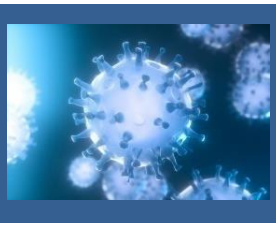
COVID-19

Jul 29 – Aug 04, 2021



RESEARCH PUBLICATIONS

Publication Date: Aug 04, 2021

Discovery of potential small molecular SARS-CoV-2 entry blockers targeting the spike protein

Abstract

An epidemic of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading worldwide. SARS-CoV-2 relies on its spike protein to invade host cells by interacting with the human receptor protein Angiotensin-Converting Enzymes 2 (ACE2). Therefore, designing an antibody or small-molecular entry blockers is of great significance for virus prevention and treatment. This study identified five potential small molecular anti-virus blockers via targeting SARS-CoV-2 spike protein by combining *in silico* technologies with in vitro experimental methods. The five molecules were natural products that binding to the RBD domain of SARS-CoV-2 was qualitatively and quantitively validated by both native Mass Spectrometry (MS) and Surface Plasmon Resonance (SPR). Anti-viral activity assays showed that the optimal molecule, H69C2, had a strong binding affinity (dissociation constant K_D) of 0.0947 μM and anti-virus IC_{50} of 85.75 μM.

Reference

https://www.nature.com/articles/s41401-021-00735-z

Gamma-irradiated SARS-CoV-2 vaccine candidate, OZG-38.61.3, confers protection from SARS-CoV-2 challenge in human ACEII-transgenic mice

Abstract

The SARS-CoV-2 virus caused the most severe pandemic around the world, and vaccine development for urgent use became a crucial issue. Inactivated virus

formulated vaccines such as Hepatitis A and smallpox proved to be reliable approaches for immunization for prolonged periods. In this study, a gamma-irradiated inactivated virus vaccine does not require an extra purification process, unlike the chemically inactivated vaccines. Hence, the novelty of the vaccine candidate (OZG-38.61.3) is that it is a non-adjuvant added, gamma-irradiated, and intradermally applied inactive viral vaccine. Efficiency and safety dose (either 1013 or 1014 viral RNA copy per dose) of OZG-38.61.3 was initially determined in BALB/c mice. This was followed by testing the immunogenicity and protective efficacy of the vaccine. Human ACE2-encoding transgenic mice were immunized and then infected with the SARS-CoV-2 virus for the challenge test. This study shows that vaccinated mice have lowered SARS-CoV-2 viral RNA copy numbers both in oropharyngeal specimens and in the histological analysis of the lung tissues along with humoral and cellular immune responses, including the neutralizing antibodies similar to those shown in BALB/c mice without substantial toxicity. Subsequently, plans are being made for the commencement of Phase 1 clinical trial of the OZG-38.61.3 vaccine for the COVID-19 pandemic.

Reference

https://www.nature.com/articles/s41598-021-95086-4

Stress-related emotional and behavioural impact following the first COVID-19 outbreak peak

Abstract

The COVID-19 pandemic poses multiple psychologically stressful challenges and is associated with an increased risk for mental illness. Previous studies have focused on the psychopathological symptoms associated with the outbreak peak. Here, the behavioural and mental-health impact of the pandemic in Israel was examined using an online survey, during the six weeks encompassing the end of the first outbreak and the beginning of the second. Clinically validated instruments were used to assess anxiety- and depression-related emotional distress, symptoms, and coping strategies, as well as questions designed to specifically assess COVID-19-related concerns. Higher emotional burden was associated with being female, younger, unemployed, living in high socioeconomic status localities, having prior medical conditions, encountering more people, and experiencing physiological symptoms. The findings highlight the

environmental context and its importance in understanding individual ability to cope with the long-term stressful challenges of the pandemic.

Reference

https://www.nature.com/articles/s41380-021-01219-6

Dysregulated hematopoiesis in bone marrow marks severe COVID-19

Abstract

Severe coronavirus disease 2019 (COVID-19) is often indicated by lymphopenia and increased myelopoiesis; however, the underlying mechanism is still unclear, especially the alteration of hematopoiesis. It is important to explore to what extent and how hematopoietic stem cells contribute to the impairment of peripheral lymphoid and myeloid compartments in COVID-19 patients. In this study, we used single-cell RNA sequencing to assess bone marrow mononuclear cells from COVID-19 patients with peripheral blood mononuclear cells as control. The results showed that the hematopoietic stem cells in these patients were mainly in the G1 phase and prone to apoptosis, with immune activation and anti-viral responses. Importantly, a significant accumulation of immature myeloid progenitors and a dramatic reduction of lymphoid progenitors in severe cases were identified, along with the up-regulation of transcription factors (such as SPI1, LMO4, ETS2, FLI1, and GATA2) that are important for the hematopoietic stem cell or multipotent progenitor to differentiate into downstream progenitors. Our results indicate a dysregulated hematopoiesis in patients with severe COVID-19.

Reference

https://www.nature.com/articles/s41421-021-00296-9

Global public health security and justice for vaccines and therapeutics in the COVID-19 pandemic

Abstract

A Lancet Commission for COVID-19 task force is shaping recommendations to achieve vaccine and therapeutics access, justice, and equity. This includes ensuring safety and effectiveness harmonized through robust systems of global pharmacovigilance and surveillance. Global production requires expanding support for development, manufacture, testing, and distribution of vaccines and therapeutics to low- and middle-income countries (LMICs). Global intellectual property rules must not stand in the way of research, production, technology transfer, or equitable access to essential health tools, and in context of pandemics to achieve increased manufacturing without discouraging innovation. Global governance around product quality requires channelling widely distributed vaccines through WHO prequalification (PQ)/emergency use listing (EUL) mechanisms and greater use of national regulatory authorities. A World Health Assembly (WHA) resolution would facilitate improvements and consistency in quality control and assurances. Global health systems require implementing steps to strengthen national systems for controlling COVID-19 and for influenza vaccinations for adults including pregnant and lactating women. A collaborative research network should strive to establish open access databases for bioinformatic analyses, together with programs directed at human capacity utilization and strengthening. Combating anti-science recognizes the urgency for countermeasures to address a global-wide disinformation movement dominating the internet and infiltrating parliaments and local governments.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00333-3/fulltext

Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2

Abstract

Background: In children, SARS-CoV-2 infection is usually asymptomatic or causes a mild illness of short duration. Persistent illness has been reported; however, its prevalence and characteristics are unclear. We aimed to determine illness duration and characteristics in symptomatic UK school-aged children tested for SARS-CoV-2 using data from the COVID Symptom Study, one of the largest UK citizen participatory epidemiological studies to date.

Methods: In this prospective cohort study, data from UK school-aged children (age 5–17 years) were reported by an adult proxy. Participants were voluntary, and used a mobile application (app) launched jointly by Zoe Limited and King's College London. Illness duration and symptom prevalence, duration, and burden were analysed for children testing positive for SARS-CoV-2 for whom illness duration could be determined, and were assessed overall and for younger (age 5–11 years) and older (age 12–17 years) groups. Children with longer than 1 week between symptomatic reports on the app were excluded from analysis. Data from symptomatic children testing negative for SARS-CoV-2, matched 1:1 for age, gender, and week of testing, were also assessed.

Findings: 258 790 Children aged 5–17 years were reported by an adult proxy between March 24, 2020, and Feb 22, 2021, of whom 75 529 had valid test results for SARS-CoV-2. 1734 children (588 younger and 1146 older children) had a positive SARS-CoV-2 test result and calculable illness duration within the study timeframe (illness onset between Sept 1, 2021, and Jan 24, 2021). The most common symptoms were headache (1079 [62·2%] of 1734 children), and fatigue (954 [55·0%] of 1734 children). Median illness duration was 6 days (IQR 3–11) versus 3 days (2–7) in children testing negative, and was positively associated with age (Spearman's rank-order rs 0·19, p<0·0001). Median illness duration was longer for older children (7 days, IQR 3–12) than younger children (5 days, 2–9). 77 (4·4%) of 1734 children had illness duration of at least 28 days, more commonly in older than younger children (59 [5·1%] of 1146 older children vs 18 [3·1%] of 588 younger children; p=0·046). The commonest symptoms experienced by these children during the first 4 weeks of illness were fatigue

(65 [84·4%] of 77), headache (60 [77·9%] of 77), and anosmia (60 [77·9%] of 77); however, after day 28 the symptom burden was low (median 2 symptoms, IQR 1–4) compared with the first week of illness (median 6 symptoms, 4–8). Only 25 (1·8%) of 1379 children experienced symptoms for at least 56 days. Few children (15 children, 0·9%) in the negatively tested cohort had symptoms for at least 28 days; however, these children experienced greater symptom burden throughout their illness (9 symptoms, IQR 7·7–11·0 vs 8, 6–9) and after day 28 (5 symptoms, IQR 1·5–6·5 vs 2, 1–4) than did children who tested positive for SARS-CoV-2.

Interpretation: Although COVID-19 in children is usually of short duration with low symptom burden, some children with COVID-19 experience prolonged illness duration. Reassuringly, symptom burden in these children did not increase with time, and most recovered by day 56. Some children who tested negative for SARS-CoV-2 also had persistent and burdensome illness. A holistic approach for all children with persistent illness during the pandemic is appropriate.

Funding: Zoe Limited, UK Government Department of Health and Social Care, Wellcome Trust, UK Engineering and Physical Sciences Research Council, UK Research and Innovation London Medical Imaging and Artificial Intelligence Centre for Value Based Healthcare, UK National Institute for Health Research, UK Medical Research Council, British Heart Foundation, and Alzheimer's Society.

Reference

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00198-X/fulltext

Thromboembolism after COVID-19 vaccine in patients with preexisting thrombocytopenia

Abstract

While vaccination is the single most effective intervention to drastically reduce severe disease and death following SARS-CoV-2 infection, as shown in UK and Israel, some serious concerns have been raised for an unusual adverse drug reaction (ADR), including vaccine-induced immune thrombotic thrombocytopenia (VITT) with concurrent low platelets as well as capillary leak syndrome. In fact, the overall safety of the vaccine is highlighted by the low frequency of ADR considering that in UK, by the early June, 40

million first doses and 29 million second doses have been injected; nonetheless, 390 thrombotic events, including 71 fatal events have been reported. Interestingly, the cases reported low platelet counts with the presence of anti-platelet factor-4 (PF4) antibodies, indicating an abnormal clotting reaction. Here, out of three referred cases, we report a post-vaccine clinical case of fatal thrombosis with postmortem examination and whole exome sequencing (WES) analysis, whose pathogenesis appeared associated to a preexisting condition of thrombocytopenia due to myelodysplasia.

Reference

https://www.nature.com/articles/s41419-021-04058-z

Induction of interferon response by high viral loads at early stage infection may protect against severe outcomes in COVID-19 patients

Abstract

Key elements for viral pathogenesis include viral strains, viral load, co-infection, and host responses. Several studies analyzing these factors in the function of disease severity of have been published; however, no studies have shown how all of these factors interplay within a defined cohort. To address this important question, we sought to understand how these four key components interplay in a cohort of COVID-19 patients. The viral loads and gene expression were determined using high throughput sequencing and various virological methods. It was found that viral loads in the upper respiratory tract in COVID-19 patients at an early phase of infection vary widely. While the majority of nasopharyngeal (NP) samples have a viral load lower than the limit of detection of infectious viruses, there are samples with an extraordinary amount of SARS-CoV-2 RNA and a high viral titer. No specific viral factors were identified that are associated with high viral loads. Host gene expression analysis showed that viral loads were strongly correlated with cellular antiviral responses. Interestingly, however, COVID-19 patients who experience mild symptoms have a higher viral load than those with severe complications, indicating that naso-pharyngeal viral load may not be a key factor of the clinical outcomes of COVID-19. The metagenomics analysis revealed that the microflora in the upper respiratory tract of COVID-19 patients with high viral loads were dominated by SARS-CoV-2, with a high degree of dysbiosis. Finally, we found a strong inverse correlation between upregulation of interferon responses and disease

severity. Overall study suggests that a high viral load in the upper respiratory tract may not be a critical factor for severe symptoms; rather, dampened antiviral responses may be a critical factor for a severe outcome from the infection.

Reference

https://www.nature.com/articles/s41598-021-95197-y

A worldwide assessment of changes in adherence to COVID-19 protective behaviours and hypothesized pandemic fatigue

Abstract

As the COVID-19 pandemic lingers, the possibility of ‘pandemic fatigue’ has raised worldwide concerns. Here, it was examined whether there was a gradual reduction in adherence to protective behaviours against COVID-19 from March through December 2020, as hypothesized in expectations of fatigue. Self-report behaviours were considered from representative samples of the populations of 14 countries ($N = 238{,}797$), as well as mobility and policy data for 124 countries. The results show that changes in adherence were empirically meaningful and geographically widespread. While a low-cost and habituating behaviour (mask wearing) exhibited a linear rise in adherence, high-cost and sensitizing behaviours (physical distancing) declined, but this decline decelerated over time, with small rebounds seen in later months. Reductions in adherence to physical distancing showed little difference across societal groups, but were less intense in countries with high interpersonal trust. Alternative underlying mechanisms and policy implications are discussed.

Reference

https://www.nature.com/articles/s41562-021-01181-x

The interplay between partisanship, forecasted COVID-19 deaths, and support for preventive policies

Abstract

The COVID-19 pandemic is a global crisis that has forced governments around the world to implement large-scale interventions such as school closures and national

lockdowns. Previous research has shown that partisanship plays a major role in explaining public attitudes towards these policies and beliefs about the intensity of the crisis. However, it remains unclear whether and how partisan differences in policy support relate to partisan gaps in beliefs about the number of deaths that the pandemic will cause. Do individuals who forecast fewer COVID-19 deaths show less agreement with preventive measures? How does partisanship correlate with people's beliefs about the intensity of the crisis and their support for COVID-19 policies? Here, it was sought to answer these questions by performing a behavioral experiment in Argentina (Experiment 1, $N = 640$) and three quasi-replication studies in Uruguay (Experiment 2, $N = 372$), Brazil (Experiment 3, $N = 353$) and the United States (Experiment 4, $N = 630$). In all settings, participants forecasted the number of COVID-19 deaths in their country after considering either a high or low number, and then rated their agreement with a series of interventions. This anchoring procedure, which experimentally induced a large variability in the forecasted number of deaths, did not modify policy preferences. Instead, each experiment provided evidence that partisanship was a key indicator of the optimism of forecasts and the degree of support for COVID-19 policies. Remarkably, it was found that the number of forecasted deaths was robustly uncorrelated with participants' agreement with preventive measures designed to prevent those deaths. These empirical observations were discussed in the light of recently proposed theories of tribal partisan behavior. Moreover, it was argued that these results may inform policy making as they suggest that even the most effective communication strategy focused on alerting the public about the severity of the pandemic would probably not translate into greater support for COVID-19 preventive measures.

Reference

https://www.nature.com/articles/s41599-021-00870-2

Immunogenicity and protective efficacy of an intranasal live-attenuated vaccine against SARS-CoV-2

Abstract

Global deployment of an effective and safe vaccine is necessary to curtail the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2). Here, a Newcastle disease virus (NDV)-based vectored-vaccine was evaluated in mice and hamsters for its immunogenicity, safety and protective efficacy against SARS-CoV-2. Intranasal administration of recombinant (r)NDV-S vaccine expressing spike (S) protein of SARS-CoV-2 to mice induced high levels of SARS-CoV-2-specific neutralizing immunoglobulin A (IgA) and IgG2a antibodies and T cell-mediated immunity. Hamsters immunised with two doses of vaccine showed complete protection from lung infection, inflammation, and pathological lesions following SARS-CoV-2 challenge. Importantly, administration of two doses of intranasal rNDV-S vaccine significantly reduced the SARS-CoV-2 shedding in nasal turbinate and lungs in hamsters. Collectively, intranasal vaccination has the potential to control infection at the site of inoculation, which should prevent both clinical disease and virus transmission to halt the spread of the COVID-19 pandemic.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00909-3

Broad betacoronavirus neutralization by a stem helix–specific human antibody

Abstract

The spillovers of β-coronaviruses in humans and the emergence of SARS-CoV-2 variants highlight the need for broad coronavirus countermeasures. Five monoclonal antibodies (mAbs) were described cross-reacting with the stem helix of multiple β-coronavirus spike glycoproteins isolated from COVID-19 convalescent individuals. Using structural and functional studies we show that the mAb with the greatest breadth (S2P6) neutralizes pseudotyped viruses from three different subgenera through inhibition of membrane fusion and delineate the molecular basis for its cross-reactivity. S2P6 reduces viral burden in hamsters challenged with SARS-CoV-2 through viral neutralization and Fc-mediated effector functions. Stem helix antibodies are rare, oftentimes of narrow specificity and can acquire neutralization breadth through somatic mutations. These data provide a framework for structure-guided design of pan-β-coronavirus vaccines eliciting broad protection.

Reference

https://science.sciencemag.org/content/early/2021/08/03/science.abj33214

Chemically modified guide RNAs enhance CRISPR-Cas13 knockdown in human cells

Abstract

RNA-targeting CRISPR-Cas13 proteins have recently emerged as a powerful platform to modulate gene expression outcomes. However, protein and CRISPR RNA (crRNA) delivery in human cells can be challenging with rapid crRNA degradation yielding transient knockdown. Here several chemical RNA modifications were compared at different positions to identify synthetic crRNAs that improve RNA targeting efficiency and half-life in human cells. It was shown that co-delivery of modified crRNAs and recombinant Cas13 enzyme in ribonucleoprotein (RNP) complexes can alter gene expression in primary CD4+ and CD8+ T cells. This system represents a robust and efficient method to modulate transcripts without genetic manipulation.

Reference

https://www.cell.com/cell-chemical-biology/fulltext/S2451-9456(21)00351-2

Computational design of SARS-CoV-2 peptide binders with better predicted binding affinities than human ACE2 receptor

Abstract

SARS-CoV-2 is coronavirus causing COVID-19 pandemic. To enter human cells, receptor binding domain of S1 subunit of SARS-CoV-2 (SARS-CoV-2-RBD) binds to peptidase domain (PD) of angiotensin-converting enzyme 2 (ACE2) receptor. Employing peptides to inhibit binding between SARS-CoV-2-RBD and ACE2-PD is a therapeutic solution for COVID-19. Previous experimental study found that 23-mer peptide (SBP1) bound to SARS-CoV-2-RBD with lower affinity than ACE2. To increase SBP1 affinity, the previous study used residues 21–45 of α1 helix of ACE2-PD (SPB25) to design peptides with predicted affinity better than SBP1 and SPB25 by increasing interactions of residues that do not form favorable interactions with SARS-CoV-2-RBD. To design SPB25 with better affinity than ACE2, we employed computational protein design to increase interactions of residues reported to form favorable interactions with SARS-CoV-2-RBD and combine newly designed mutations with the best single

mutations from our previous study. Molecular dynamics show that predicted binding affinities of three peptides (SPB25Q22R, SPB25F8R/K11W/L25R and SPB25F8R/K11F/Q22R/L25R) are better than ACE2. Moreover, their predicted stabilities may be slightly higher than SBP1 as suggested by their helicities. This study developed an approach to design SARS-CoV-2 peptide binders with predicted binding affinities better than ACE2. These designed peptides are promising candidates as SARS-CoV-2 inhibitors.

Reference

https://www.nature.com/articles/s41598-021-94873-3

Malignant cerebral infarction after ChAdOx1 nCov-19 vaccination: A catastrophic variant of vaccine-induced immune thrombotic thrombocytopenia

Abstract

Vaccine-induced thrombotic thrombocytopenia with cerebral venous thrombosis is a syndrome recently described in young adults within two weeks from the first dose of the ChAdOx1 nCoV-19 vaccine. Here two cases of malignant middle cerebral artery (MCA) infarct and thrombocytopenia were reported, 9-10 days following ChAdOx1 nCoV-19 vaccination. The two cases arrived in the facility around the same time but from different geographical areas, potentially excluding epidemiological links; meanwhile, no abnormality was found in the respective vaccine batches. Patient 1 was a 57-year-old woman who underwent decompressive craniectomy despite two prior, successful mechanical thrombectomies. Patient 2 was a 55-year-old woman who developed a fatal bilateral malignant MCA infarct. Both patients manifested pulmonary and portal vein thrombosis and high level of antibodies to platelet factor 4-polyanion complexes. None of the patients had ever received heparin in the past before stroke onset. The observations of rare arterial thrombosis may contribute to assessment of possible adverse effects associated with COVID-19 vaccination.

Reference

https://www.nature.com/articles/s41467-021-25010-x

The incremental value of computed tomography of COVID-19 pneumonia in predicting ICU admission

Abstract

Triage is crucial for patient's management and estimation of the required intensive care unit (ICU) beds is fundamental for health systems during the COVID-19 pandemic. It was assessed whether chest computed tomography (CT) of COVID-19 pneumonia has an incremental role in predicting patient's admission to ICU. Volumetric and texture analysis of the areas of the affected lung were performed in CT of 115 outpatients with COVID-19 infection presenting to the emergency room with dyspnea and unresponsive hypoxyemia. Admission blood laboratory including lymphocyte count, serum lactate dehydrogenase, D-dimer and C-reactive protein and the ratio between the arterial partial pressure of oxygen and inspired oxygen were collected. By calculating the areas under the receiver-operating characteristic curves (AUC), the performance of blood laboratory-arterial gas analyses features alone was compared and combined with the CT features in two hybrid models (Hybrid radiological and Hybrid radiomics)for predicting ICU admission. Following a machine learning approach, 63 patients were allocated to the training and 52 to the validation set. Twenty-nine (25%) of patients were admitted to ICU. The Hybrid radiological model comprising the lung %consolidation performed significantly ($p = 0.04$) better in predicting ICU admission in the validation (AUC = 0.82; 95% confidence interval 0.73–0.97) set than the blood laboratory-arterial gas analyses features alone (AUC = 0.71; 95% confidence interval 0.56–0.86). A risk calculator for ICU admission was derived and is available at: https://github.com/cgplab/covidapp. The volume of the consolidated lung in CT of patients with COVID-19 pneumonia has a mild but significant incremental value in predicting ICU admission.

Reference

https://www.nature.com/articles/s41598-021-95114-3

SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation

Abstract

Excessive inflammatory responses induced upon SARS-CoV-2 infection are associated with severe symptoms of COVID-19. Inflammasomes activated in response to SARS-CoV-2 infection are also associated with COVID-19 severity. Here, a distinct mechanism was shown by which SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. N protein facilitates maturation of proinflammatory cytokines and induces proinflammatory responses in cultured cells and mice. Mechanistically, N protein interacts directly with NLRP3 protein, promotes the binding of NLRP3 with ASC, and facilitates NLRP3 inflammasome assembly. More importantly, N protein aggravates lung injury, accelerates death in sepsis and acute inflammation mouse models, and promotes IL-1β and IL-6 activation in mice. Notably, N-induced lung injury and cytokine production are blocked by MCC950 (a specific inhibitor of NLRP3) and Ac-YVAD-cmk (an inhibitor of caspase-1). Therefore, this study reveals a distinct mechanism by which SARS-CoV-2 N protein promotes NLRP3 inflammasome activation and induces excessive inflammatory responses.

Reference

https://www.nature.com/articles/s41467-021-25015-6

Studying SARS-CoV-2 infectivity and therapeutic responses with complex organoids

Abstract

Clinical management of patients with severe complications of COVID-19 has been hindered by a lack of effective drugs and a failure to capture the extensive heterogeneity of the disease with conventional methods. Here the emerging roles of complex organoids were reviewed in the study of SARS-CoV-2 infection, modelling of COVID-19 disease pathology and in drug, antibody and vaccine development. Opportunities for COVID-19 research and remaining challenges were discussed in the application of organoids.

Reference

https://www.nature.com/articles/s41556-021-00721-x

Publication Date: Aug 01, 2021

Longitudinal analysis of SARS-CoV-2 seroprevalence using multiple serology platforms

Abstract

Current SARS-CoV-2 serological tests are based on the full-length spike (S), the receptor binding domain (RBD), or the nucleoprotein (NP) as substrates. Here, samples from health care workers (HCWs) were used to perform a longitudinal analysis of the antibody responses using a research-grade RBD and spike based enzyme-linked immunosorbent assay (ELISA), a commercial RBD and spike based ELISA, and a commercial NP based chemiluminescent microparticle immunoassay. Seroprevalence ranged around 28% early during the pandemic and a good correlation was observed between RBD and spike based ELISAs. Modest correlations were observed between NP and both RBD and spike based assays. The antibody levels in HCWs declined over time, however the overall seroprevalence measured by RBD and spike based assays remained unchanged, while the seroprevalence of NP reactive antibodies significantly declined. Moreover, RBD and spike based assays effectively detected seroconversion in vaccinees. Overall, the results consolidate the strength of different serological assays to assess the magnitude and duration of antibodies to SARS-CoV-2.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00905-6

"Bucket brigade" using lysine residues in RNA-dependent RNA polymerase of SARS-CoV-2

Abstract

The RNA-dependent RNA polymerase (RdRp) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a promising drug target for coronavirus disease 2019 (COVID-19) because it plays the most important role in the replication of the RNA genome. Nucleotide analogs such as remdesivir and favipiravir are thought to interfere

with the RNA replication by RdRp. More specifically, they are expected to compete with nucleoside triphosphates, such as adenosine triphosphate (ATP). However, the process in which these drug candidates and nucleoside triphosphates are taken up by RdRp remains unknown. In this study, all-atom molecular dynamics were performed simulations to clarify the recognition mechanism of RdRp for these drug candidates and ATP that were at a distance. The ligand recognition ability of RdRp decreased in the order of remdesivir, favipiravir, and ATP. It was also identified six recognition paths. Three of them were commonly found in all ligands, and the remaining three paths were ligand-dependent ones. In the common two paths, it was observed that the multiple lysine residues of RdRp carried the ligands to the binding site like a “bucket brigade”. In the remaining common path, the ligands directly reached the binding site. The findings contribute to the understanding of the efficient ligand recognition by RdRp at the atomic level.

Reference

https://www.cell.com/biophysj/fulltext/S0006-3495(21)00634-2

Publication Date: Jul 31, 2021

Effect of co-infection with intestinal parasites on COVID-19 severity: A prospective observational cohort study

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection results in a spectrum of clinical presentations. Evidence from Africa indicates that significantly less COVID-19 patients suffer from serious symptoms than in the industrialized world. We and others previously postulated a partial explanation for this phenomenon, being a different, more activated immune system due to parasite infections. Here, we aimed to test this hypothesis by investigating a potential correlation of co-infection with parasites with COVID-19 severity in an endemic area in Africa.

Methods: Ethiopian COVID-19 patients were enrolled and screened for intestinal parasites, between July 2020 and March 2021. The primary outcome was the proportion of patients with severe COVID-19. Ordinal logistic regression models were used to estimate the association between parasite infection, and COVID-19 severity. Models

were adjusted for sex, age, residence, education level, occupation, body mass index, and comorbidities.

Findings: 751 SARS-CoV-2 infected patients were enrolled, of whom 284 (37.8%) had intestinal parasitic infection. Only 27/255 (10.6%) severe COVID-19 patients were co-infected with intestinal parasites, while 257/496 (51.8%) non-severe COVID-19 patients were parasite positive (p<0.0001). Patients co-infected with parasites had lower odds of developing severe COVID-19, with an adjusted odds ratio (aOR) of 0.23 (95% CI 0.17–0.30; p<0.0001) for all parasites, aOR 0.37 ([95% CI 0.26–0.51]; p<0.0001) for protozoa, and aOR 0.26 ([95% CI 0.19–0.35]; p<0.0001) for helminths. When stratified by species, co-infection with Entamoeba spp., Hymenolepis nana, Schistosoma mansoni, and Trichuris trichiura implied lower probability of developing severe COVID-19. There were 11 deaths (1.5%), and all were among patients without parasites (p = 0.009).

Interpretation: Parasite co-infection is associated with a reduced risk of severe COVID-19 in African patients. Parasite-driven immunomodulatory responses may mute hyper-inflammation associated with severe COVID-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00334-5/fulltext

The effect of COVID-19 isolation measures on the cognition and mental health of people living with dementia: A rapid systematic review of one year of quantitative evidence

Abstract

Background: COVID-19 prevention and control policies have entailed lockdowns and confinement. This study aimed to summarize the global research evidence describing the effect of COVID-19 isolation measures on the health of people living with dementia.

Methods: Pubmed, PsycINFO and CINAHL were searched up to 27th of February 2021 for peer-reviewed quantitative studies about the effects of isolation during COVID-19 on the cognitive, psychological and functional symptoms of people with dementia or mild cognitive impairment. The Joanna Briggs Institute critical appraisal tool was used to conduct the quality assessment. PROSPERO registration: CRD42021229259.

Findings: 15 Eligible papers were identified, examining a total of 6442 people with dementia. 13/15 studies investigated people living in the community and 2 in care homes. Out of 15 studies, 9 (60%) reported changes in cognition and 14 (93%) worsening or new onset of behavioral and psychological symptoms. Six studies (46%) reported a functional decline in daily activities in a variable proportion of the population analyzed.

Interpretation: COVID-19 isolation measures have damaged the cognitive and mental health of people with dementia across the world. It is urgent to issue guidance that balances infection control measures against the principles of non-maleficence to guarantee fair and appropriate care during pandemic times for this population.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00327-8/fulltext

Publication Date: Jul 30, 2021

Post-viral effects of COVID-19 in the olfactory system and their implications

Abstract

Background: The mechanisms by which any upper respiratory virus, including SARS-CoV-2, impairs chemosensory function are not known. COVID-19 is frequently associated with olfactory dysfunction after viral infection, which provides a research opportunity to evaluate the natural course of this neurological finding. Clinical trials and prospective and histological studies of new-onset post-viral olfactory dysfunction have been limited by small sample sizes and a paucity of advanced neuroimaging data and neuropathological samples. Although data from neuropathological specimens are now available, neuroimaging of the olfactory system during the acute phase of infection is still rare due to infection control concerns and critical illness and represents a substantial gap in knowledge.

Recent developments: The active replication of SARS-CoV-2 within the brain parenchyma (ie, in neurons and glia) has not been proven. Nevertheless, post-viral olfactory dysfunction can be viewed as a focal neurological deficit in patients with COVID-19. Evidence is also sparse for a direct causal relation between SARS-CoV-2 infection and abnormal brain findings at autopsy, and for trans-synaptic spread of the

virus from the olfactory epithelium to the olfactory bulb. Taken together, clinical, radiological, histological, ultrastructural, and molecular data implicate inflammation, with or without infection, in either the olfactory epithelium, the olfactory bulb, or both. This inflammation leads to persistent olfactory deficits in a subset of people who have recovered from COVID-19. Neuroimaging has revealed localised inflammation in intracranial olfactory structures. To date, histopathological, ultrastructural, and molecular evidence does not suggest that SARS-CoV-2 is an obligate neuropathogen.

Where next? The prevalence of CNS and olfactory bulb pathosis in patients with COVID-19 is not known. We postulate that, in people who have recovered from COVID-19, a chronic, recrudescent, or permanent olfactory deficit could be prognostic for an increased likelihood of neurological sequelae or neurodegenerative disorders in the long term. An inflammatory stimulus from the nasal olfactory epithelium to the olfactory bulbs and connected brain regions might accelerate pathological processes and symptomatic progression of neurodegenerative disease. Persistent olfactory impairment with or without perceptual distortions (i.e., parosmias or phantosmias) after SARS-CoV-2 infection could, therefore, serve as a marker to identify people with an increased long-term risk of neurological disease.

Reference

https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(21)00182-4/fulltext

The association of COVID-19 infection in pregnancy with preterm birth: A retrospective cohort study in California

Abstract

Background: The understanding of the association between coronavirus disease 19 (COVID-19) and preterm or early term birth among racially and ethnically diverse populations and people with chronic medical conditions is limited.

Methods: It was determined that the association between COVID-19 and preterm (PTB) birth among live births documented by California Vital Statistics birth certificates between July 2020 and January 2021 (n=240,147). We used best obstetric estimate of gestational age to classify births as very preterm (VPTB, <32 weeks), PTB (< 37 weeks), early term (37 and 38 weeks), and term (39-44 weeks), as each confer

independent risks to infant health and development. Separately, we calculated the joint effects of COVID-19 diagnosis, hypertension, diabetes, and obesity on PTB and VPTB.

Findings: COVID-19 diagnoses on birth certificates increased for all racial/ethnic groups between July 2020 and January 2021 and were highest for American Indian/Alaska Native (12.9%), Native Hawaiian/Pacific Islander (11.4%), and Latinx (10.3%) birthing people. COVID-19 diagnosis was associated with an increased risk of VPTB (aRR 1.6, 95% CI [1.4, 1.9]), PTB (aRR 1.4, 95% CI [1.3, 1.4]), and early term birth (aRR 1.1, 95% CI [1.1, 1.2]). There was no effect modification of the overall association by race/ethnicity or insurance status. COVID-19 diagnosis was associated with elevated risk of PTB in people with hypertension, diabetes, and/or obesity.

Interpretation: In a large population-based study, COVID-19 diagnosis increased the risk of VPTB, PTB, and early term birth, particularly among people with medical comorbidities. Considering increased circulation of COVID-19 variants, preventative measures, including vaccination, should be prioritized for birthing persons.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00019-3/fulltext

Multimodal single-cell omics analysis identifies epithelium–immune cell interactions and immune vulnerability associated with sex differences in COVID-19

Abstract

Sex differences in the susceptibility of SARS-CoV-2 infection and severity have been controversial, and the underlying mechanisms of COVID-19 in a sex-specific manner remain understudied. Here sex differences were inspected in SARS-CoV-2 infection, hospitalization, admission to the intensive care unit (ICU), sera inflammatory biomarker profiling, and single-cell RNA-sequencing (scRNA-seq) profiles across nasal, bronchoalveolar lavage fluid (BALF), and peripheral blood mononuclear cells (PBMCs) from COVID-19 patients with varying degrees of disease severities. The propensity score-matching observations revealed that male individuals have a 29% elevated likelihood of SARS-CoV-2 positivity, with a hazard ratio (HR) 1.32 (95% confidence interval [CI] 1.18–1.48) for hospitalization and HR 1.51 (95% CI 1.24–1.84) for

admission to ICU. Sera from male patients at hospital admission had elevated neutrophil–lymphocyte ratio and elevated expression of inflammatory markers (C-reactive protein and procalcitonin). It was found that SARS-CoV-2 entry factors, including ACE2, TMPRSS2, FURIN, and NRP1, have elevated expression in nasal squamous cells from male individuals with moderate and severe COVID-19. Male-biased transcriptional activation was observed in SARS-CoV-2-infected macrophages from BALF and sputum samples, which offers potential molecular mechanism for sex-biased susceptibility to viral infection. Cell–cell interaction network analysis reveals potential epithelium–immune cell interactions and immune vulnerability underlying male-elevated disease severity and mortality in COVID-19. Mechanistically, monocyte-elevated expression of Toll-like receptor 7 (TLR7) and Bruton tyrosine kinase (BTK) is associated with severe outcomes in males with COVID-19. In summary, these findings provide basis to decipher immune responses underlying sex differences and designing sex-specific targeted interventions and patient care for COVID-19.

Reference

https://www.nature.com/articles/s41392-021-00709-x

Antibody responses after first and second COVID-19 vaccination in patients with chronic lymphocytic leukaemia

Abstract

B-cell chronic lymphocytic leukaemia (CLL) is associated with immunosuppression and patients are at increased clinical risk following SARS-CoV-2 infection. Covid-19 vaccines offer the potential for protection against severe infection but relatively little is known regarding the profile of the antibody response following first or second vaccination. Spike-specific antibody responses were studied following first and/or second Covid-19 vaccination in 299 patients with CLL compared with healthy donors. 286 patients underwent extended interval (10–12 week) vaccination. 154 patients received the BNT162b2 mRNA vaccine and 145 patients received ChAdOx1. Blood samples were taken either by venepuncture or as dried blood spots on filter paper. Spike-specific antibody responses were detectable in 34% of patients with CLL after one vaccine (n = 267) compared to 94% in healthy donors with antibody titres 104-fold lower in the patient group. Antibody responses increased to 75% after second vaccine

(n = 55), compared to 100% in healthy donors, although titres remained lower. Multivariate analysis showed that current treatment with BTK inhibitors or IgA deficiency were independently associated with failure to generate an antibody response after the second vaccine. This work supports the need for optimisation of vaccination strategy in patients with CLL including the potential utility of booster vaccines.

Reference

https://nature.com/articles/s41408-021-00528-x

COVID-19 vaccines that reduce symptoms but do not block infection need higher coverage and faster rollout to achieve population impact

Abstract

Trial results for two COVID-19 vaccines suggest at least 90% efficacy against symptomatic disease (VEDIS). It remains unknown whether this efficacy is mediated by lowering SARS-CoV-2 infection susceptibility (VESUSC) or development of symptoms after infection (VESYMP). It was aimed to assess and compare the population impact of vaccines with different efficacy profiles (VESYMP and VESUSC) satisfying licensure criteria. A mathematical model of SARS-CoV-2 transmission was developed, calibrated to data from King County, Washington. Rollout scenarios starting December 2020 were simulated with combinations of VESUSC and VESYMP resulting in up to 100% VEDIS. No reduction of infectivity was assumed upon infection conditional on presence of symptoms. Proportions of cumulative infections, hospitalizations and deaths prevented over 1 year from vaccination start are reported. Rollouts of 1 M vaccinations (5000 daily) using vaccines with 50% VEDIS are projected to prevent 23–46% of infections and 31–46% of deaths over 1 year. In comparison, vaccines with 90% VEDIS are projected to prevent 37–64% of infections and 46–64% of deaths over 1 year. In both cases, there is a greater reduction if VEDIS is mediated mostly by VESUSC. The use of a “symptom reducing” vaccine will require twice as many people vaccinated than a “susceptibility reducing” vaccine with the same 90% VEDIS to prevent 50% of the infections and death over 1 year. Delaying the start of the vaccination by 3 months decreases the expected population impact by more than 50%. Vaccines which prevent COVID-19 disease but not SARS-CoV-2 infection, and thereby shift symptomatic infections to asymptomatic infections, will prevent fewer infections and require larger

and faster vaccination rollouts to have population impact, compared to vaccines that reduce susceptibility to infection. If uncontrolled transmission across the U.S. continues, then expected vaccination in Spring 2021 will provide only limited benefit.

Reference

https://www.nature.com/articles/s41598-021-94719-y

A synthetic nanobody targeting RBD protects hamsters from SARS-CoV-2 infection

Abstract

SARS-CoV-2, the causative agent of COVID-19, features a receptor-binding domain (RBD) for binding to the host cell ACE2 protein. Neutralizing antibodies that block RBD-ACE2 interaction are candidates for the development of targeted therapeutics. Llama-derived single-domain antibodies (nanobodies, ~15 kDa) offer advantages in bioavailability, amenability, and production and storage owing to their small sizes and high stability. Here, the rapid selection of 99 synthetic nanobodies (sybodies) were reported against RBD by *in vitro* selection using three libraries. The best sybody, MR3 binds to RBD with high affinity (K_D = 1.0 nM) and displays high neutralization activity against SARS-CoV-2 pseudoviruses (IC_{50} = 0.42 μg mL^{-1}). Structural, biochemical, and biological characterization suggests a common neutralizing mechanism, in which the RBD-ACE2 interaction is competitively inhibited by sybodies. Various forms of sybodies with improved potency have been generated by structure-based design, biparatopic construction, and divalent engineering. Two divalent forms of MR3 protect hamsters from clinical signs after live virus challenge and a single dose of the Fc-fusion construct of MR3 reduces viral RNA load by 6 Log_{10}. The results pave the way for the development of therapeutic nanobodies against COVID-19 and present a strategy for rapid development of targeted medical interventions during an outbreak.

Reference

https://www.nature.com/articles/s41467-021-24905-z

Correlative multi-scale cryo-imaging unveils SARS-CoV-2 assembly and egress

Abstract

Since the outbreak of the SARS-CoV-2 pandemic, there have been intense structural studies on purified viral components and inactivated viruses. However, structural and ultrastructural evidence on how the SARS-CoV-2 infection progresses in the native cellular context is scarce, and there is a lack of comprehensive knowledge on the SARS-CoV-2 replicative cycle. To correlate cytopathic events induced by SARS-CoV-2 with virus replication processes in frozen-hydrated cells, a unique multi-modal, multi-scale cryo-correlative platform was established to image SARS-CoV-2 infection in Vero cells. This platform combines serial cryoFIB/SEM volume imaging and soft X-ray cryo-tomography with cell lamellae-based cryo-electron tomography (cryoET) and subtomogram averaging. Here critical SARS-CoV-2 structural events were reported – e.g. viral RNA transport portals, virus assembly intermediates, virus egress pathway, and native virus spike structures, in the context of whole-cell volumes revealing drastic cytppathic changes. This integrated approach allows a holistic view of SARS-CoV-2 infection, from the whole cell to individual molecules.

Reference

https://www.nature.com/articles/s41467-021-24887-y

Acute kidney injury in critically Ill children and young adults with suspected SARS-CoV2 infection

Abstract

Background: It was aimed to study the association of suspected versus confirmed infection with the novel SARS-CoV2 virus with the prevalence of acute kidney injury (AKI) in critically ill children.

Methods: Sequential point-prevalence study of children and young adults aged 7 days to 25 years admitted to intensive care units under investigation for SARS-CoV2 infection. AKI was staged in the first 14 days of enrollment using KDIGO creatinine-based staging. SARS-CoV2 positive (CONFIRMED) were compared to SUSPECTED (negative or unknown). Outcome data was censored at 28-days.

Results: In 331 patients of both sexes, 179 (54.1%) were CONFIRMED, 4.2% (14) died. AKI occurred in 124 (37.5%) and severe AKI occurred in 63 (19.0%). Incidence of AKI in CONFIRMED was 74/179 (41.3%) versus 50/152 (32.9%) for SUSPECTED; severe AKI occurred in 35 (19.6%) of CONFIRMED and 28 (18.4%) of SUSPECTED. Mortality was 6.2% (n = 11) in CONFIRMED, but 9.5% (n = 7) in those CONFIRMED with AKI. On multivariable analysis, only Hispanic ethnicity (relative risk 0.5, 95% CI 0.3–0.9) was associated with less AKI development among those CONFIRMED.

Conclusions: AKI and severe AKI occur commonly in critically ill children with SARS-CoV2 infection, more than double the historical standard. Further investigation is needed during this continuing pandemic to describe and refine the understanding of pediatric AKI epidemiology and outcomes.

Reference

https://www.nature.com/articles/s41390-021-01667-4

Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: A phase 4 trial

Abstract

CoronaVac, an inactivated SARS-CoV-2 vaccine, has been approved for emergency use in several countries. However, its immunogenicity in immunocompromised individuals has not been well established. A prospective phase 4 controlled trial (no. NCT04754698, CoronavRheum) was initiated in 910 adults with autoimmune rheumatic diseases (ARD) and 182 age- and sex-frequency-matched healthy adults (control group, CG), who received two doses of CoronaVac. The primary outcomes were reduction of ≥15% in both anti-SARS-CoV-2 IgG seroconversion (SC) and neutralizing antibody (NAb) positivity 6 weeks (day 69 (D69)) after the second dose in the ARD group compared with that in the CG. Secondary outcomes were IgG SC and NAb positivity at D28, IgG titers and neutralizing activity at D28 and D69 and vaccine safety. Prespecified endpoints were met, with lower anti-SARS-Cov-2 IgG SC (70.4 versus 95.5%, $P < 0.001$) and NAb positivity (56.3 versus 79.3%, $P < 0.001$) at D69 in the ARD group than in the CG. Moreover, IgG titers (12.1 versus 29.7, $P < 0.001$) and median neutralization activity (58.7 versus 64.5%, $P = 0.013$) were also lower at D69 in patients with ARD. At D28, patients with ARD presented with lower IgG frequency (18.7 versus

34.6%, $P < 0.001$) and NAb positivity (20.6 versus 36.3%, $P < 0.001$) than that of the CG. There were no moderate/severe adverse events. These data support the use of CoronaVac in patients with ARD, suggesting reduced but acceptable short-term immunogenicity. The trial is still ongoing to evaluate the long-term effectiveness/immunogenicity.

Reference

https://www.nature.com/articles/s41591-021-01469-5

JAK inhibitors dampen activation of interferon-activated transcriptomes and the SARS-CoV-2 receptor ACE2 in human renal proximal tubules

Abstract

SARS-CoV-2 infections initiate cytokine storms and activate genetic programs leading to progressive hyperinflammation in multiple organs of COVID-19 patients. While it is known that COVID-19 impacts kidney function, leading to increased mortality, cytokine response of renal epithelium has not been studied in detail. Here, a report on the genetic programs activated in Human Primary Proximal Tubule (HPPT) cells by interferons and their suppression by ruxolitinib, a Janus kinase (JAK) inhibitor used in COVID-19 treatment was presented. Integration of the data with those form acute kidney injury and COVID-19 patients, as well as other tissues, permitted the identification of kidney-specific interferon responses. Additionally, we investigated the regulation of the recently discovered isoform (dACE2) of the angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 receptor. Using ChIP-seq, we identified candidate interferon-activated enhancers controlling the ACE2 locus, including the intronic dACE2 promoter. Taken together, our study provides an in-depth understanding of genetic programs activated in kidney cells.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00896-8

Affinity maturation of SARS-CoV-2 neutralizing antibodies confers potency, breadth, and resilience to viral escape mutations

Abstract

Antibodies elicited by infection accumulate somatic mutations in germinal centers that can increase affinity for cognate antigens. 6 Independent groups of clonally related severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Spike receptor-binding domain (RBD)-specific antibodies were analyzed from 5 individuals shortly after infection and later in convalescence to determine the impact of maturation over months. In addition to increased affinity and neutralization potency, antibody evolution changed the mutational pathways for the acquisition of viral resistance and restricted neutralization escape options. For some antibodies, maturation imposed a requirement for multiple substitutions to enable escape. For certain antibodies, affinity maturation enabled the neutralization of circulating SARS-CoV-2 variants of concern and heterologous sarbecoviruses. Antibody-antigen structures revealed that these properties resulted from substitutions that allowed additional variability at the interface with the RBD. These findings suggested that increasing antibody diversity through prolonged or repeated antigen exposure may improve protection against diversifying SARS-CoV-2 populations, and perhaps against other pandemic threat coronaviruses.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00294-6

Cross-tissue single-cell landscape of human monocytes and macrophages in health and disease

Abstract

Mononuclear phagocytes (MNPs) encompass dendritic cells, monocytes, and macrophages (MoMac), which exhibit antimicrobial, homeostatic, and immunoregulatory functions. 178,651 MNPs were integrated from 13 tissues across 41 datasets to generate a MNP single-cell RNA compendium (MNP-VERSE), a publicly available tool to map MNPs and define conserved gene signatures of MNP populations. Next, a MoMac-focused compendium was generated that revealed an array of specialized cell subsets widely distributed across multiple tissues. Specific pathological forms were

expanded in cancer and inflammation. All neoplastic tissues contained conserved tumor-associated macrophage populations. In particular, it was focused on IL4I1+CD274(PD-L1)+IDO1+ macrophages, which accumulated in the tumor periphery in a T cell-dependent manner via interferon-γ (IFN-γ) and CD40/CD40L-induced maturation from IFN-primed monocytes. IL4I1_Macs exhibited immunosuppressive characteristics through tryptophan degradation and promoted the entry of regulatory T cell into tumors. This integrated analysis provides a robust online-available platform for uniform annotation and dissection of specific macrophage functions in healthy and pathological states.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00293-4

The SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) in myalgic encephalomyelitis/chronic fatigue syndrome: A meta-analysis of public DNA methylation and gene expression data

Abstract

People with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) often report a high frequency of viral infections and flu-like symptoms during their disease course. Given that this reporting agrees with different immunological abnormalities and altered gene expression profiles observed in the disease, it was aimed at answering whether the expression of the human angiotensin-converting enzyme 2 (ACE2), the major cell entry receptor for SARS-CoV-2, is also altered in these patients. In particular, a low expression of ACE2 could be indicative of a high risk of developing COVID-19. It was then performed a meta-analysis of public data on CpG DNA methylation and gene expression of this enzyme and its homologous ACE protein in peripheral blood mononuclear cells and related subsets. It was found that patients with ME/CFS have decreased methylation levels of four CpG probes in the ACE locus (cg09920557, cg19802564, cg21094739, and cg10468385) and of another probe in the promoter region of the ACE2 gene (cg08559914). It was also found a decreased expression of ACE2 but not of ACE in patients when compared to healthy controls. Accordingly, in newly collected data, there was evidence for a significant higher proportion of samples with an ACE2 expression below the limit of detection in patients than healthy controls.

Altogether, patients with ME/CFS can be at a higher COVID-19 risk and, if so, they should be considered a priority group for vaccination by public health authorities. To further support this conclusion, similar research is recommended for other human cell entry receptors and cell types, namely, those cells targeted by the virus.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)01768-0

Publication Date: Jul 29, 2021

Early detection of COVID-19 in the UK using self-reported symptoms: A large-scale, prospective, epidemiological surveillance study

Abstract

Background: Self-reported symptoms during the COVID-19 pandemic have been used to train artificial intelligence models to identify possible infection foci. To date, these models have only considered the culmination or peak of symptoms, which is not suitable for the early detection of infection. We aimed to estimate the probability of an individual being infected with SARS-CoV-2 on the basis of early self-reported symptoms to enable timely self-isolation and urgent testing.

Methods: In this large-scale, prospective, epidemiological surveillance study, we used prospective, observational, longitudinal, self-reported data from participants in the UK on 19 symptoms over 3 days after symptoms onset and COVID-19 PCR test results extracted from the COVID-19 Symptom Study mobile phone app. We divided the study population into a training set (those who reported symptoms between April 29, 2020, and Oct 15, 2020) and a test set (those who reported symptoms between Oct 16, 2020, and Nov 30, 2020), and used three models to analyse the self-reported symptoms: the UK's National Health Service (NHS) algorithm, logistic regression, and the hierarchical Gaussian process model we designed to account for several important variables (eg, specific COVID-19 symptoms, comorbidities, and clinical information). Model performance to predict COVID-19 positivity was compared in terms of sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) in the test set. For the hierarchical Gaussian process model, we also evaluated the relevance of

symptoms in the early detection of COVID-19 in population subgroups stratified according to occupation, sex, age, and body-mass index.

Findings: The training set comprised 182 991 participants and the test set comprised 15 049 participants. When trained on 3 days of self-reported symptoms, the hierarchical Gaussian process model had a higher prediction AUC (0·80 [95% CI 0·80–0·81]) than did the logistic regression model (0·74 [0·74–0·75]) and the NHS algorithm (0·67 [0·67–0·67]). AUCs for all models increased with the number of days of self-reported symptoms, but were still high for the hierarchical Gaussian process model at day 1 (0·73 [95% CI 0·73–0·74]) and day 2 (0·79 [0·78–0·79]). At day 3, the hierarchical Gaussian process model also had a significantly higher sensitivity, but a non-statistically lower specificity, than did the two other models. The hierarchical Gaussian process model also identified different sets of relevant features to detect COVID-19 between younger and older subgroups, and between health-care workers and non-health-care workers. When used during different pandemic periods, the model was robust to changes in populations.

Interpretation: Early detection of SARS-CoV-2 infection is feasible with our model. Such early detection is crucial to contain the spread of COVID-19 and efficiently allocate medical resources.

Reference

https://www.thelancet.com/journals/landig/article/PIIS2589-7500(21)00131-X/fulltext

Seropositivity of COVID-19 among asymptomatic healthcare workers: A multi-site prospective cohort study from Northern Virginia, United States

Abstract

Background: Because of their direct patient contact, healthcare workers (HCW) face an unprecedented risk of exposure to COVID-19. The aim of this study was to examine incidence of COVID-19 disease among asymptomatic HCW and community participants in Northern Virginia during 6 months of follow-up.

Methods: This is a prospective cohort study that enrolled healthy HCW and residents who never had a symptomatic COVID-19 infection prior to enrolment from the community in Northern Virginia from April to November 2020. All participants were

invited to enrol in study, and they were followed at 2-, and 6-months intervals. Participants were evaluated by commercial chemiluminescence SARS-CoV-2 serology assays as part of regional health system and public health surveillance program to monitor the spread of COVID-19 disease.

Findings: Of a total of 1,819 asymptomatic HCW enrolled, 1,473 (96%) had data at two-months interval, and 1,323 (73%) participants had data at 6-months interval. At baseline, 21 (1.15%) were found to have prior COVID-19 exposure. At two-months interval, COVID-19 rate was 2.8% and at six months follow-up, the overall incidence rate increased to 4.8%, but was as high as 7.9% among those who belong to the youngest age group (20–29 years). Seroconversion rates in HCW were comparable to the seropositive rates in the Northern Virginia community. The overall incidence of COVID-19 in the community was 4.5%, but the estimate was higher among Hispanic ethnicity (incidence rate = 15.3%) potentially reflecting different socio-economic factors among the community participants and the HCW group. Using cross-sectional logistic regression and spatio-temporal mixed effects models, significant factors that influence the transmission rate among HCW include age, race/ethnicity, resident ZIP-code, and household exposure, but not direct patient contact.

Interpretation: In Northern Virginia, the seropositive rate of COVID-19 disease among HCW was comparable to that in the community.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00022-3/fulltext

Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up

Abstract

Background: Neurologic manifestations are well-recognized features of coronavirus disease 2019 (COVID-19). However, the longitudinal association of biomarkers reflecting CNS impact and neurological symptoms is not known. We sought to determine whether plasma biomarkers of CNS injury were associated with neurologic sequelae after COVID-19.

Methods: Patients with confirmed acute COVID-19 were studied prospectively. Neurological symptoms were recorded during the acute phase of the disease and at six months follow-up, and blood samples were collected longitudinally. Healthy age-matched individuals were included as controls. We analysed plasma concentrations of neurofilament light-chain (NfL), glial fibrillary acidic protein (GFAp), and growth differentiation factor 15 (GDF-15).

Findings: One hundred patients with mild (n = 24), moderate (n = 28), and severe (n = 48) COVID-19 were followed for a median (IQR) of 225 (187–262) days. In the acute phase, patients with severe COVID-19 had higher concentrations of NfL than all other groups (all $p < 0{\cdot}001$), and higher GFAp than controls ($p < 0{\cdot}001$). GFAp was also significantly increased in moderate disease ($p < 0{\cdot}05$) compared with controls. NfL ($r = 0{\cdot}53$, $p < 0{\cdot}001$) and GFAp ($r = 0{\cdot}39$, $p < 0{\cdot}001$) correlated with GDF-15 during the acute phase. After six months, NfL and GFAp concentrations had normalized, with no persisting group differences. Despite this, 50 patients reported persistent neurological symptoms, most commonly fatigue (n = 40), “brain-fog” (n = 29), and changes in cognition (n = 25). We found no correlation between persistent neurological symptoms and CNS injury biomarkers in the acute phase.

Interpretation: The normalization of CNS injury biomarkers in all individuals, regardless of previous disease severity or persisting neurological symptoms, indicates that post COVID-19 neurological sequelae are not accompanied by ongoing CNS injury.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00305-4/fulltext

A dried blood spot protocol for high throughput analysis of SARS-CoV-2 serology based on the Roche Elecsys anti-N assay

Abstract

Background: Since 2020 SARS-CoV-2 spreads pandemically, infecting more than 119 million people, causing >2·6 million fatalities. Symptoms of SARS-CoV-2 infection vary greatly, ranging from asymptomatic to fatal. Different populations react differently to the disease, making it very hard to track the spread of the infection in a population. Measuring specific anti-SARS-CoV-2 antibodies is an important tool to assess the

spread of the infection or successful vaccinations. To achieve sufficient sample numbers, alternatives to venous blood sampling are needed not requiring medical personnel or cold-chains. Dried-blood-spots (DBS) on filter-cards have been used for different studies, but not routinely for serology.

Methods: We developed a semi-automated protocol using self-sampled DBS for SARS-CoV-2 serology. It was validated in a cohort of matched DBS and venous-blood samples (n = 1710). Feasibility is demonstrated with two large serosurveys with 10247 company employees and a population cohort of 4465 participants.

Findings: Sensitivity and specificity reached 99·20% and 98·65%, respectively. Providing written instructions and video tutorials, 99·87% (4465/4471) of the unsupervised home sampling DBS cards could be analysed.

Interpretation: DBS-sampling is a valid and highly reliable tool for large scale serosurveys. We demonstrate feasibility and accuracy with a large validation cohort including unsupervised home sampling. This protocol might be of big importance for surveillance in resource-limited settings, providing low-cost highly accurate serology data.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00295-4/fulltext

Human embryonic stem cell-derived cardiomyocyte platform screens inhibitors of SARS-CoV-2 infection

Abstract

Patients with cardiovascular comorbidities are more susceptible to severe infection with SARS-CoV-2, known to directly cause pathological damage to cardiovascular tissue. A screening platform was outlined using human embryonic stem cell-derived cardiomyocytes, confirmed to express the protein machinery critical for SARS-CoV-2 infection, and a SARS-CoV-2 spike-pseudotyped virus system. The method has allowed us to identify benztropine and DX600 as novel inhibitors of SARS-CoV-2 infection in a clinically relevant stem cell-derived cardiomyocyte line. Discovery of new medicines will be critical for protecting the heart in patients with SARS-CoV-2, and for individuals where vaccination is contraindicated.

Reference

https://www.nature.com/articles/s42003-021-02453-y

Comprehensive virtual screening of 4.8 k flavonoids reveals novel insights into allosteric inhibition of SARS-CoV-2 M^{PRO}

Abstract

SARS-CoV-2 main protease is a common target for inhibition assays due to its high conservation among coronaviruses. Since flavonoids show antiviral activity, several in silico works have proposed them as potential SARS-CoV-2 main protease inhibitors. Nonetheless, there is reason to doubt certain results given the lack of consideration for flavonoid promiscuity or main protease plasticity, usage of short library sizes, absence of control molecules and/or the limitation of the methodology to a single target site. Here, a virtual screening study was reported where dorsilurin E, euchrenone a11, sanggenol O and CHEMBL2171598 are proposed to inhibit main protease through different pathways. Remarkably, novel structural mechanisms were observed after sanggenol O and CHEMBL2171598 bound to experimentally proven allosteric sites. The former drastically affected the active site, while the latter triggered a hinge movement which has been previously reported for an inactive SARS-CoV main protease mutant. The use of a curated database of 4.8 k flavonoids, combining two well-known docking software (AutoDock Vina and AutoDock4.2), molecular dynamics and MMPBSA, guaranteed an adequate analysis and robust interpretation. These criteria can be considered for future screening campaigns against SARS-CoV-2 main protease.

Reference

https://www.nature.com/articles/s41598-021-94951-6

Structural and functional basis for pan-CoV fusion inhibitors against SARS-CoV-2 and its variants with preclinical evaluation

Abstract

The COVID-19 pandemic poses a global threat to public health and economy. The continuously emerging SARS-CoV-2 variants present a major challenge to the development of antiviral agents and vaccines. In this study, it was identified that EK1 and cholesterol-coupled derivative of EK1, EK1C4, as pan-CoV fusion inhibitors, exhibit

potent antiviral activity against SARS-CoV-2 infection in both lung- and intestine-derived cell lines (Calu-3 and Caco2, respectively). They are also effective against infection of pseudotyped SARS-CoV-2 variants B.1.1.7 (Alpha) and B.1.1.248 (Gamma) as well as those with mutations in S protein, including N417T, E484K, N501Y, and D614G, which are common in South African and Brazilian variants. Crystal structure revealed that EK1 targets the HR1 domain in the SARS-CoV-2 S protein to block virus-cell fusion and provide mechanistic insights into its broad and effective antiviral activity. Nasal administration of EK1 peptides to hACE2 transgenic mice significantly reduced viral titers in lung and intestinal tissues. EK1 showed good safety profiles in various animal models, supporting further clinical development of EK1-based pan-CoV fusion inhibitors against SARS-CoV-2 and its variants.

Reference

https://www.nature.com/articles/s41392-021-00712-2

Immune responses to a single dose of the AZD1222/Covishield vaccine in health care workers

Abstract

Several COVID-19 vaccines have received emergency approval. Here the immunogenicity of a single dose of the AZD1222 vaccine was assessed, at one month, in a cohort of health care workers (HCWs) (629 naïve and 26 previously infected). 93.4% of naïve HCWs seroconverted, irrespective of age and gender. Haemagglutination test for antibodies to the receptor binding domain (RBD), surrogate neutralization assay (sVNT) and *ex vivo* IFNγ ELISpot assays were carried out in a sub-cohort. ACE2 blocking antibodies (measured by sVNT) were detected in 67/69 (97.1%) of naïve HCWs. Antibody levels to the RBD of the wild-type virus were higher than to RBD of B.1.1.7, and titres to B.1.351 were very low. *Ex vivo* T cell responses were observed in 30.8% to 61.7% in naïve HCWs. Previously infected HCWs, developed significantly higher ($p < 0.0001$) ACE2 blocking antibodies and antibodies to the RBD for the variants B.1.1.7 and B.1.351. This study shows high seroconversion after one vaccine dose, but also suggests that one vaccine dose may be insufficient to protect against emerging variants.

Reference

https://www.nature.com/articles/s41467-021-24579-7

SARS-CoV-2 specific T cell responses are lower in children and increase with age and time after infection

Abstract

SARS-CoV-2 infection of children leads to a mild illness and the immunological differences with adults are unclear. Here, SARS-CoV-2 specific T cell responses were reported in infected adults and children, and find that the acute and memory $CD4^+$ T cell responses to structural SARS-CoV-2 proteins increase with age, whereas $CD8^+$ T cell responses increase with time post-infection. Infected children have lower $CD4^+$ and $CD8^+$ T cell responses to SARS-CoV-2 structural and ORF1ab proteins when compared with infected adults, comparable T cell polyfunctionality and reduced $CD4^+$ T cell effector memory. Compared with adults, children have lower levels of antibodies to β-coronaviruses, indicating differing baseline immunity. Total T follicular helper responses are increased, whilst monocyte numbers are reduced, indicating rapid adaptive co-ordination of the T and B cell responses and differing levels of inflammation. Therefore, reduced prior β-coronavirus immunity and reduced T cell activation in children might drive milder COVID-19 pathogenesis.

Reference

https://www.nature.com/articles/s41467-021-24938-4

Endogenous control of inflammation characterizes pregnant women with asymptomatic or paucisymptomatic SARS-CoV-2 infection

Abstract

SARS-CoV-2 infection can affect all human beings, including pregnant women. Thus, understanding the immunological changes induced by the virus during pregnancy is nowadays of pivotal importance. Here, using peripheral blood from 14 pregnant women with asymptomatic or mild SARS-CoV-2 infection, we investigate cell proliferation and cytokine production, measure plasma levels of 62 cytokines, and perform a 38-parameter mass cytometry analysis. The results show an increase in low density

neutrophils but no lymphopenia or gross alterations of white blood cells, which display normal levels of differentiation, activation or exhaustion markers and show well preserved functionality. Meanwhile, the plasma levels of anti-inflammatory cytokines such as interleukin (IL)-1RA, IL-10 and IL-19 are increased, those of IL-17, PD-L1 and D-dimer are decreased, but IL-6 and other inflammatory molecules remain unchanged. The profiling of antiviral immune responses may thus help develop therapeutic strategies to avoid virus-induced damages during pregnancy.

Reference

https://www.nature.com/articles/s41467-021-24940-w

Mathematical model of the feedback between global supply chain disruption and COVID-19 dynamics

Abstract

The pandemic of COVID-19 has become one of the greatest threats to human health, causing severe disruptions in the global supply chain, and compromising health care delivery worldwide. Although government authorities sought to contain the spread of SARS-CoV-2, by restricting travel and in-person activities, failure to deploy time-sensitive strategies in ramping-up of critical resource production exacerbated the outbreak. Here, a mathematical model was developed to analyze the effects of the interaction between supply chain disruption and infectious disease dynamics using coupled production and disease networks built on global data. Analysis of the supply chain model suggests that time-sensitive containment strategies could be created to balance objectives in pandemic control and economic losses, leading to a spatiotemporal separation of infection peaks that alleviates the societal impact of the disease. A lean resource allocation strategy can reduce the impact of supply chain shortages from 11.91 to 1.11% in North America. The model highlights the importance of cross-sectoral coordination and region-wise collaboration to optimally contain a pandemic and provides a framework that could advance the containment and model-based decision making for future pandemics.

Reference

https://www.nature.com/articles/s41598-021-94619-1

Differential immune responses in pregnant patients recovered from COVID-19

Abstract

Pregnant women are generally more susceptible to viral infection. Although the impact of SARS-CoV-2 in pregnancy remains to be determined, evidence indicates that the risk factors for severe COVID-19 are similar in pregnancy to the general population. Here it was systemically analyzed the clinical characteristics of pregnant and non-pregnant female COVID-19 patients who were hospitalized during the same period and found that pregnant patients developed marked lymphopenia and higher inflammation evident by higher C-reactive protein and IL-6. To elucidate the pathways that might contribute to immunopathology or protective immunity against COVID-19 during pregnancy, we applied single-cell mRNA sequencing to profile peripheral blood mononuclear cells from four pregnant and six non-pregnant female patients after recovery along with four pregnant and three non-pregnant healthy donors. We found normal clonal expansion of T cells in the pregnant patients, heightened activation and chemotaxis in NK, NKT, and MAIT cells, and differential interferon responses in the monocyte compartment. The data present a unique feature in both innate and adaptive immune responses in pregnant patients recovered from COVID-19.

Reference

https://www.nature.com/articles/s41392-021-00703-3

Response to mRNA vaccination for COVID-19 among patients with multiple myeloma Studying

Abstract

Multiple myeloma (MM) patients are at higher risk for severe COVID-19. Their mRNA vaccination response against SARS-CoV-2 is unknown. Thus, responses were analyzed to mRNA vaccination against COVID-19 among these patients. Using an ELISA-based assay that detects IgG antibodies to SARS-CoV-2 spike protein, we determined serum antibody levels prior to immunization and 12–21 and 14–21 days following the first and second vaccinations, respectively, with mRNA-1273 (Moderna) or BNT162b2 (Pfizer/BioNTech) among 103 MM patients (96 and 7 with active and smoldering disease, respectively). Patients were stratified into clinically relevant

responders (>250 IU/mL), partial responders (50–250 IU/mL, which was above pre-COVID-19 background), and nonresponders (<50 IU/mL). Smoldering MM patients responded better than those with active disease. Only 45% of active MM patients developed an adequate response, while 22% had a partial response. Lower spike antibody levels were associated with older age, impaired renal function, low lymphocyte counts, reduced uninvolved immunoglobulin levels, > second line of treatment, and among those not in complete remission. Patients who received mRNA-1273 vaccine had higher anti-spike antibody levels than those who were vaccinated with BNT162b2. Thus, most MM patients have impaired responses to mRNA vaccination against COVID-19, and specific clinical and myeloma-related characteristics predict vaccine responsiveness.

Reference

https://www.nature.com/articles/s41375-021-01354-7

Immune correlates of protection by mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates

Abstract

Immune correlates of protection can be used as surrogate endpoints for vaccine efficacy. Here, nonhuman primates (NHPs) received either no vaccine or doses ranging from 0.3 to 100 μg of SARS-CoV-2 vaccine, mRNA-1273. mRNA-1273 vaccination elicited robust circulating and mucosal antibody responses in a dose-dependent manner. Viral replication was significantly reduced in bronchoalveolar lavages and nasal swabs following SARS-CoV-2 challenge in vaccinated animals and most strongly correlated with levels of anti-S antibody and neutralizing activity. Lower antibody levels are needed for reduction of viral replication in the lower airway than in the upper airway. Passive transfer of mRNA-1273-induced IgG to naïve hamsters was sufficient to mediate protection. Thus, mRNA-1273 vaccine-induced humoral immune responses are a mechanistic correlate of protection against SARS-CoV-2 in NHPs.

Reference

https://science.sciencemag.org/content/early/2021/07/29/science.abj0299

CORRESPONDANCE

Publication Date: Jul 29, 2021

Heterologous prime–boost vaccination with ChAdOx1 nCoV-19 and BNT162b2

The Oxford-AstraZeneca COVID-19 vaccine ChAdOx1 nCoV-19 is associated with a risk for vaccine-induced immune thrombosis with thrombocytopenia syndrome in the range of one to two cases per 100 000 vaccinations, with younger women showing the highest risk. Additional cases have been reported for the Johnson & Johnson adenoviral vector-based Ad26.CoV2.S COVID-19 vaccine. Vaccine-induced antibodies against platelet factor 4 have been implicated in the pathogenesis. These antibodies might be amplified by booster vaccination with an adenoviral vector, which prompted recommendations to boost with an mRNA-based vaccine instead, although data on safety and efficacy of heterologous prime–boost regimens are sparse.

The vaccine-induced antibody response was quantified in vaccinees in Germany who received a heterologous COVID-19 vaccination scheme using ChAdOx1 nCoV-19 as prime and BNT162b2 mRNA (BioNTech-Pfizer) as boost vaccination. The results were compared with those of cohorts of health-care workers or volunteers who received homologous BNT162b2 or ChAdOx1 nCoV-19 vaccination regimens, respectively. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00420-5/fulltext

REPORT

Publication Date: Aug 03, 2021

Differential effects of the second SARS-CoV-2 mRNA vaccine dose on T cell immunity in naïve and COVID-19 recovered individuals

The rapid development of mRNA-based vaccines against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) led to the design of accelerated vaccination schedules that have been extremely effective in naïve individuals. While a two-dose immunization regimen with the BNT162b2 vaccine has been demonstrated to provide a 95% efficacy in naïve individuals, the effects of the second vaccine dose in individuals who have previously recovered from natural SARS-CoV-2 infection has not been investigated in detail. Here, SARS-CoV-2 spike-specific humoral and cellular immunity was characterized in naïve and previously infected individuals during and after two-doses of BNT162b2 vaccination. The results demonstrate that, while the second dose increases both the humoral and cellular immunity in naïve individuals, COVID-19 recovered individuals reach their peak of immunity after the first dose. These results suggested that a second dose, according to the current standard regimen of vaccination, may be not necessary in individuals previously infected with SARS-CoV-2.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01004-4

PERSPECTIVE

Publication Date: Aug 02, 2021

Accelerated COVID-19 vaccine development: Mmilestones, lessons, and prospects

The development of effective vaccines to combat infectious diseases is a complex multi-year and multi-stakeholder process. To accelerate the development of vaccines for coronavirus disease 2019 (COVID-19), a novel pathogen emerging in late 2019 and spreading globally by early 2020, the United States government (USG) mounted an operation bridging public and private sector expertise and infrastructure. The success of the endeavor can be seen in the rapid advanced development of multiple vaccine candidates, with several demonstrating efficacy and now being administered around the globe. Here, the milestones were reviewed enabling the USG-led effort, the methods utilized, and ensuing outcomes. The current status of COVID-19 vaccine development was discussed and a perspective was provided for how partnership and preparedness can be better utilized in response to future public-health pandemic emergencies.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00303-4

Publication Date: Jul 30, 2021

The road to addressing Long Covid

The risk of COVID-19 has been largely communicated only in terms of deaths and hospital capacity, with recovery and survival conflated with each other. Around one in three people with symptomatic COVID-19 still experience symptoms 12 weeks after onset. Long Covid can be experienced by all age groups and not only those with acute severe disease. The debilitating symptoms are wide-ranging, multisystemic, and predominantly fluctuating or relapsing. There is still much to understand about Long Covid, but what is not well understood should not be ignored.

Long Covid is likely the first illness in history that has been defined by patients through social media platforms such as Twitter and Facebook. People with Long Covid formed a

movement that demanded recognition of what was happening to them. During the first wave of the pandemic in 2020, online testimonials of prolonged symptoms following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, were the only source of reassurance to others with a similar experience, including this author. In the absence of any guidance or recognition about the possibility of a persistent illness, peer support is all that people with Long Covid had. Many previously healthy and active people described persistent symptoms of the acute illness that fluctuated, with new symptoms appearing weeks later. In many countries, most nonhospitalized people did not have lab confirmation of SARS-CoV-2 infection owing to lack of access to community testing, so their symptoms remained without a diagnosis.

By summer 2020, thousands were joining social media support groups. A common theme started to emerge: lack of recognition by the medical profession. Patients, including doctors, with Long Covid were consulting their health care providers, and their symptoms were commonly minimized, dismissed, or labeled as anxiety. A narrative emerged of people struggling to make sense of their symptoms and forming their own groups to understand and research what was happening to them in an international citizen science movement. The testimonials of people living with Long Covid demonstrated themes of stigma and discrimination. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/373/6554/491

No shortcuts to SARS-CoV-2 antivirals

When the COVID-19 pandemic hit, there was massive investment into the discovery of new treatments. Given the urgent need, repurposing of approved or clinically pretested drugs appeared especially attractive because that strategy promised fast initiation of antiviral clinical studies. On page 541 of this issue, the study by Tummino *et al.* raises concerns that many drug candidates that showed antiviral activity in hypothesis-free cellular screens and were then repurposed to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections may be scientific dead ends. Their study is a warning that even amid the pressure of a pandemic, scientific diligence is still essential.

Early in the pandemic, an international team of scientists undertook a comprehensive study to identify human proteins that interact with proteins from SARS-CoV-2. The idea was that if one or more of these human proteins were required for viral production, then there may be drugs that target them “on the shelf” that could be repurposed to treat COVID-19 patients. The team identified several candidate drug targets, among which were the sigma receptors. They went on to show that drugs targeting these receptors potently inhibited viral production in cell culture, providing preliminary “validation” of sigma receptors as COVID-19 drug targets.

However, as members of the same team began to investigate their potential for clinical studies, they became concerned. In testing 50 different sigma receptor drugs to find the most suitable one, they found no correlation between the potency with which the drugs inhibited the receptor and their antiviral activity. What was going on? Tummino *et al*. show that the antiviral activity in cell-culture assays had nothing to do with modulation of the sigma receptors but rather correlated with certain chemical properties of the compounds. The subset of drugs that had antiviral activity were all cationic and amphiphilic, features known to induce phospholipidosis, which is an aberrant accumulation of phospholipids in the lysosome. Potent sigma receptor drugs that did not induce phospholipidosis showed no antiviral activity. Drug-induced phospholipidosis is a side effect of cationic amphiphilic drugs (CADs), and these drugs are known to inhibit the production of many other viruses in cell culture. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/373/6554/488