic acid-based vaccines, and vector vaccines, have already entered clinical trials. In this review, we provide an overview of the experimental and clinical data obtained from recent SARS-CoV-2 vaccines trials, and highlight certain potential safety issues that require consideration when developing vaccines. Furthermore, we summarize several strategies utilized in the development of vaccines against other infectious viruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), with the aim of aiding in the design of effective therapeutic approaches against SARS-CoV-2.

Reference

https://www.nature.com/articles/s41392-020-00352-y

Lack of tocilizumab effect on mortality in COVID19 patients

Abstract

Off-label tocilizumab use in COVID-19 patients reflects concern for cytokine release syndrome. Comparison of matched COVID-19 pneumonia patients found elevated IL-6 levels correlated with mortality that did not change with tocilizumab administration. Correlating mortality with increased IL-6 doesn't imply causality however lack of improvement by tocilizumab requires further clinical trial alterations.

Reference

https://www.nature.com/articles/s41598-020-74328-x

Acute psychological effects of Coronavirus Disease 2019 outbreak among healthcare workers in China: A cross-sectional study

Abstract

To study the acute psychological effects of Coronavirus Disease 2019 (COVID-19) outbreak among healthcare workers (HCWs) in China, a cross-sectional survey was conducted among HCWs during the early period of COVID-19 outbreak. The acute psychological effects including symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD) were assessed using the Patient Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder (GAD-7) questionnaire, and the Impact of Event Scale-Revised (IES-R). The prevalence of depression, anxiety, and PTSD was estimated at 15.0%, 27.1%, and 9.8%, respectively. Having an intermediate technical title, working at the frontline, receiving insufficient training for protection, and lacking confidence in protection measures were significantly associated with increased risk for depression and anxiety. Being a nurse, having an intermediate technical title, working at the frontline, and lacking confidence in protection measures were risk factors for PTSD. Meanwhile, not worrying about infection was a protective factor for developing depression, anxiety, and PTSD. Psychological interventions should be implemented among HCWs during the COVID-19 outbreak to reduce acute psychological effects and prevent long-term psychological comorbidities. Meanwhile, HCWs should be well trained and well protected before their frontline exposure.

Reference

https://www.nature.com/articles/s41398-020-01031-w

Nebulized ivermectin for COVID-19 and other respiratory diseases, a proof of concept, dose-ranging study in rats

Abstract

Ivermectin is a widely used antiparasitic drug with known efficacy against several single-strain RNA viruses. Recent data shows significant reduction of SARS-CoV-2 replication in vitro by ivermectin concentrations not achievable with safe doses orally. Inhaled therapy has been used with success for other antiparasitics. An ethanol-based ivermectin formulation was administered once to 14 rats using a nebulizer capable of delivering particles with alveolar deposition. Rats were randomly assigned into three target dosing groups, lower dose (80–90 mg/kg), higher dose (110–140 mg/kg) or ethanol vehicle only. A toxicology profile including behavioral and weight monitoring, full blood count, biochemistry, necropsy and histological examination of the lungs was conducted. The pharmacokinetic profile of ivermectin in plasma and lungs was determined in all animals. There were no relevant changes in behavior or body weight. There was a delayed elevation in muscle enzymes compatible with rhabdomyolysis, that was also seen in the control group and has been attributed to the ethanol dose which was up to 11 g/kg in some animals. There were no histological anomalies in the lungs of any rat. Male animals received a higher ivermectin dose adjusted by adipose weight and reached higher plasma concentrations than females in the same dosing group (mean Cmax 86.2 ng/ml vs. 26.2 ng/ml in the lower dose group and 152 ng/ml vs. 51.8 ng/ml in the higher dose group). All subjects had detectable ivermectin concentrations in the lungs at seven days post intervention, up to 524.3 ng/g for high-dose male and 27.3 ng/g for low-dose females. nebulized ivermectin can reach pharmacodynamic concentrations in the lung tissue of rats, additional experiments are required to assess the safety of this formulation in larger animals.

Reference

https://www.nature.com/articles/s41598-020-74084-y

Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury

Abstract

Elevations in troponin levels have been shown to predict mortality in patients with coronavirus disease 2019 (COVID-19). The role of inflammation in myocardial injury remains unclear. It was sought to determine the association of elevated troponin with mortality in a large, ethnically diverse population of patients hospitalized with COVID-19, and to determine the association of elevated inflammatory markers with increased troponin levels. All patients that were admitted at our health system with COVID-19 from March 1 to April 27, 2020 were reviewed, who had a troponin assessment within 48 hours of admission. Logistic regression was used to calculate odds ratios (ORs) for mortality during hospitalization, controlling for demographics, comorbidities, and markers of inflammation. Of 11159 patients hospitalized with COVID-19, 6247 had a troponin assessment within 48 hours. Of these, 4426 (71%) patients had normal, 919 (15%) had mildly elevated, and 902 (14%) had severely elevated troponin. Acute phase and inflammatory markers were significantly elevated in patients with mildly and severely elevated troponin compared to normal troponin. Patients with elevated troponin had significantly increased odds of death for mildly elevated compared to normal troponin (adjusted OR, 2.06; 95% CI, 1.68-2.53; P < .001) and for severely elevated compared to normal troponin (OR, 4.51; 95% CI, 3.66-5.54; P < .001) independently of elevation in inflammatory markers. In conclusion, patients hospitalized with COVID-19 and elevated troponin had markedly increased mortality compared to patients with normal troponin levels. This risk was independent of cardiovascular comorbidities and elevated markers of inflammation.

Reference

https://www.sciencedirect.com/science/article/pii/S0002914920310973

SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF-barrier in human brain organoids

Abstract

Coronavirus disease-19 (COVID-19), caused by the SARS-CoV-2 virus, leads to respiratory symptoms that can be fatal. However, neurological symptoms have also been observed in some patients. The cause of these complications is currently unknown. Here, we use human pluripotent stem cell-derived brain organoids to examine SARS-CoV-2 neurotropism. Expression of viral receptor ACE2 was found in mature choroid plexus cells expressing abundant lipoproteins, but not in neurons or other cell types. We challenge organoids with SARS-CoV-2 spike pseudovirus and live virus to demonstrate viral tropism for choroid plexus epithelial cells, but little to no infection of neurons or glia. It was found that infected cells are apolipoprotein and ACE2 expressing cells of the choroid plexus epithelial barrier. Finally, it was shown that infection with SARS-CoV-2 damages the choroid plexus epithelium, leading to leakage across this important barrier that normally prevents entry of pathogens, immune cells and cytokines into cerebrospinal fluid and the brain.

Reference

https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(20)30495-1

SARS-CoV-2 immunity: Review and applications to phase 3 vaccine candidates

Abstract

Understanding immune responses to severe acute respiratory syndrome coronavirus 2 is crucial to understanding disease pathogenesis and the usefulness of bridge therapies, such as hyperimmune globulin and convalescent human plasma, and to developing vaccines, antivirals, and monoclonal antibodies. A mere 11 months ago, the canvas we call COVID-19 was blank. Scientists around the world have worked collaboratively to fill in this blank canvas. In this Review, we discuss what is currently known about human humoral and cellular immune responses to severe acute respiratory syndrome coronavirus 2 and relate this knowledge to the COVID-19 vaccines currently in phase 3 clinical trials.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32137-1/fulltext

Impact of COVID-19 mitigation measures on the incidence of preterm birth: A national quasi-experimental study

Abstract

Background: Preterm birth is the leading cause of child mortality globally, with many survivors experiencing long-term adverse consequences. Preliminary evidence suggests that numbers of preterm births greatly reduced following implementation of policy measures aimed at mitigating the effects of the COVID-19 pandemic. We aimed to study the impact of the COVID-19 mitigation measures implemented in the Netherlands in a stepwise fashion on March 9, March 15, and March 23, 2020, on the incidence of preterm birth.

Methods: We used a national quasi-experimental difference-in-regression-discontinuity approach. We used data from the neonatal dried blood spot screening programme (2010–20) cross-validated against national perinatal registry data. Stratified analyses were done according to gestational age subgroups, and sensitivity analyses were done to assess robustness of the findings. We explored potential effect modification by neighbourhood socioeconomic status, sex, and small-for-gestational-age status.

Findings: Data on 1 599 547 singleton neonates were available, including 56 720 births that occurred after implementation of COVID-19 mitigation measures on March 9, 2020. Consistent reductions in the incidence of preterm birth were seen across various time windows surrounding March 9 (± 2 months [n=531 823] odds ratio [OR] 0·77, 95% CI 0·66–0·91, p=0·0026; ± 3 months [n=796 531] OR 0·85, 0·73–0·98, p=0·028; ± 4 months [n=1 066 872] OR 0·84, 0·73–0·97, p=0·023). Decreases in incidence observed following the March 15 measures were of smaller magnitude, but not statistically significant. No changes were observed after March 23. Reductions in the incidence of preterm births after March 9 were consistent across gestational age strata and robust in sensitivity analyses. They appeared confined to neighbourhoods of high socioeconomic status, but effect modification was not statistically significant.

Interpretation: In this national quasi-experimental study, initial implementation of COVID-19 mitigation measures was associated with a substantial reduction in the incidence of preterm births in the following months, in agreement with preliminary observations elsewhere. Integration of comparable data from across the globe is needed to further substantiate these findings and start exploring underlying mechanisms.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30223-1/fulltext

COVID-19 in New Zealand and the impact of the national response: A descriptive epidemiological study

Abstract

Background: In early 2020, during the COVID-19 pandemic, New Zealand implemented graduated, risk-informed national COVID-19 suppression measures aimed at disease elimination. Their impacts on the epidemiology of the first wave of COVID-19 were investigated in the country and response performance measures.

Methods: A descriptive epidemiological study was done of all laboratory-confirmed and probable cases of COVID-19 and all patients tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in New Zealand from Feb 2 to May 13, 2020, after which time community transmission ceased. Data was extracted from the national notifiable diseases database and the national SARS-CoV-2 test results repository. Demographic features and disease outcomes, transmission patterns (source of infection, outbreaks, household transmission), time-to-event intervals, and testing coverage were described over five phases of the response, capturing different levels of non-pharmaceutical interventions. Risk factors for severe outcomes (hospitalisation or death) were examined with multivariable logistic regression and time-to-event intervals were analysed by fitting parametric distributions using maximum likelihood estimation.

Findings: 1503 cases were detected over the study period, including 95 (6·3%) hospital admissions and 22 (1·5%) COVID-19 deaths. The estimated case infection rate per million people per day peaked at 8·5 (95% CI 7·6–9·4) during the 10-day period of rapid

response escalation, declining to 3·2 (2·8–3·7) in the start of lockdown and progressively thereafter. 1034 (69%) cases were imported or import related, tending to be younger adults, of European ethnicity, and of higher socioeconomic status. 702 (47%) cases were linked to 34 outbreaks. Severe outcomes were associated with locally acquired infection (crude odds ratio [OR] 2·32 [95% CI 1·40–3·82] compared with imported), older age (adjusted OR ranging from 2·72 [1·40–5·30] for 50–64 year olds to 8·25 [2·59–26·31] for people aged ≥80 years compared with 20–34 year olds), aged residential care residency (adjusted OR 3·86 [1·59–9·35]), and Pacific peoples (adjusted OR 2·76 [1·14–6·68]) and Asian (2·15 [1·10–4·20]) ethnicities relative to European or other. Times from illness onset to notification and isolation progressively decreased and testing increased over the study period, with few disparities and increasing coverage of females, Māori, Pacific peoples, and lower socioeconomic groups.

Interpretation: New Zealand's response resulted in low relative burden of disease, low levels of population disease disparities, and the initial achievement of COVID-19 elimination.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30225-5/fulltext

Publication Date: Oct 12, 2020

Impact of novel coronavirus disease (COVID-19) on Egyptian dentists' fear and dental practice (a cross-sectional survey)

Abstract

Objectives: This study aimed to evaluate the fear of infection among Egyptian dentists practicing during the current coronavirus disease 2019 (COVID-19) pandemic and to explore the dentist's knowledge about guidelines to fight the virus and to assess various modifications in dental practice.

Methods: An online survey was submitted to dental professionals. Data were collected through a validated questionnaire consisting of 23 closed-ended questions. The gathered data were statistically analyzed.

Results: An overall 216 dentists completed the survey. A total of 200 (92.6%) dental professionals were afraid of becoming infected with COVID-19 while 196 (90.7%) became anxious to treat patients showing suspicious symptoms. The majority of the participants were aware of the mode of transmission of COVID-19 and a lot of them were updated with the current Disease Control and Prevention (CDC) or World Health Organization (WHO) guidelines for cross-infection control.

Conclusions: COVID-19 pandemic has a significant impact on dental professionals.

Reference

https://www.nature.com/articles/s41405-020-00047-0

Type 2 and interferon inflammation regulate SARS-CoV-2 entry factor expression in the airway epithelium

Abstract

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, an emerging virus that utilizes host proteins ACE2 and TMPRSS2 as entry factors. Understanding the factors affecting the pattern and levels of expression of these genes is important for deeper understanding of SARS-CoV-2 tropism and pathogenesis. Here we explore the role of genetics and co-expression networks in regulating these genes in the airway, through the analysis of nasal airway transcriptome data from 695 children. We identify expression quantitative trait loci for both ACE2 and TMPRSS2, that vary in frequency across world populations. It was found TMPRSS2 is part of a mucus secretory network, highly upregulated by type 2 (T2) inflammation through the action of interleukin-13, and that the interferon response to respiratory viruses highly upregulates ACE2 expression. IL-13 and virus infection mediated effects on ACE2 expression were also observed at the protein level in the airway epithelium. Finally, it was defined that airway responses to common coronavirus infections in children, finding that these infections generate host responses similar to other viral species, including upregulation of IL6 and ACE2. The results revealed possible mechanisms influencing SARS-CoV-2 infectivity and COVID-19 clinical outcomes.

Reference

https://www.nature.com/articles/s41467-020-18781-2

Analysis of SARS-CoV-2 vertical transmission during pregnancy

Abstract

The impact of SARS-CoV-2 infection during gestation remains unclear. Here, the viral genome was analyzed on maternal and newborns nasopharyngeal swabs, vaginal swabs, maternal and umbilical cord plasma, placenta and umbilical cord biopsies, amniotic fluids and milk from 31 mothers with SARS-CoV-2 infection. In addition, specific anti-SARS-CoV-2 antibodies were tested and expression of genes involved in inflammatory responses in placentas, and in maternal and umbilical cord plasma. SARS-CoV-2 genome was detected in one umbilical cord blood and in two at-term placentas, in one vaginal mucosa and in one milk specimen. Furthermore, the presence of specific anti-SARS-CoV-2 IgM and IgG antibodies were reported in one umbilical cord blood and in one milk specimen. Finally, in the three documented cases of vertical transmission, SARS-CoV-2 infection was accompanied by a strong inflammatory response. Together, these data support the hypothesis that in utero SARS-CoV-2 vertical transmission, while low, is possible. These results might help defining proper obstetric management of COVID-19 pregnant women, or putative indications for mode and timing of delivery.

Reference

https://www.nature.com/articles/s41467-020-18933-4

SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies

Abstract

The COVID-19 pandemic presents an urgent health crisis. Human neutralizing antibodies (hNAbs) that target the host ACE2 receptor-binding domain (RBD) of the SARS-CoV-2 spike show therapeutic promise and are being evaluated clincally. To determine structural correlates of SARS-CoV-2 neutralization, 8 new structures of distinct COVID-19 hNAbs5 in complex with SARS-CoV-2 spike trimer or RBD were

solved. Structural comparisons allowed classification into categories: (1) VH3-53 hNAbs with short CDRH3s that block ACE2 and bind only to “up” RBDs, (2) ACE2-blocking hNAbs that bind both “up” and “down” RBDs and can contact adjacent RBDs, (3) hNAbs that bind outside the ACE2 site and recognize “up” and “down” RBDs, and (4) Previously-described antibodies that do not block ACE2 and bind only “up” RBDs. Class 2 comprised four hNAbs whose epitopes bridged RBDs, including a VH3-53 hNAb that used a long CDRH3 with a hydrophobic tip to bridge between adjacent “down” RBDs, thereby locking the spike into a closed conformation. Epitope/paratope mapping revealed few interactions with host-derived N-glycans and minor contributions of antibody somatic hypermutations to epitope contacts. Affinity measurements and mapping of naturally-occurring and in vitro-selected spike mutants in 3D provided insight into the potential for SARS-CoV-2 escape from antibodies elicited during infection or delivered therapeutically. These classifications and structural analyses provide rules for assigning current and future human RBD-targeting antibodies into classes, evaluating avidity effects, suggesting combinations for clinical use, and providing insight into immune responses against SARS-CoV-2.

Reference

https://www.nature.com/articles/s41586-020-2852-1

Drug binding dynamics of the dimeric SARS-CoV-2 main protease, determined by molecular dynamics simulation

Abstract

Molecular dynamics simulation was performed of the dimeric SARS-CoV-2 (severe acute respiratory syndrome corona virus 2) main protease (Mpro) to examine the binding dynamics of small molecular ligands. Seven HIV inhibitors, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir, were used as the potential lead drugs to investigate access to the drug binding sites in Mpro. The frequently accessed sites on Mpro were classified based on contacts between the ligands and the protein, and the differences in site distributions of the encounter complex were observed among the ligands. All seven ligands showed binding to the active site at least twice in 28 simulations of 200 ns each. The variations in the complex structure of the active site

with the ligands were also investigated, using microsecond order simulations. Results revealed a wide variation in the shapes of the binding sites and binding poses of the ligands. Additionally, the C-terminal region of the other chain often interacted with the ligands and the active site. Collectively, these findings indicate the importance of dynamic sampling of protein–ligand complexes and suggest the possibilities of further drug optimisations.

Reference

https://www.nature.com/articles/s41598-020-74099-5

Structure-Based Design with Tag-based purification and in-process biotinylation enable streamlined development of SARS-CoV-2 spike molecular probes

Abstract

Biotin-labeled molecular probes, comprising specific regions of the SARS-CoV-2 spike, would be helpful in the isolation and characterization of antibodies targeting this recently emerged pathogen. Here, we design constructs incorporating an N-terminal purification tag, a site-specific protease-cleavage site, the probe region of interest, and a C-terminal sequence targeted by biotin ligase. Probe regions include full-length spike ectodomain as well as various subregions, and we also design mutants that eliminate recognition of the ACE2 receptor. Yields of biotin-labeled probes from transient transfection range from ~0.5 mg/L for the complete ectodomain to >5 mg/L for several subregions. Probes are characterized for antigenicity and ACE2 recognition, and the structure of the spike ectodomain probe is determined by cryo-electron microscopy. Antibody-binding specificities and cell-sorting capabilities of the biotinylated probes were also characterized. Altogether, structure-based design coupled to efficient purification and biotinylation processes can thus enable streamlined development of SARS-CoV-2 spike-ectodomain probes.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31311-5

Genomic evidence for reinfection with SARS-CoV-2: A case study

Abstract

Background: The degree of protective immunity conferred by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently unknown. As such, the possibility of reinfection with SARS-CoV-2 is not well understood. An investigation of two instances of SARS-CoV-2 infection was described in the same individual.

Methods: A 25-year-old man who was a resident of Washoe County in the US state of Nevada presented to health authorities on two occasions with symptoms of viral infection, once at a community testing event in April, 2020, and a second time to primary care then hospital at the end of May and beginning of June, 2020. Nasopharyngeal swabs were obtained from the patient at each presentation and twice during follow-up. Nucleic acid amplification testing was done to confirm SARS-CoV-2 infection. Next-generation sequencing of SARS-CoV-2 extracted from nasopharyngeal swabs was done. Sequence data were assessed by two different bioinformatic methodologies. A short tandem repeat marker was used for fragment analysis to confirm that samples from both infections came from the same individual.

Findings: The patient had two positive tests for SARS-CoV-2, the first on April 18, 2020, and the second on June 5, 2020, separated by two negative tests done during follow-up in May, 2020. Genomic analysis of SARS-CoV-2 showed genetically significant differences between each variant associated with each instance of infection. The second infection was symptomatically more severe than the first.

Interpretation: Genetic discordance of the two SARS-CoV-2 specimens was greater than could be accounted for by short-term in vivo evolution. These findings suggest that the patient was infected by SARS-CoV-2 on two separate occasions by a genetically distinct virus. Thus, previous exposure to SARS-CoV-2 might not guarantee total immunity in all cases. All individuals, whether previously diagnosed with COVID-19 or not, should take identical precautions to avoid infection with SARS-CoV-2. The implications of reinfections could be relevant for vaccine development and application.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30764-7/fulltext

The role of death domain proteins in host response upon SARS-CoV-2 infection: Modulation of programmed cell death and translational applications

Abstract

The current pandemic of novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) poses a significant global public health threat. While urgent regulatory measures in control of the rapid spread of this virus are essential, scientists around the world have quickly engaged in this battle by studying the molecular mechanisms and searching for effective therapeutic strategies against this deadly disease. At present, the exact mechanisms of programmed cell death upon SARS-CoV-2 infection remain to be elucidated, though there is increasing evidence suggesting that cell death pathways play a key role in SARS-CoV-2 infection. There are several types of programmed cell death, including apoptosis, pyroptosis, and necroptosis. These distinct programs are largely controlled by the proteins of the death domain (DD) superfamily, which play an important role in viral pathogenesis and host antiviral response. Many viruses have acquired the capability to subvert the program of cell death and evade the host immune response, mainly by virally encoded gene products that control cell signaling networks. In this mini-review, we will focus on SARS-CoV-2, and discuss the implication of restraining the DD-mediated signaling network to potentially suppress viral replication and reduce tissue damage.

Reference

https://www.nature.com/articles/s41420-020-00331-w

Caregiver willingness to vaccinate their children against COVID-19: Cross sectional survey

Abstract

Background: More than 100 COVID-19 vaccine candidates are in development since the SARS-CoV-2 genetic sequence was published in January 2020. The uptake of a COVID-19 vaccine among children will be instrumental in limiting the spread of the

disease as herd immunity may require vaccine coverage of up to 80% of the population. Prior history of pandemic vaccine coverage was as low as 40% among children in the United States during the 2009 H1N1 influenza pandemic.

Purpose: To investigate predictors associated with global caregivers' intent to vaccinate their children against COVID-19, when the vaccine becomes available.

Method: An international cross sectional survey of 1541 caregivers arriving with their children to 16 pediatric Emergency Departments (ED) across six countries from March 26 to May 31, 2020.

Results: 65% (n = 1005) of caregivers reported that they intend to vaccinate their child against COVID-19, once a vaccine is available. A univariate and subsequent multivariate analysis found that increased intended uptake was associated with children that were older, children with no chronic illness, when fathers completed the survey, children up-to-date on their vaccination schedule, recent history of vaccination against influenza, and caregivers concerned their child had COVID-19 at the time of survey completion in the ED. The most common reason reported by caregivers intending to vaccinate was to protect their child (62%), and the most common reason reported by caregivers refusing vaccination was the vaccine's novelty (52%).

Conclusions: The majority of caregivers intend to vaccinate their children against COVID-19, though uptake will likely be associated with specific factors such as child and caregiver demographics and vaccination history. Public health strategies need to address barriers to uptake by providing evidence about an upcoming COVID-19 vaccine's safety and efficacy, highlighting the risks and consequences of infection in children, and educating caregivers on the role of vaccination.

Reference

https://www.sciencedirect.com/science/article/pii/S0264410X20313177

A prediction model to prioritize individuals for SARS-CoV-2 test built from national symptom surveys

Abstract

Background: The gold standard for COVID-19 diagnosis is detection of viral RNA through PCR. Due to global limitations in testing capacity, effective prioritization of individuals for testing is essential.

Methods: A model was devised estimating the probability of an individual to test positive for COVID-19 based on answers to 9 simple questions that have been associated with COVID-19 infection. Our model was devised from a subsample of a national symptom survey that was answered over 2 million times in Israel in its first 2 months and a targeted survey distributed to all residents of several cities in Israel. Overall, 43,752 adults were included, from which 498 self-reported as being COVID-19 positive.

Findings: Our model was validated on a held-out set of individuals from Israel where it achieved an auROC of 0.737 (CI: 0.712-0.759), auPR of 0.144 (CI: 0.119-0.177) and demonstrated its applicability outside of Israel in an independently-collected symptom survey dataset from the U.S., U.K. and Sweden. Our analyses revealed interactions between several symptoms and age, suggesting variation in the clinical manifestation of the disease in different age groups.

Conclusions: Our tool can be used online and without exposure to suspected patients, thus suggesting worldwide utility in combating COVID-19 by better directing the limited testing resources through prioritization of individuals for testing, thereby increasing the rate at which positive individuals can be identified. Moreover, individuals at high risk for a positive test result can be isolated prior to testing.

Reference

https://www.cell.com/med/fulltext/S2666-6340(20)30019-2

Development and evaluation of an artificial intelligence system for COVID-19 diagnosis

Abstract

Early detection of COVID-19 based on chest CT enables timely treatment of patients and helps control the spread of the disease. An artificial intelligence (AI) system was proposed for rapid COVID-19 detection and performed extensive statistical analysis of CTs of COVID-19 based on the AI system. System on a large dataset with more than 10 thousand CT volumes from COVID-19, influenza-A/B, non-viral community acquired pneumonia (CAP) and non-pneumonia subjects was developed and evaluated. In such a difficult multi-class diagnosis task, our deep convolutional neural network-based system is able to achieve an area under the receiver operating characteristic curve (AUC) of 97.81% for multi-way classification on test cohort of 3,199 scans, AUC of 92.99% and 93.25% on two publicly available datasets, CC-CCII and MosMedData respectively. In a reader study involving five radiologists, the AI system outperforms all of radiologists in more challenging tasks at a speed of two orders of magnitude above them. Diagnosis performance of chest X-ray (CXR) is compared to that of CT. Detailed interpretation of deep network is also performed to relate system outputs with CT presentations. The code is available at https://github.com/ChenWWWeixiang/diagnosis_covid19.

Reference

https://www.nature.com/articles/s41467-020-18685-1

A comprehensive study on classification of COVID-19 on computed tomography with pretrained convolutional neural networks

Abstract

The use of imaging data has been reported to be useful for rapid diagnosis of COVID-19. Although computed tomography (CT) scans show a variety of signs caused by the viral infection, given a large amount of images, these visual features are difficult and can take a long time to be recognized by radiologists. Artificial intelligence methods for

automated classification of COVID-19 on CT scans have been found to be very promising. However, current investigation of pretrained convolutional neural networks (CNNs) for COVID-19 diagnosis using CT data is limited. This study presents an investigation on 16 pretrained CNNs for classification of COVID-19 using a large public database of CT scans collected from COVID-19 patients and non-COVID-19 subjects. The results show that, using only 6 epochs for training, the CNNs achieved very high performance on the classification task. Among the 16 CNNs, DenseNet-201, which is the deepest net, is the best in terms of accuracy, balance between sensitivity and specificity, F1 score, and area under curve. Furthermore, the implementation of transfer learning with the direct input of whole image slices and without the use of data augmentation provided better classification rates than the use of data augmentation. Such a finding alleviates the task of data augmentation and manual extraction of regions of interest on CT images, which are adopted by current implementation of deep-learning models for COVID-19 classification.

Reference

https://www.nature.com/articles/s41598-020-74164-z

Development and evaluation of an artificial intelligence system for COVID-19 diagnosis

Abstract

Early detection of COVID-19 based on chest CT enables timely treatment of patients and helps control the spread of the disease. An artificial intelligence (AI) system was proposed for rapid COVID-19 detection and performed extensive statistical analysis of CTs of COVID-19 based on the AI system. A system was developed and evaluated on a large dataset with more than 10 thousand CT volumes from COVID-19, influenza-A/B, non-viral community acquired pneumonia (CAP) and non-pneumonia subjects. In such a difficult multi-class diagnosis task, our deep convolutional neural network-based system is able to achieve an area under the receiver operating characteristic curve (AUC) of 97.81% for multi-way classification on test cohort of 3,199 scans, AUC of 92.99% and 93.25% on two publicly available datasets, CC-CCII and MosMedData respectively. In a reader study involving five radiologists, the AI system outperforms all

of radiologists in more challenging tasks at a speed of two orders of magnitude above them. Diagnosis performance of chest x-ray (CXR) is compared to that of CT. Detailed interpretation of deep network is also performed to relate system outputs with CT presentations. The code is available at https://github.com/ChenWWWeixiang/diagnosis_covid19.

Reference

ttps://www.nature.com/articles/s41467-020-18685-1

Vascular disease and thrombosis in SARS-CoV-2-infected rhesus macaques

Abstract

The COVID-19 pandemic has led to extensive morbidity and mortality throughout the world. Clinical features that drive SARS-CoV-2 pathogenesis in humans include inflammation and thrombosis, but the mechanistic details underlying these processes remain to be determined. In this study, we demonstrate endothelial disruption and vascular thrombosis in histopathologic sections of lungs from both humans and rhesus macaques infected with SARS-CoV-2. To define key molecular pathways associated with SARS-CoV-2 pathogenesis in macaques, we performed transcriptomic analyses of bronchoalveolar lavage and peripheral blood and proteomic analyses of serum. We observed macrophage infiltrates in lung and upregulation of macrophage, complement, platelet activation, thrombosis, and proinflammatory markers, including C-reactive protein, MX1, IL-6, IL-1, IL-8, TNFα, and NF-κB. These results suggest a model in which critical interactions between inflammatory and thrombosis pathways lead to SARS-CoV-2-induced vascular disease. Our findings suggest potential therapeutic targets for COVID-19.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31311-8

A CRISPR-Cas12a-based specific enhancer for more sensitive detection of SARS-CoV-2 infection

Abstract

Background: Real-time reverse transcription-PCR (rRT-PCR) has been the most effective and widely implemented diagnostic technology since the beginning of the COVID-19 pandemic. However, fuzzy rRT-PCR readouts with high Ct values are frequently encountered, resulting in uncertainty in diagnosis.

Methods: A Specific Enhancer for PCR-amplified Nucleic Acid (SENA) was developed based on the Cas12a trans-cleavage activity, which is specifically triggered by the rRT-PCR amplicons of the SARS-CoV-2 Orf1ab (O) and N fragments. SENA was first characterized to determine its sensitivity and specificity, using a systematic titration experiment with pure SARS-CoV-2 RNA standards, and was then verified in several hospitals, employing a couple of commercial rRT-PCR kits and testing various clinical specimens under different scenarios.

Findings: The ratio (10 min/5 min) of fluorescence change (FC) with mixed SENA reaction (mix-FCratio) was defined for quantitative analysis of target O and N genes, and the Limit of Detection (LoD) of mix-FCratio with 95% confidence interval was 1.2≤1.6≤2.1. Totally, 295 clinical specimens were analyzed, among which 21 uncertain rRT-PCR cases as well as 4 false negative and 2 false positive samples were characterized by SENA and further verified by next-generation sequencing (NGS). The cut-off values for mix-FCratio were determined as 1.145 for positive and 1.068 for negative.

Interpretation: SENA increases both the sensitivity and the specificity of rRT-PCR, solving the uncertainty problem in COVID-19 diagnosis and thus providing a simple and low-cost companion diagnosis for combating the pandemic.

Reference

Huang, Weiren, Lei Yu, Donghua Wen, Dong Wei, Yangyang Sun, Huailong Zhao, Yu Ye et al. "A CRISPR-Cas12a-based specific enhancer for more sensitive detection of SARS-CoV-2 infection." *medRxiv* (2020).

A case-control and cohort study to determine the relationship between ethnic background and severe COVID-19

Abstract

Background: People of minority ethnic backgrounds may be disproportionately affected by severe COVID-19. Whether this relates to increased infection risk, more severe disease progression, or worse in-hospital survival is unknown. The contribution of comorbidities or socioeconomic deprivation to ethnic patterning of outcomes is also unclear.

Methods: We conducted a case-control and a cohort study in an inner city primary and secondary care setting to examine whether ethnic background affects the risk of hospital admission with severe COVID-19 and/or in-hospital mortality. Inner city adult residents admitted to hospital with confirmed COVID-19 (n = 872 cases) were compared with 3,488 matched controls randomly sampled from a primary healthcare database comprising 344,083 people residing in the same region. For the cohort study, we studied 1827 adults consecutively admitted with COVID-19. The primary exposure variable was self-defined ethnicity. Analyses were adjusted for socio-demographic and clinical variables.

Findings: The 872 cases comprised 48.1% Black, 33.7% White, 12.6% Mixed/Other and 5.6% Asian patients. In conditional logistic regression analyses, Black and Mixed/Other ethnicity were associated with higher admission risk than white (OR 3.12 [95% CI 2.63–3.71] and 2.97 [2.30–3.85] respectively). Adjustment for comorbidities and deprivation modestly attenuated the association (OR 2.24 [1.83–2.74] for Black, 2.70 [2.03–3.59] for Mixed/Other). Asian ethnicity was not associated with higher admission risk (adjusted OR 1.01 [0.70–1.46]). In the cohort study of 1827 patients, 455 (28.9%) died over a median (IQR) of 8 (4–16) days. Age and male sex, but not Black (adjusted HR 1.06 [0.82–1.37]) or Mixed/Other ethnicity (adjusted HR 0.72 [0.47–1.10]), were associated with in-hospital mortality. Asian ethnicity was associated with higher in-hospital mortality but with a large confidence interval (adjusted HR 1.71 [1.15–2.56]).

Interpretation: Black and Mixed ethnicity are independently associated with greater admission risk with COVID-19 and may be risk factors for development of severe

disease, but do not affect in-hospital mortality risk. Comorbidities and socioeconomic factors only partly account for this and additional ethnicity-related factors may play a large role. The impact of COVID-19 may be different in Asians.

Reference

Zakeri, Rosita, Rebecca Bendayan, Mark Ashworth, Daniel M. Bean, Hiten Dodhia, Stevo Durbaba, Kevin O'Gallagher *et al.* "A case-control and cohort study to determine the relationship between ethnic background and severe COVID-19." *EClinicalMedicine* (2020): 100574.

Publication Date: Oct 08, 2020

Two distinct immunopathological profiles in autopsy lungs of COVID-19

Abstract

Coronavirus Disease 19 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has grown to a worldwide pandemic with substantial mortality. Immune mediated damage has been proposed as a pathogenic factor, but immune responses in lungs of COVID-19 patients remain poorly characterized. Here we show transcriptomic, histologic and cellular profiles of post mortem COVID-19 (n = 34 tissues from 16 patients) and normal lung tissues (n = 9 tissues from 6 patients). Two distinct immunopathological reaction patterns of lethal COVID-19 are identified. One pattern shows high local expression of interferon stimulated genes (ISGhigh) and cytokines, high viral loads and limited pulmonary damage, the other pattern shows severely damaged lungs, low ISGs (ISGlow), low viral loads and abundant infiltrating activated CD8+ T cells and macrophages. ISGhigh patients die significantly earlier after hospitalization than ISGlow patients. Our study may point to distinct stages of progression of COVID-19 lung disease and highlights the need for peripheral blood biomarkers that inform about patient lung status and guide treatment.

Reference

https://www.nature.com/articles/s41467-020-18854-2

CORRESPONDANCE

Publication Date: Oct 09, 2020

Beyond COVID-19—a paradigm shift in infection management?

The health and economic impact of multidrug-resistant (MDR) bacteria has continuously grown over the past years, reaching an estimated peak of approximately 700 000 attributable deaths per year. Neglected hygiene, poor compliance with infection control procedures, inappropriate antimicrobial use, and insufficient availability of diagnostics and new effective antibiotics have contributed to this inglorious global record. Despite these alarming figures, infection prevention and treatment have not been considered top priorities on the agendas of most industrialised countries.

This mindset changed abruptly with the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The exponential expansion of the pandemic catapulted COVID-19 to the top of national and international priority lists, and people judge the performance of their political leaders on the basis of success in containing the pandemic. The more we realise how much SARS-CoV-2 has changed the world, the more we question the suitability of our prevention, management, and drug development strategies with respect to other major pathogens.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30789-1/fulltext

PERSPECTIVE

Publication Date: Oct 13, 2020

The rise of robots in surgical environments during COVID-19

The COVID-19 pandemic has changed our world and impacted multiple layers of our society. All frontline workers and in particular those in direct contact with patients have been exposed to major risk. To mitigate pathogen spread and protect healthcare workers and patients, medical services have been largely restricted, including cancellation of elective surgeries, which has posed a substantial burden for patients and immense economic loss for various hospitals. The integration of a robot as a shielding layer, physically separating the healthcare worker and patient, is a powerful tool to combat the omnipresent fear of pathogen contamination and maintain surgical volumes. In this Perspective, scenarios in the pre-, intra- and postoperative care were outlined, in which the use of robots and artificial intelligence can mitigate infectious contamination and aid patient management in the surgical environment during times of immense patient influx. Cost-effectiveness and benefits of surgical robotic systems were also discussed beyond their use in pandemics. The current pandemic creates unprecedented demands for hospitals. Digitization and machine intelligence are gaining significance in healthcare to combat the virus. Their legacy may well outlast the pandemic and revolutionize surgical performance and management.

Reference

https://www.nature.com/articles/s42256-020-00238-2

Publication Date: Oct 09, 2020

Inhibiting Ebola virus and SARS-CoV-2 entry

Viruses must gain entry into the host cell to replicate. In the case of EBOV, an enveloped virus, virions are internalized by macropinocytosis. Once virions reach endosomes, host cathepsin proteases cleave viral glycoproteins. The glycoproteins then fuse with the lysosomal membrane, which is followed by release of the viral genome

into the host cell cytoplasm, where viral replication can occur. Thus, cathepsin-mediated cleavage is a critical step in the entry of many enveloped viruses, including EBOV, into the host cell. Similar to EBOV, coronaviruses, including SARS-CoV-2, are enveloped viruses that undergo a series of entry steps culminating in genome release. Coronavirus entry also requires delivery of incoming viral particles to host lysosomes, where the coronavirus spike protein is cleaved by cathepsins to facilitate fusion between virus and host membranes (***3***, ***4***). However, in contrast to EBOV, SARS-CoV-2 also requires the activity of transmembrane serine protease 2 (TMPRSS2) to prime the viral spike protein (***5***). Thus, despite their differences in size and shape, EBOV and SARS-CoV-2 rely on similar proteolytic processes to gain entry into a target cell. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/370/6513/167

HIGHLIGHTS

Publication Date: Oct 10, 2020

Azvudine (FNC): A promising clinical candidate for COVID-19 treatment

A very recent work published in Advanced Science by our group reveals that 2′-deoxy-2′-β-fluoro-4′-azidocytidine (Azvudine, FNC), a clinical candidate originally developed for HIV treatment, has entered clinical trial in China for evaluating its efficacy and safety (ChiCTR2000029853), showing promise for treating novel coronavirus disease 2019 (COVID-19).1 This work suggests that nucleoside-based antivirus agents could be repurposed for COVID-19 treatment. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41392-020-00351-z

EDITORIAL

Publication Date: Oct 09, 2020

The road less traveled: SARS-CoV-2 and cell-mediated immunity

When it comes to SARS-CoV-2 (severe acute respiratory syndrome-associated coronavirus 2), the dominant narrative seems to be all about antibodies to achieve sterile immunity. If it is not one of a myriad of vaccine candidates and their purported protective antibody titers, then it is convalescent antibodies or perhaps one of the several new broadly neutralizing antibody approaches to treat CoV-2 infection. It is impressive how much money and effort is ongoing in the development of antibodies to deal with CoV-2 despite studies from several decades ago indicating that, while protection from coronavirus infection is achievable with antibodies, these antibodies cannot eradicate ongoing infection and therefore most likely have little therapeutic impact. Why then, so much effort would be spend on convalescent antibody approaches, for instance? It is not even clear that convalescent antibodies are effective and, even if a modest fraction of these antibodies were found to have some efficacy against the virus or coronavirus disease 2019 (COVID-19), how would such an approach be scaled up and distributed or even experimentally vetted without proper controlled studies and a standardized therapeutic?

What does appear important, based on previous coronavirus studies, is that antibody responses are only protective if they are expressed at the time of infection. But is it even possible to achieve stable protective antibody concentrations at the time of infection in humans through vaccination? In ongoing studies, only ∼4%–6% of Swedes sampled have antibodies to CoV-2. Surely more than 6% of the Swedish population must have been exposed to CoV-2 and may, in fact, have some level of immunity. More interesting are observations that antibodies to CoV-2 wane quickly in individuals who have recovered from COVID-19, while, to date, only a few individuals have become re-infected with CoV-2. So what drives immunity to CoV-2 if not antibodies and the humoral response? There seem to be signs in the literature that cell-mediated immunity may play a large and underappreciated role and that antibodies, and in general the T

helper cell type 2 (Th2) humoral immune response, comprise only a small part of host responses to coronaviruses. Have we missed the forest for the trees?

Early studies noted distinct differences in the Th1 response to SARS-CoV-1 infection, which, similar to CoV-2, also results in acute respiratory distress syndromes (ARDSs). Most notable are the differences observed between young and old mice exposed to virus, with the older infected mice succumbing to ARDS within the first week following infection while younger mice remain largely resistant to the infection. A fundamental observable difference between the two outcomes is that the young mice mounted a Th1 response, which included interferon gamma (IFN-γ) and interleukins IL-10 and IL-13. These observations have been recapitulated in studies with strain-dependent variation in another coronavirus, murine hepatitis virus 3 (MHV3), which found that Th1 and macrophage responses were crucial in resistance of naive mice to virus challenge. These collective observations suggest that INF-γ expression is a key correlate with regards to responding to and controlling coronavirus infections. Notably, INF-γ has been found to downregulate expression of ACE2 (the receptor for SARS-CoV-2), and this downregulation in macrophages is correlated with the latter becoming refractory to infection with the closely related coronavirus MHV3. Collectively, these noteworthy studies suggest that perhaps we may have largely focused on the wrong arm of the immune response. These insights bode well for those vaccines, such as mRNA or DNA vaccines, that express viral proteins from within the context of a cell to induce a cell-mediated response. Knowledge of Th1 responses, the role of INF-γ in ARDS, and to what extent macrophages may harbor CoV-2 infection and affect the local Th1 response should probably be paramount as we develop a vaccine. These aspects should be considered to eventually overcome many of the issues associated with SARS-CoV-2 infection and COVID-19 disease so as not to repeat the experiments of the past.

Reference

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(20)30537-2

REPORT

Publication Date: Oct 13, 2020

Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low Prevalence Communities and Reveal Durable Humoral Immunity

Abstract

A serological study was conducted to define correlates of immunity against SARS-CoV-2. Relative to mild COVID-19 cases, individuals with severe disease exhibited elevated virus-neutralizing titers and antibodies against nucleocapsid (N) and the receptor binding domain (RBD) of spike protein. Age and sex played lesser roles. All cases, including asymptomatic individuals, seroconverted by 2 weeks post-PCR confirmation. Spike RBD and S2 and neutralizing antibodies remained detectable through 5-7 months post-onset, whereas α-N titers diminished. Testing of 5882 members of the local community revealed only 1 sample with seroreactivity to both RBD and S2 that lacked neutralizing antibodies. This fidelity could not be achieved with either RBD or S2 alone. Thus, inclusion of multiple independent assays improved the accuracy of antibody tests in low seroprevalence communities and revealed differences in antibody kinetics depending on the antigen. It was concluded that neutralizing antibodies are stably produced for at least 5-7 months after SARS-CoV-2 infection.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(20)30445-3

Publication Date: Oct 09, 2020

REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters

Abstract

An urgent global quest for effective therapies to prevent and treat COVID-19 disease is ongoing. REGN-COV2 was previously described, which is a cocktail of two potent neutralizing antibodies (REGN10987+REGN10933) targeting non-overlapping epitopes on the SARS-CoV-2 spike protein. In this report, *in vivo* efficacy of this antibody cocktail

in both rhesus macaques was evaluated, which may model mild disease, and golden hamsters, which may model more severe disease. It is demonstrated that REGN-COV-2 can greatly reduce virus load in lower and upper airways and decrease virus induced pathological sequelae when administered prophylactically or therapeutically in rhesus macaques. Similarly, administration in hamsters limits weight loss and decreases lung titers and evidence of pneumonia in the lungs. The results provide evidence of the therapeutic potential of this antibody cocktail.

Reference

https://science.sciencemag.org/content/early/2020/10/14/science.abe2402

VIEW POINT

Publication Date: Oct 09, 2020

An urgent global quest for effective Imperfect storm: is interleukin-33 the Achilles heel of COVID-19?

Abstract

The unique cytokine signature of COVID-19 might provide clues to disease mechanisms and possible future therapies. Here, we propose a pathogenic model in which the alarmin cytokine, interleukin (IL)-33, is a key player in driving all stages of COVID-19 disease (ie, asymptomatic, mild–moderate, severe–critical, and chronic–fibrotic). In susceptible individuals, IL-33 release by damaged lower respiratory cells might induce dysregulated GATA-binding factor 3-expressing regulatory T cells, thereby breaking immune tolerance and eliciting severe acute respiratory syndrome coronavirus 2-induced autoinflammatory lung disease. Such disease might be initially sustained by IL-33-differentiated type-2 innate lymphoid cells and locally expanded γδ T cells. In severe COVID-19 cases, the IL-33–ST2 axis might act to expand the number of pathogenic granulocyte–macrophage colony-stimulating factor-expressing T cells, dampen antiviral interferon responses, elicit hyperinflammation, and favour thromboses. In patients who survive severe COVID-19, IL-33 might drive pulmonary fibrosis by inducing myofibroblasts and epithelial–mesenchymal transition. We discuss the therapeutic implications of these hypothetical pathways, including use of therapies that target IL-33 (eg, anti-ST2), T helper 17-like γδ T cells, immune cell homing, and cytokine balance.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30340-4/fulltext

IN BRIEF

Publication Date: Oct 13, 2020

Intestinal attenuation of COVID-19 inflammation

Abstract

Gastrointestinal (GI) symptoms are observed in patients with COVID-19, but the link between GI immune responses and disease outcomes is unclear. This preprint shows that COVID-19 severity and mortality, and levels of circulating inflammatory cytokines, are reduced in patients with GI symptoms. The SARS-CoV-2 receptor ACE2 was highly expressed in small intestinal enterocytes and viral particles were detected in these cells in patients with COVID-19. GI inflammation was absent in patients with COVID-19, as shown by a reduction of cellular inflammatory subsets and downregulation of inflammatory pathways. This study provides a basis for exploring the mechanisms involved in attenuation of SARS-CoV-2-associated GI inflammation to aid a comprehensive understanding of organ-specific immune responses in COVID-19.

Reference

https://www.nature.com/articles/s41577-020-00466-y

IL-18-dependent MAIT cell activation in COVID-19

Abstract

Flament *et al*. report a marked reduction of circulating mucosal-associated invariant T (MAIT) cells in patients with severe COVID-19, compared with controls sharing co-morbidities. These MAIT cells had very high levels of activation that correlated with disease severity. Among T cells, alterations in MAIT cells preferentially associated with mortality, and high CD69 expression correlated with poor outcome. Severe inflammation, particularly high levels of IL-18, was associated with increased cytotoxicity of circulating MAIT cells. Co-culture studies of in vitro SARS-CoV-2-infected macrophages with MAIT cells suggest a two-step process of MAIT cell activation, through type I IFN and later IL-18. Together with other reports, this preprint supports a

pivotal role for MAIT cells, through an IL-18-dependent mechanism, in the pathology of COVID-19.

Reference

https://www.nature.com/articles/s41577-020-00467-x