COVID-19

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RESEARCH PUBLICATIONS

Publication Date: Sep 23, 2020

Furin inhibitors block SARS-CoV-2 spike protein cleavage to suppress virus production and cytopathic effects

Abstract

Development of specific antivirals is an urgent unmet need for SARS-coronavirus 2 (SARS-CoV-2) infections. This study focuses on host proteases that proteolytically activate the SARS-CoV-2 spike protein, critical for its fusion after binding to angiotensin-converting enzyme 2 (ACE2), as antiviral targets. We first validated cleavage at a putative furin substrate motif at SARS-CoV-2 spike by expressing it in VeroE6 cells and found prominent syncytium formation. Both cleavage and syncytium were abolished by treatment with furin inhibitors decanoyl-RVKR-chloromethylketone (CMK) and naphthofluorescein but not by transmembrane protease serine 2 (TMPRSS2) inhibitor camostat. CMK and naphthofluorescein showed antiviral effects in SARS-CoV-2-infected cells by decreasing viral production and cytopathic effects. Further analysis revealed that, similar to camostat, CMK blocks virus entry, but it further suppresses the cleavage of spike and syncytium. Naphthofluorescein instead acts primarily by suppressing viral RNA transcription. Therefore, furin inhibitors may become promising antivirals for prevention and treatment of SARS-CoV-2 infections.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31243-2

SARS-CoV-2 infection boosts MX1 antiviral effector in COVID-19 patients

Abstract

In a published case-control study (GSE152075) from SARS-CoV-2 positive (n=403) and negative patients (n=50), we analyzed the response to infection assessing gene expression of host cell receptors and antiviral proteins. The expression analysis associated with reported risk factors for COVID-19 was also assessed. SARS-CoV-2 cases had higher ACE2, but lower TMPRSS2, BSG/CD147 and CTSB expression compared with negative cases. COVID-19 patients' age negatively affected ACE2 expression. MX1 and MX2 were higher in COVID-19 patients. A negative trend for MX1 and MX2 was observed as patients' age increased. Principal Component Analysis determined that ACE2, MX1, MX2, and BSG/CD147 expression was able to cluster non-COVID-19 and COVID-19 individuals. Multivariable regression showed that MX1 expression significantly increased for each unit of viral load increment. Altogether, these findings support differences in ACE2, MX1, MX2, and BSG/CD147 expression between COVID-19 and non-COVID-19 patients and point out to MX1 as a critical responder in SARS-CoV-2 infection.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(20)30777-X

Performance characteristics of five immunoassays for SARS-CoV-2: A head-to-head benchmark comparison

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic in 2020. Testing is crucial for mitigating public health and economic effects. Serology is considered key to population-level surveillance and potentially individual-level risk assessment. However, immunoassay performance has not been compared on large, identical sample sets. We aimed to investigate the performance of four high-throughput commercial SARS-CoV-2 antibody immunoassays and a novel 384-well ELISA.

Methods: We did a head-to-head assessment of SARS-CoV-2 IgG assay (Abbott, Chicago, IL, USA), LIAISON SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Saluggia, Italy), Elecsys Anti-SARS-CoV-2 assay (Roche, Basel, Switzerland), SARS-CoV-2 Total assay (Siemens, Munich, Germany), and a novel 384-well ELISA (the Oxford immunoassay). We derived sensitivity and specificity from 976 pre-pandemic blood samples (collected between Sept 4, 2014, and Oct 4, 2016) and 536 blood samples from patients with laboratory-confirmed SARS-CoV-2 infection, collected at least 20 days post symptom onset (collected between Feb 1, 2020, and May 31, 2020). Receiver operating characteristic (ROC) curves were used to assess assay thresholds.

Findings: At the manufacturers' thresholds, for the Abbott assay sensitivity was 92·7% (95% CI 90·2–94·8) and specificity was 99·9% (99·4–100%); for the DiaSorin assay sensitivity was 95·0% (92·8–96·7) and specificity was 98·7% (97·7–99·3); for the Oxford immunoassay sensitivity was 99·1% (97·8–99·7) and specificity was 99·0% (98·1–99·5); for the Roche assay sensitivity was 97·2% (95·4–98·4) and specificity was 99·8% (99·3–100); and for the Siemens assay sensitivity was 98·1% (96·6–99·1) and specificity was 99·9% (99·4–100%). All assays achieved a sensitivity of at least 98% with thresholds optimised to achieve a specificity of at least 98% on samples taken 30 days or more post symptom onset.

Interpretation: Four commercial, widely available assays and a scalable 384-well ELISA can be used for SARS-CoV-2 serological testing to achieve sensitivity and specificity of at least 98%. The Siemens assay and Oxford immunoassay achieved these metrics without further optimisation. This benchmark study in immunoassay assessment should enable refinements of testing strategies and the best use of serological testing resource to benefit individuals and population health.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30634-4/fulltext

SARS-CoV-2 antibody prevalence in Brazil: Results from two successive nationwide serological household surveys

Abstract

Background: Population-based data on COVID-19 are essential for guiding policies. There are few such studies, particularly from low or middle-income countries. Brazil is currently a hotspot for COVID-19 globally. We aimed to investigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody prevalence by city and according to sex, age, ethnicity group, and socioeconomic status, and compare seroprevalence estimates with official statistics on deaths and cases.

Methods: In this repeated cross-sectional study, we did two seroprevalence surveys in 133 sentinel cities in all Brazilian states. We randomly selected households and randomly selected one individual from all household members. We excluded children younger than 1 year. Presence of antibodies against SARS-CoV-2 was assessed using a lateral flow point-of-care test, the WONDFO SARS-CoV-2 Antibody Test (Wondfo Biotech, Guangzhou, China), using two drops of blood from finger prick samples. This lateral-flow assay detects IgG and IgM isotypes that are specific to the SARS-CoV-2 receptor binding domain of the spike protein. Participants also answered short questionnaires on sociodemographic information (sex, age, education, ethnicity, household size, and household assets) and compliance with physical distancing measures.

Findings: We included 25 025 participants in the first survey (May 14–21) and 31 165 in the second (June 4–7). For the 83 (62%) cities with sample sizes of more than 200 participants in both surveys, the pooled seroprevalence increased from 1·9% (95% CI 1·7–2·1) to 3·1% (2·8–3·4). City-level prevalence ranged from 0% to 25·4% in both surveys. 11 (69%) of 16 cities with prevalence above 2·0% in the first survey were located in a stretch along a 2000 km of the Amazon river in the northern region. In the second survey, we found 34 cities with prevalence above 2·0%, which included the same 11 Amazon cities plus 14 from the northeast region, where prevalence was increasing rapidly. Prevalence levels were lower in the south and centre-west, and intermediate in the southeast, where the highest level was found in Rio de Janeiro (7·5% [4·2–12·2]). In the second survey, prevalence was similar in men and women, but an increased prevalence was observed in participants aged 20–59 years and those living in crowded

conditions (4·4% [3·5–5·6] for those living with households with six or more people). Prevalence among Indigenous people was 6·4% (4·1–9·4) compared with 1·4% (1·2–1·7) among White people. Prevalence in the poorest socioeconomic quintile was 3·7% (3·2–4·3) compared with 1·7% (1·4–2·2) in the wealthiest quintile.

Interpretation: Antibody prevalence was highly heterogeneous by country region, with rapid initial escalation in Brazil's north and northeast. Prevalence is strongly associated with Indigenous ancestry and low socioeconomic status. These population subgroups are unlikely to be protected if the policy response to the pandemic by the national government continues to downplay scientific evidence.

Reference

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30387-9/fulltext

Diagnosis of physical and mental health conditions in primary care during the COVID-19 pandemic: A retrospective cohort study

Abstract

Background: To date, research on the indirect impact of the COVID-19 pandemic on the health of the population and the health-care system is scarce. We aimed to investigate the indirect effect of the COVID-19 pandemic on general practice health-care usage, and the subsequent diagnoses of common physical and mental health conditions in a deprived UK population.

Methods: A retrospective cohort study was done using routinely collected primary care data that was recorded in the Salford Integrated Record between Jan 1, 2010, and May 31, 2020. We extracted the weekly number of clinical codes entered into patient records overall, and for six high-level categories: symptoms and observations, diagnoses, prescriptions, operations and procedures, laboratory tests, and other diagnostic procedures. Negative binomial regression models were applied to monthly counts of first diagnoses of common conditions (common mental health problems, cardiovascular and cerebrovascular disease, type 2 diabetes, and cancer), and corresponding first prescriptions of medications indicative of these conditions. We used these models to predict the expected numbers of first diagnoses and first prescriptions between March 1

and May 31, 2020, which were then compared with the observed numbers for the same time period.

Findings: Between March 1 and May 31, 2020, 1073 first diagnoses of common mental health problems were reported compared with 2147 expected cases (95% CI 1821 to 2489) based on preceding years, representing a 50·0% reduction (95% CI 41·1 to 56·9). Compared with expected numbers, 456 fewer diagnoses of circulatory system diseases (43·3% reduction, 95% CI 29·6 to 53·5), and 135 fewer type 2 diabetes diagnoses (49·0% reduction, 23·8 to 63·1) were observed. The number of first prescriptions of associated medications was also lower than expected for the same time period. However, the gap between observed and expected cancer diagnoses (31 fewer; 16·0% reduction, −18·1 to 36·6) during this time period was not statistically significant.

Interpretation: In this deprived urban population, diagnoses of common conditions decreased substantially between March and May 2020, suggesting a large number of patients have undiagnosed conditions. A rebound in future workload could be imminent as COVID-19 restrictions ease and patients with undiagnosed conditions or delayed diagnosis present to primary and secondary health-care services. Such services should prioritise the diagnosis and treatment of these patients to mitigate potential indirect harms to protect public health.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30201-2/fulltext

Pharmacological and cardiovascular perspectives on the treatment of COVID-19 with chloroquine derivatives

Abstract

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and an ongoing severe pandemic. Curative drugs specific for COVID-19 are currently lacking. Chloroquine phosphate and its derivative hydroxychloroquine, which have been used in the treatment and prevention of malaria and autoimmune diseases for decades, were found to inhibit SARS-CoV-2 infection with high potency in vitro and have shown clinical and virologic benefits in COVID-19 patients.

Therefore, chloroquine phosphate was first used in the treatment of COVID-19 in China. Later, under a limited emergency-use authorization from the FDA, hydroxychloroquine in combination with azithromycin was used to treat COVID-19 patients in the USA, although the mechanisms of the anti-COVID-19 effects remain unclear. Preliminary outcomes from clinical trials in several countries have generated controversial results. The desperation to control the pandemic overrode the concerns regarding the serious adverse effects of chloroquine derivatives and combination drugs, including lethal arrhythmias and cardiomyopathy. The risks of these treatments have become more complex as a result of findings that COVID-19 is actually a multisystem disease. While respiratory symptoms are the major clinical manifestations, cardiovascular abnormalities, including arrhythmias, myocarditis, heart failure, and ischemic stroke, have been reported in a significant number of COVID-19 patients. Patients with preexisting cardiovascular conditions (hypertension, arrhythmias, *etc.*) are at increased risk of severe COVID-19 and death. From pharmacological and cardiovascular perspectives, therefore, the treatment of COVID-19 with chloroquine and its derivatives should be systematically evaluated, and patients should be routinely monitored for cardiovascular conditions to prevent lethal adverse events.

Reference

https://www.nature.com/articles/s41401-020-00519-x

Massive and rapid COVID-19 testing is feasible by extraction-free SARS-CoV-2 RT-PCR

Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is commonly diagnosed by reverse transcription polymerase chain reaction (RT-PCR) to detect viral RNA in patient samples, but RNA extraction constitutes a major bottleneck in current testing. Methodological simplification could increase diagnostic availability and efficiency, benefitting patient care and infection control. Here, we describe methods circumventing RNA extraction in COVID-19 testing by performing RT-PCR directly on heat-inactivated or lysed samples. Our data, including benchmarking using 597 clinical patient samples and a standardised diagnostic system,

demonstrate that direct RT-PCR is viable option to extraction-based tests. Using controlled amounts of active SARS-CoV-2, we confirm effectiveness of heat inactivation by plaque assay and evaluate various generic buffers as transport medium for direct RT-PCR. Significant savings in time and cost are achieved through RNA-extraction-free protocols that are directly compatible with established PCR-based testing pipelines. This could aid expansion of COVID-19 testing.

Reference

https://www.nature.com/articles/s41467-020-18611-5

Publication Date: Sep 22, 2020

Genetic lesions of type I interferon signalling in human antiviral immunity

Abstract

Inborn errors of immunity affecting all key molecular components of the interferon (IFN)-I signalling pathway [IFN-alpha/beta receptor (IFNAR)1, IFNAR2, Janus kinase 1 (JAK1), tyrosine kinase 2 (TYK2), signal transducer and activator of transcription (STAT)1, STAT2, and interferon regulatory factor 9 (IRF9)] have been identified in humans.

Deficiency of IFNAR results in potentially fatal susceptibility to live-attenuated viral vaccines, but without general susceptibility to common childhood viral diseases. Clinically evident vulnerability to a broader spectrum of viral diseases, including respiratory viruses such as influenza as well as live-attenuated viral vaccines, often accompanies deficiency of STAT2 and IRF9. These molecules transduce signals downstream of IFN-I and IFN-III, suggesting that the latter provides compensatory antiviral defence in IFNAR-deficient patients. Children with defects in IFN-I and IFN-III signalling are not particularly susceptible to viruses such as cytomegalovirus (CMV), suggesting that this virus has successfully evolved mechanisms to overcome IFN-I/III restriction.

STAT1-deficient patients, who lack signalling in response to all types of IFN (I, II, and III), show the widest viral susceptibility of all. Pathological dissemination of parenterally delivered live-viral vaccines in otherwise healthy children should signify an inborn error of IFN-I immunity until proved otherwise. The concept that type I interferons (IFN-I) are

essential to antiviral immunity derives from studies on animal models and cell lines. Virtually all pathogenic viruses have evolved countermeasures to IFN-I restriction, and genetic loss of viral IFN-I antagonists leads to virus attenuation. But just how important is IFN-I to antiviral defence in humans? The recent discovery of genetic defects of IFN-I signalling illuminates this and other questions of IFN biology, including the role of the mucosa-restricted type III IFNs (IFN-III), informing our understanding of the place of the IFN system within the concerted antiviral response. Here we review monogenic lesions of IFN-I signalling pathways and summarise the organising principles which emerge.

Reference

https://www.cell.com/trends/genetics/fulltext/S0168-9525(20)30231-6

Short-term and long-term health impacts of air pollution reductions from COVID-19 lockdowns in China and Europe: A modelling study

Abstract

Background: Exposure to poor air quality leads to increased premature mortality from cardiovascular and respiratory diseases. Among the far-reaching implications of the ongoing COVID-19 pandemic, a substantial improvement in air quality was observed worldwide after the lockdowns imposed by many countries. We aimed to assess the implications of different lockdown measures on air pollution levels in Europe and China, as well as the short-term and long-term health impact.

Methods: For this modelling study, observations of fine particulate matter (PM2·5) concentrations from more than 2500 stations in Europe and China during 2016–20 were integrated with chemical transport model simulations to reconstruct PM2·5 fields at high spatiotemporal resolution. The health benefits, expressed as short-term and long-term avoided mortality from PM2·5 exposure associated with the interventions imposed to control the COVID-19 pandemic, were quantified on the basis of the latest epidemiological studies. To explore the long-term variability in air quality and associated premature mortality, we built different scenarios of economic recovery (immediate or gradual resumption of activities, a second outbreak in autumn, and permanent lockdown for the whole of 2020).

Findings: The lockdown interventions led to a reduction in population-weighted PM2·5 of 14·5 μg m−3 across China (−29·7%) and 2·2 μg m−3 across Europe (−17·1%), with unprecedented reductions of 40 μg m−3 in bimonthly mean PM2·5 in the areas most affected by COVID-19 in China. In the short term, an estimated 24 200 (95% CI 22 380–26 010) premature deaths were averted throughout China between Feb 1 and March 31, and an estimated 2190 (1960–2420) deaths were averted in Europe between Feb 21 and May 17. We also estimated a positive number of long-term avoided premature fatalities due to reduced PM2·5 concentrations, ranging from 76 400 (95% CI 62 600–86 900) to 287 000 (233 700–328 300) for China, and from 13 600 (11 900–15 300) to 29 500 (25 800–33 300) for Europe, depending on the future scenarios of economic recovery adopted.

Interpretation: These results indicate that lockdown interventions led to substantial reductions in PM2·5 concentrations in China and Europe. We estimated that tens of thousands of premature deaths from air pollution were avoided, although with significant differences observed in Europe and China. Our findings suggest that considerable improvements in air quality are achievable in both China and Europe when stringent emission control policies are adopted.

Reference

https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(20)30224-2/fulltext

Determinants of the outcomes of patients with cancer infected with SARS-CoV-2: Results from the Gustave Roussy cohort

Abstract

Patients with cancer are presumed to be at increased risk of severe COVID-19 outcomes due to underlying malignancy and treatment-induced immunosuppression. Of the first 178 patients managed for COVID-19 at the Gustave Roussy Cancer Centre, 125 (70.2%) were hospitalized, 47 (26.4%) developed clinical worsening and 31 (17.4%) died. An age of over 70 years, smoking status, metastatic disease, cytotoxic chemotherapy and an Eastern Cooperative Oncology Group score of ≥2 at the last visit were the strongest determinants of increased risk of death. In multivariable analysis, the Eastern Cooperative Oncology Group score remained the only predictor of death. In contrast, immunotherapy,

hormone therapy and targeted therapy did not increase clinical worsening or death risk. Biomarker studies found that C-reactive protein and lactate dehydrogenase levels were significantly associated with an increased risk of clinical worsening, while C-reactive protein and D-dimer levels were associated with an increased risk of death. COVID-19 management impacted the oncological treatment strategy, inducing a median 20 d delay in 41% of patients and adaptation of the therapeutic strategy in 30% of patients.

Reference

https://www.nature.com/articles/s43018-020-00120-5

Serum inflammatory factors are positively correlated with the production of specific antibodies in coronavirus disease 2019 patients

Abstract

The ongoing spread of coronavirus disease 2019 (COVID-19) constitutes an international concern on an unprecedented scale. To date, over 23 million people have been diagnosed with COVID-19 worldwide, and this disease has caused more than 800,000 deaths. Hyperinflammation elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported to contribute to illness severity and death. Humoral immune responses play important roles in therapy and prophylaxis for SARS-CoV-2 infection. Since the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S) glycoprotein binds to angiotensin-converting enzyme 2 to trigger virion endocytosis, antibodies against this domain may be able to neutralize SARS-CoV-2 and possibly provide protective immunity in COVID-19 patients Clinical trials investigating the administration of convalescent plasma and the interleukin (IL)-6 antagonist tocilizumab to treat COVID-19 patients are currently underway, but the overly robust expansion of antibody-secreting cells (ASCs) could play a major role in the pathogenicity of SARS-CoV-2 in COVID-19 patients. Thus, a detailed characterization of the associations between humoral immune responses and inflammatory factors could result in a better understanding of SARS-CoV-2-host interactions in COVID-19 patients.

In the current study, the levels of RBD-specific IgG, RBD-specific IgA, and the frequencies of ASCs and ICOS+ T follicular helper (TFH) cells were found to be higher in severely affected COVID-19 patients than those in nonseverely affected patients. Follow-up

analysis of COVID-19 patients demonstrated that humoral immune responses were positively correlated with the levels of IL-6, C-X-C motif chemokine 10 (CXCL10), and C5a. Positive correlations between the serum CXCL13 level and the levels of IL-6 and CXCL10 were also noted in COVID-19 patients. Taken together, these results indicate that there is a close relationship between humoral immunity and inflammatory factors, and the generation of protective humoral immunity could be a double-edged sword in COVID-19 patients.

Reference

https://www.nature.com/articles/s41423-020-00551-1

Publication Date: Sep 21, 2020

Human pluripotent stem cell-derived neural cells and brain organoids reveal SARS-COV-2 neurotropism predominates in choroid plexus epithelium

Abstract

Neurological complications are common in patients with COVID-19. While SARS-CoV-2, the causal pathogen of COVID-19, has been detected in some patient brains, its ability to infect brain cells and impact their function are not well understood. Here we investigated the susceptibility of human induced pluripotent stem cell (hiPSC)-derived monolayer brain cells and region-specific brain organoids to SARS-CoV-2 infection. We found that neurons and astrocytes were sparsely infected, but choroid plexus epithelial cells underwent robust infection. We optimized a protocol to generate choroid plexus organoids from hiPSCs and showed that productive SARS-CoV-2 infection of these organoids is associated with increased cell death and transcriptional dysregulation indicative of an inflammatory response and cellular function deficits. Together, our findings provide evidence for selective SARS-CoV-2 neurotropism and support the use of hiPSC-derived brain organoids as a platform to investigate SARS-CoV-2 infection susceptibility of brain cells, mechanisms of virus-induced brain dysfunction, and treatment strategies.

Reference

https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(20)30463-X

Oral SARS-CoV-2 inoculation establishes subclinical respiratory infection with virus shedding in golden Syrian hamsters

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted largely by respiratory droplets or airborne aerosols. Despite being frequently found in the immediate environment and faeces of patients, evidence supporting oral acquisition of SARS-CoV-2 is unavailable. Utilizing Syrian hamster model, we demonstrate that the severity of pneumonia induced by intranasal inhalation of SARS-CoV-2 increases with virus inoculum. SARS-CoV-2 retains its infectivity in vitro in simulated human fed-gastric and fasted-intestinal fluid after two hours. Oral inoculation with the highest intranasal inoculum(105PFU) causes mild pneumonia in 67% (4/6) of the animals with no weight loss. The lung histopathology score and viral load are significantly lower than those infected by the lowest intranasal inoculum(100PFU). However, 83% oral infection (10/12 hamsters) have similar level of detectable viral shedding from oral swabs and faeces as that of intranasally infected hamsters. Our findings indicate oral acquisition of SARS-CoV-2 can establish subclinical respiratory infection with less efficiency.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30163-4

The characteristics of COVID-19 transmission from case to high-risk contact, a statistical analysis from contact tracing data

Abstract

Background: As of 24th of August 2020, the number of global COVID-19 confirmed cases is nearly 24 million. In the same period, the number of recorded infections in Thailand has remained at approximately 3300. This paper explores the specifics of COVID-19 or SARS-CoV-2 transmissions in Phuket, Thailand's second most visited tourist destination

Methods: High-risk contacts recorded by Phuket Provincial Public Health Office were analysed using the Probit model to investigate the risk factors for transmission from confirmed COVID-19 cases to their high-risk contacts. The analysis was further focused

on the impact of quarantine measures in state provided facilities on contacts' probability of infection.

Findings: 15.6% of 1108 high-risk contacts were found to be infected, and they accounted for 80% of 214 confirmed cases in Phuket till 29th April 2020. Moreover, 10.68% of all high-risk contacts were confirmed to be infected before the quarantine, and 4.55% after the policy was enforced. In addition, a contact who lived within the same household with a confirmed case was 25% more exposed to infection when compared to a contact who did not share a household.

Interpretation: Results confirmed that the quarantine policy, which mandated individual isolation in the state provided facilities for all high-risk contacts, diminished contact's chance of infection from the confirmed cases, especially in the epicenter districts. Our findings confirmed that sharing accommodation with an infected case, and exposure to a case with several documented secondary transmission, generally increased the SARS-CoV-2 infection probability. Finally, some confirmed cases do exhibit a higher risk of spreading SARS-CoV-2 to their contacts compared to a typical confirmed case. Further studies of high reproduction groups of infected patients are recommended.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30287-X/fulltext

Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years

Abstract

The future trajectory of the Covid-19 pandemic hinges on the dynamics of adaptive immunity against SARS-CoV2; however, salient features of the immune response elicited by natural infection or vaccination are still uncertain. We use simple epidemiological models to explore estimates for the magnitude and timing of future Covid-19 cases given different protective efficacy and duration of the adaptive immune response to SARS-CoV-2, as well as its interaction with vaccines and nonpharmaceutical interventions. We find that variations in the immune response to primary SARS-CoV-2 infections and a potential vaccine can lead to dramatically different immune landscapes and burdens of critically

severe cases, ranging from sustained epidemics to near elimination. Our findings illustrate likely complexities in future Covid-19 dynamics, and highlight the importance of immunological characterization beyond the measurement of active infections for adequately projecting the immune landscape generated by SARS-CoV-2 infections.

Reference

https://science.sciencemag.org/content/early/2020/09/18/science.abd7343?rss=1

COVID-19 image classification using deep features and fractional-order marine predators algorithm

Abstract

Currently, the severe spread of the pandemic of the new Corona virus, COVID-19 was witnessed, which causes dangerous symptoms to humans and animals, its complications may lead to death. Although convolutional neural networks (CNNs) is considered the current state-of-the-art image classification technique, it needs massive computational cost for deployment and training. In this paper, an improved hybrid classification approach was proposed for COVID-19 images by combining the strengths of CNNs (using a powerful architecture called Inception) to extract features and a swarm-based feature selection algorithm (Marine Predators Algorithm) to select the most relevant features. A combination of fractional-order and marine predators algorithm (FO-MPA) is considered an integration among a robust tool in mathematics named fractional-order calculus (FO). The proposed approach was evaluated on two public COVID-19 X-ray datasets which achieves both high performance and reduction of computational complexity. The two datasets consist of X-ray COVID-19 images by international Cardiothoracic radiologist, researchers and others published on Kaggle. The proposed approach selected successfully 130 and 86 out of 51 K features extracted by inception from dataset 1 and dataset 2, while improving classification accuracy at the same time. The results are the best achieved on these datasets when compared to a set of recent feature selection algorithms. By achieving 98.7%, 98.2% and 99.6%, 99% of classification accuracy and F-Score for dataset 1 and dataset 2, respectively, the proposed approach outperforms several CNNs and all recent works on COVID-19 images.

Reference

https://www.nature.com/articles/s41598-020-71294-2

Circulating levels of soluble Dipeptidylpeptidase-4 are reduced in human subjects hospitalized for severe COVID-19 infections

Abstract

Dipeptidylpeptidase (DPP)-4 is a key regulator of the incretin system. For several years DPP-4 inhibitors in addition to GLP-1 analogues are of major importance in the clinical management of obesity and type 2 diabetes. DPP-4 is also known as CD26 and represents a membrane bound protease on the surface of several eukaryotic cell types. Of interest, DPP-4, like ACE2, has been shown to serve as a binding partner for corona-like viruses to enter host immune cells. Since metabolic diseases are major risk factors for the present COVID-19 pandemic, we examined circulating soluble DPP-4 serum concentrations in patients suffering from severe COVID-19 infection and in healthy human subjects in a case control design. In this analysis sDPP-4 levels were significantly lower in COVID-19 patients compared to controls (242.70 ± 202.12 ng/mL versus 497.70 ± 188.13 ng/mL, $p = 0.02$). We also examined sDPP-4 serum concentrations in patients suffering from sepsis not due to corona-like viruses. In these subjects, sDPP-4 levels were not different compared to healthy case controls ($p = 0.14$), which might suggest the decrease of sDPP-4 to be specific for corona-like virus infections. Currently, most data point towards membrane bound ACE2 in contrast to DPP-4 as the major binding partner for COVID-19 internalization into host immune cells. However, the finding that the circulating soluble form of DPP-4 is reduced in hospitalized patients might suggest a regulatory role for both, ACE and DPP-4, in COVID-19 infections, especially since obesity and type 2 diabetes are major risk factor for a severe course of the disease.

Reference

https://www.nature.com/articles/s41366-020-00689-y

Publication Date: Sep 20, 2020

Retinal findings in patients with COVID-19: Results from the SERPICO-19 study

Abstract

Background: Coronavirus disease 2019 (COVID-19) has been associated to microvascular alterations. We screened the fundus of patients with COVID-19 to detect alterations of the retina and its vasculature and to assess possible correlations with clinical parameters.

Methods: Cross-sectional study. The presence of retinal alterations in patients with COVID-19 and subjects unexposed to the virus was assessed using fundus photographs and their prevalence was compared. Mean arteries diameter (MAD) and mean veins diameter (MVD) were compared between patients and unexposed subjects with multiple linear regression including age, sex, ethnicity, body mass index, smoking/alcohol consumption, hypertension, hyperlipidaemia, diabetes as covariates. The influence of clinical/lab parameters on retinal findings was tested in COVID-19 patients.

Findings: 54 patients and 133 unexposed subjects were enrolled. Retinal findings in COVID-19 included: haemorrhages (9·25%), cotton wools spots (7·4%), dilated veins (27·7%), tortuous vessels (12·9%). Both MAD and MVD were higher in COVID-19 patients compared to unexposed subjects (98·3 ± 15·3 μm vs 91·9 ± 11·7 μm, p = 0.006 and 138·5 ± 21·5 μm vs 123·2 ± 13·0 μm, p<0.0001, respectively). In multiple regression accounting for covariates MVD was positively associated with COVID-19 both in severe (coefficient 30·3, CI95% 18·1–42·4) and non-severe (coefficient 10·3, CI95% 1·6–19·0) cases compared to unexposed subjects. In COVID-19 patients MVD was negatively correlated with the time from symptoms onset (coefficient −1·0, CI 95% −1·89 to −0·20) and positively correlated with disease severity (coefficient 22·0, CI 95% 5·2–38·9).

Interpretation: COVID-19 can affect the retina. Retinal veins diameter seems directly correlated with the disease severity. Its assessment could have possible applications in the management of COVID-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30294-7/fulltext

An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19

Abstract

Background: Epidemic outbreaks caused by SARS-CoV-2 are worsening around the world, and there are no target drugs to treat COVID-19. IFN-κ inhibits the replication of SARS-CoV-2; and TFF2 is a small secreted polypeptide that promotes the repair of mucosal injury and reduces the inflammatory responses. We used the synergistic effect of both proteins to treat COVID-19.

Methods: An open-label, randomized, clinical trial involving patients with moderate COVID-19 was conducted. Patients were assigned in a 1:1 ratio to receive either aerosol inhalation treatment with IFN-κ and TFF2 every 24 h for six consecutive dosages in addition to standard care (experimental group) or standard care alone (control group). The primary endpoint was the time until a viral RNA negative conversion for SARS-CoV-2 in all clinical samples. The secondary clinical endpoint was the time of CT imaging improvement. Data analysis was performed per protocol. This study was registered with chictr.org.cn, ChiCTR2000030262.

Findings: Between March 23 and May 23 of 2020, 86 COVID-19 patients with symptoms of moderate illness were recruited, and 6 patients were excluded due to not matching the inclusion criteria (patients with pneumonia through chest radiography). Among the remaining 80 patients, 40 patients were assigned to experimental group, and the others were assigned to control group to only receive standard care. Efficacy and safety were evaluated for both groups. The time of viral RNA negative conversion in experimental group (Mean, 3·80 days, 95% CI 2·07–5·53), was significantly shorter than that in control group (7·40 days, 95% CI 4·57 to 10·23) (p = 0.031), and difference between means was 3·60 days. The percentage of patients in experimental group with reversion to negative viral RNA was significantly increased compared with control group on all sampling days (every day during the 12-day observation period) (p = 0·037). For the secondary endpoint, the experimental group had a significantly shorter time until improvement was seen by CT (Mean 6·21 days, N = 38/40, 95% CI 5·11–7·31) than that in control group (8·76 days, N = 34/40, 95% CI 7·57–9·96) (p = 0.002), and difference between means was 2·55 days.

No discomfort or complications during aerosol inhalation were reported to the nurses by any experimental patients.

Interpretation: In conclusion, it is found that aerosol inhalation of IFN-κ plus TFF2 in combination with standard care is safe and superior to standard care alone in shortening the time up to viral RNA negative conversion in all clinical samples. In addition, the patients in experimental group had a significantly shortened CT imaging improvement time than those in control group. This study suggested that this combination treatment is able to facilitate clinical improvement (negative for virus, improvement by CT, reduced hospitalization stay) and thereby result in an early release from the hospital. These data support the need for exploration with a large-scale trial of IFN-κ plus TFF2 to treat COVID-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30291-1/fulltext

The spectrum of biochemical alterations associated with organ dysfunction and inflammatory status and their association with disease outcomes in severe COVID-19: A longitudinal cohort and time-series design study

Abstract

Background: In patients with severe COVID-19, no data are available on the longitudinal evolution of biochemical abnormalities and their ability to predict disease outcomes.

Methods: Using a retrospective, longitudinal cohort study design on consecutive patients with severe COVID-19, we used an extensive biochemical dataset of serial data and time-series design to estimate the occurrence of organ dysfunction and the severity of the inflammatory reaction and their association with acute respiratory failure (ARF) and death.

Findings: On the 162 studied patients, 1151 biochemical explorations were carried out for up to 59 biochemical markers, totaling 15,260 biochemical values. The spectrum of biochemical abnormalities and their kinetics were consistent with a multi-organ involvement, including lung, kidney, heart, liver, muscle, and pancreas, along with a severe inflammatory syndrome. The proportion of patients who developed an acute

kidney injury (AKI) stage 3, increased significantly during follow-up (0·9%, day 0; 21·4%, day 14; *P*<0·001). On the 20 more representative biochemical markers (>250 iterations), only CRP >90 mg/L (odds ratio [OR] 6·87, 95% CI, 2·36–20·01) and urea nitrogen >0·36 g/L (OR 3·91, 95% CI, 1·15–13·29) were independently associated with the risk of ARF. Urea nitrogen >0·42 g/L was the only marker associated with the risk of COVID-19 related death.

Interpretation: The results point out the lack of the association between the inflammatory markers and the risk of death but rather highlight a significant association between renal dysfunction and the risk of COVID-19 related acute respiratory failure and death.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30298-4/fulltext

Publication Date: Sep 19, 2020

Evasion of type-I interferon by SARS-CoV-2

Abstract

The coronavirus disease 2019 (COVID-19) is determined by SARS-CoV-2 replication and host immune response, but studies evaluating viral evasion of immune response are lacking. Here we employed unbiased screening to identify SARS-CoV-2 proteins that antagonize type-I interferon (IFN-I) response. Three proteins were found to antagonize IFN-I production via distinct mechanisms: nsp6 binds TBK1 to suppress IRF3 phosphorylation; nsp13 binds and blocks TBK1 phosphorylation; and ORF6 binds importin KPNA2 to inhibit IRF3 nuclear translocation. Two sets of viral proteins were identified to antagonize IFN-I signaling through blocking STAT1/STAT2 phosphorylation or nuclear translocation. Remarkably, SARS-CoV-2 nsp1 and nsp6 suppressed IFN-I signaling more efficiently than SARS-CoV and MERS-CoV. Thus, when treated with IFN-I, a SARS-CoV2 replicon replicated to a higher level than chimeric replicons containing nsp1 or nsp6 from SARS-CoV or MERS-CoV. Altogether, the study has provided insights on SARS-CoV-2 evasion of IFN-I response and its potential impact on viral transmission and pathogenesis.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31223-7

A SARS-CoV-2 host infection model network based on genomic Human Transcription Factors (TFs) depletion

Abstract

In December 2019 a new beta-coronavirus was isolated and characterized by sequencing samples from pneumonia patients in Wuhan, Hubei Province, China. Coronaviruses are positive-sense RNA viruses widely distributed among different animal species and humans in which they cause respiratory, enteric, liver and neurological symptomatology. Six species of coronavirus have been described (HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1) that cause cold-like symptoms in immunocompetent or immunocompromised subjects and two strains of sometimes fatal zoonotic origin that cause severe acute respiratory syndrome (SARS-CoV and MERS-CoV).The SARS-CoV-2 strain is the emerging seventh member of the coronavirus family, which is actually determining a global emergency.

In silico analysis is a promising approach for understanding biological events in complex diseases and due to serious worldwide emergency and serious threat to global health, it is extremely important to use bioinformatics methods able to study an emerging pathogen like SARS-CoV-2. Herein, we report on in silico comparative analysis between complete genome of SARS-CoV, MERS-CoV, HCoV-OC43 and SARS-CoV-2 strains, to identify the occurrence of specific conserved motifs on viral genomic sequences which should be able to bind and therefore induce a subtraction of host's Transcription Factors (TFs) which lead to a depletion, an effect comparable to haploinsufficiency (a genetic dominant condition in which a single copy of wild-type allele at a locus, in heterozygous combination with a variant allele, is insufficient to produce the correct quantity of transcript and, therefore, of protein, for a correct standard phenotypic expression).

In this competitive scenario, virus versus host, the proposed *in silico* protocol identified the TFs same as the distribution of TFBSs (Transcription Factor Binding Sites) on analyzed viral strains, potentially able to influence genes and pathways with biological functions confirming that this approach could brings useful insights regarding SARS-CoV-

2. According to our results obtained by this in silico approach it is possible to hypothesize that TF-binding motifs could be of help in the explanation of the complex and heterogeneous clinical presentation in SARS-CoV-2 and subsequently predict possible interactions regarding metabolic pathways, and drug or target relationships.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)31853-3

Publication Date: Sep 18, 2020

SARS-CoV-2 infection of pluripotent stem cell-derived human lung alveolar type 2 cells elicits a rapid epithelial-intrinsic inflammatory response

Abstract

A hallmark of severe COVID-19 pneumonia is SARS-CoV-2 infection of the facultative progenitors of lung alveoli, the alveolar epithelial type 2 cells (AT2s). However, inability to access these cells from patients, particularly at early stages of disease, limits an understanding of disease inception. Here we present an in vitro human model that simulates the initial apical infection of alveolar epithelium with SARS-CoV-2, using induced pluripotent stem cell-derived AT2s that have been adapted to air-liquid interface culture. We find a rapid transcriptomic change in infected cells, characterized by a shift to an inflammatory phenotype with upregulation of NF-kB signaling and loss of the mature alveolar program. Drug testing confirms the efficacy of remdesivir as well as TMPRSS2 protease inhibition, validating a putative mechanism used for viral entry in alveolar cells. Our model system reveals cell-intrinsic responses of a key lung target cell to SARS-CoV-2 infection and should facilitate drug development.

Reference

Huang, Jessie, Adam J. Hume, Kristine M. Abo, Rhiannon B. Werder, Carlos Villacorta-Martin, Konstantinos-Dionysios Alysandratos, Mary Lou Beermann et al. "SARS-CoV-2 Infection of Pluripotent Stem Cell-derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response." *Cell Stem Cell* (2020). https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(20)30459-8 (I.F.: 20.860).

Artificial intelligence in COVID-19 drug repurposing

Abstract

Drug repurposing or repositioning is a technique whereby existing drugs are used to treat emerging and challenging diseases, including COVID-19. Drug repurposing has become a promising approach because of the opportunity for reduced development timelines and overall costs. In the big data era, artificial intelligence (AI) and network medicine offer cutting-edge application of information science to defining disease, medicine, therapeutics, and identifying targets with the least error. In this Review, we introduce guidelines on how to use AI for accelerating drug repurposing or repositioning, for which AI approaches are not just formidable but are also necessary. We discuss how to use AI models in precision medicine, and as an example, how AI models can accelerate COVID-19 drug repurposing. Rapidly developing, powerful, and innovative AI and network medicine technologies can expedite therapeutic development. This Review provides a strong rationale for using AI-based assistive tools for drug repurposing medications for human disease, including during the COVID-19 pandemic.

Reference

Zhou, Yadi, Fei Wang, Jian Tang, Ruth Nussinov, and Feixiong Cheng. "Artificial intelligence in COVID-19 drug repurposing." *The Lancet Digital Health* (2020). https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30192-8/fulltext (I.F.: 5.03).

Predictive factors for a new positive nasopharyngeal swab among patients recovered from COVID-19

Abstract

Introduction: As an emerging infectious disease, the clinical and virologic course of coronavirus disease 2019 (COVID-19) require better investigation. The aim of the present study is to identify potential risk factors associated with persistent positive nasopharyngeal swab real-time reverse transcription polymerase chain reaction (RT-PCR) tests in a large sample of patients who recovered from COVID-19.

Methods: After the acute phase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic infection, the Fondazione Policlinico A. Gemelli IRCSS of Rome established a post-acute care service for patients discharged from the hospital and recovered from COVID-19. Between April 21 and May 21, 2020, a total of 137 individuals who officially recovered from COVID-19 were enrolled in the present study. All patients were tested for the SARS-CoV-2 virus with nucleic acid RT-PCR tests. Analysis was conducted in June 2020.

Results: Of the 131 patients who repeated the nasopharyngeal swab, 22 patients (16.7%) tested positive again. Some symptoms such as fatigue (51%), dyspnea (44%), and coughing (17%) were still present in a significant percentage of patients, with no difference between patients with a negative test compared to those who tested positive. The likelihood of testing positive for SARS-CoV-2 infection was significantly higher among participants with persistent sore throat (prevalence ratio=6.50, 95% CI=1.38, 30.6) and symptoms of rhinitis (prevalence ratio=3.72, 95% CI=1.10, 12.5).

Conclusions: This study is the first to provide a given rate of patients (16.7%) who test positive on RT-PCR test for SARS-CoV-2 nucleic acid after recovering from COVID-19. These findings suggest that a significant proportion of recovered COVID-19 patients still could be potential carriers of the virus. In particular, if patients continue to have symptoms related to COVID-19, such as sore throat and rhinitis, it is reasonable to be cautious by avoiding close contact, wearing a face mask, and possibly repeating a nasopharyngeal swab.

Reference

Landi, Francesco, Angelo Carfi, Francesca Benvenuto, Bradi Vincenzo, Francesca Ciciarello, Maria Rita Lo Monaco, Anna Maria Martone et al. "Predictive Factors for a New Positive Nasopharyngeal Swab Among Patients Recovered From COVID-19." American *Journal of Preventive Medicine* (2020). https://www.sciencedirect.com/science/article/pii/S0749379720303937 (I.F.: 4.527).

Ultrasensitive high-resolution profiling of early seroconversion in patients with COVID-19

Abstract

Sensitive assays are essential for the accurate identification of individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Here, a multiplexed assay was reported for the fluorescence-based detection of seroconversion in infected individuals from less than 1 μl of blood, and as early as the day of the first positive nucleic acid test after symptom onset. The assay uses dye-encoded antigen-coated beads to quantify the levels of immunoglobulin G (IgG), IgM and IgA antibodies against four SARS-CoV-2 antigens. A logistic regression model trained using samples collected during the pandemic and samples collected from healthy individuals and patients with respiratory infections before the first outbreak of coronavirus disease 2019 (COVID-19) was 99% accurate in the detection of seroconversion in a blinded validation cohort of samples collected before the pandemic and from patients with COVID-19 five or more days after a positive nasopharyngeal test by PCR with reverse transcription. The high-throughput serological profiling of patients with COVID-19 allows for the interrogation of interactions between antibody isotypes and viral proteins, and should help us to understand the heterogeneity of clinical presentations.

Reference

Norman, Maia, Tal Gilboa, Alana F. Ogata, Adam M. Maley, Limor Cohen, Evan L. Busch, Roey Lazarovits et al. "Ultrasensitive high-resolution profiling of early seroconversion in patients with COVID-19." *Nature Biomedical Engineering* (2020): 1-8. https://www.nature.com/articles/s41551-020-00611-x (I.F.: 10.87).

The role of CARDPC in response to COVID-19 in primary care in China

Abstract

COVID-19 is wreaking havoc around the world, which is a serious challenge to all our health systems. China reacted quickly in the early stage of the pandemic, and accumulated a lot of experiences, especially in the prevention and control of COVID-19 at the primary care level. Here, we would like to share how the Chinese Alliance for

Respiratory Diseases in Primary Care (CARDPC) played a role in the pandemic, hoping to provide guidance and hope for effective control of the outbreak worldwide, for future public health emergencies and for systematic management of chronic respiratory diseases in the community.

Reference

Pan, Zihan, Ting Yang, Chunhua Chi, and Chen Wang. "The role of CARDPC in response to COVID-19 in primary care in China." *npj Primary Care Respiratory Medicine* 30, no. 1 (2020): 1-4. https://www.nature.com/articles/s41533-020-00199-4 (I.F.: 2.650).

Publication Date: Sep 17, 2020

Assessing a novel, lab-free, point-of-care test for SARS-CoV-2 (CovidNudge): A diagnostic accuracy study

Abstract

Background: Access to rapid diagnosis is key to the control and management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Laboratory RT-PCR testing is the current standard of care but usually requires a centralised laboratory and significant infrastructure. The diagnostic accuracy assessment of a novel, rapid point-of-care real time RT-PCR CovidNudge test was described, which requires no laboratory handling or sample pre-processing.

Methods: Between April and May, 2020, we obtained two nasopharyngeal swab samples from individuals in three hospitals in London and Oxford (UK). Samples were collected from three groups: self-referred health-care workers with suspected COVID-19; patients attending emergency departments with suspected COVID-19; and hospital inpatient admissions with or without suspected COVID-19. For the CovidNudge test, nasopharyngeal swabs were inserted directly into a cartridge which contains all reagents and components required for RT-PCR reactions, including multiple technical replicates of seven SARS-CoV-2 gene targets (rdrp1, rdrp2, e-gene, n-gene, n1, n2 and n3) and human ribonuclease P (RNaseP) as sample adequacy control. Swab samples were tested in parallel using the CovidNudge platform, and with standard laboratory RT-PCR using swabs in viral transport medium for processing in a central laboratory. The primary

analysis was to compare the sensitivity and specificity of the point-of-care CovidNudge test with laboratory-based testing.

Findings: It is obtained 386 paired samples: 280 (73%) from self-referred health-care workers, 15 (4%) from patients in the emergency department, and 91 (23%) hospital inpatient admissions. Of the 386 paired samples, 67 tested positive on the CovidNudge point-of-care platform and 71 with standard laboratory RT-PCR. The overall sensitivity of the point-of-care test compared with laboratory-based testing was 94% (95% CI 86–98) with an overall specificity of 100% (99–100). The sensitivity of the test varied by group (self-referred healthcare workers 93% [95% CI 84–98]; patients in the emergency department 100% [48–100]; and hospital inpatient admissions 100% [29–100]). Specificity was consistent between groups (self-referred health-care workers 100% [95% CI 98–100%]; patients in the emergency department 100% [69–100]; and hospital inpatient admissions 100% [96–100]). Point of care testing performance was similar during a period of high background prevalence of laboratory positive tests (25% [95% 20–31] in April, 2020) and low prevalence (3% [95% 1–9] in inpatient screening). Amplification of viral nucleocapsid (n1, n2, and n3) and envelope protein gene (e-gene) were most sensitive for detection of spiked SARS-CoV-2 RNA.

Interpretation: The CovidNudge platform was a sensitive, specific, and rapid point of care test for the presence of SARS-CoV-2 without laboratory handling or sample pre-processing. The device, which has been implemented in UK hospitals since May, 2020, could enable rapid decisions for clinical care and testing programmes.

Reference

Gibani, Malick M., Christofer Toumazou, Mohammadreza Sohbati, Rashmita Sahoo, Maria Karvela, Tsz-Kin Hon, Sara De Mateo et al. "Assessing a novel, lab-free, point-of-care test for SARS-CoV-2 (CovidNudge): a diagnostic accuracy study." *The Lancet Microbe* (2020). https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30121-X/fulltext

Severe COVID-19 is marked by a dysregulated myeloid cell compartment

Abstract

Coronavirus disease 2019 (COVID-19) is a mild to moderate respiratory tract infection, however, a subset of patients progress to severe disease and respiratory failure. The mechanism of protective immunity in mild forms and the pathogenesis of severe COVID-19 associated with increased neutrophil counts and dysregulated immune responses remain unclear. In a dual-center, two-cohort study, we combined single-cell RNA-sequencing and single-cell proteomics of whole-blood and peripheral-blood mononuclear cells to determine changes in immune cell composition and activation in mild versus severe COVID-19 (242 samples from 109 individuals) over time. HLA-DR^{hi}CD11c^{hi} inflammatory monocytes with an interferon-stimulated gene signature were elevated in mild COVID-19. Severe COVID-19 was marked by occurrence of neutrophil precursors, as evidence of emergency myelopoiesis, dysfunctional mature neutrophils, and HLA-DRlo monocytes. Our study provides detailed insights into the systemic immune response to SARS-CoV-2 infection and reveals profound alterations in the myeloid cell compartment associated with severe COVID-19.

Reference

Schulte-Schrepping, Jonas, Nico Reusch, Daniela Paclik, Kevin Baßler, Stephan Schlickeiser, Bowen Zhang, Benjamin Krämer et al. "Severe COVID-19 is marked by a dysregulated myeloid cell compartment." *Cell* 182, no. 6 (2020): 1419-1440. https://www.sciencedirect.com/science/article/pii/S0092867420309922 (I.F.: 38.637).

Clinical characterization and risk factors associated with cytokine release syndrome induced by COVID-19 and chimeric antigen receptor T-cell therapy

Abstract

An excessive immune response during coronavirus disease (COVID-19) can induce cytokine release syndrome (CRS), which is associated with life-threatening complications and disease progression. This retrospective study evaluated the clinical characteristics of severe CRS (sCRS, grade 3–4) induced by severe COVID-19 (40 patients) or chimeric antigen receptor T-cell (CAR-T) therapy as a comparator (41 patients). Grade 4 CRS was

significantly more common in the COVID-19 group (15/40 (35.7%) vs. 5/41 (12.2%), P = 0.008). The CAR-T group had more dramatic increase in cytokines, including IL-2, IL-6, IL-10, and IFN-γ. Interestingly, COVID-19 group had significantly higher levels for TNF-α (31.1 pg/ml (16.1–70.0) vs. 3.3 (1.8–9.6), P < 0.001) and lg viral loads were correlated with lg IL-6 (R2 = 0.101; P < 0.001) and lg IL-10 (R2 = 0.105; P < 0.001). The independent risk factor for COVID-19-related sCRS was hypertension history (OR: 4.876, 95% CI: 2.038–11.668; P < 0.001). Our study demonstrated that there were similar processes but different intensity of inflammatory responses of sCRS in COVID-19 and CAR-T group. The diagnose and management of severe COVID-19-related sCRS can learn lessons from treatment of sCRS induced by CAR-T therapy.

Reference

Hong, Ruimin, Houli Zhao, Yiyun Wang, Yu Chen, Hongliu Cai, Yongxian Hu, Guoqing Wei, and He Huang. "Clinical characterization and risk factors associated with cytokine release syndrome induced by COVID-19 and chimeric antigen receptor T-cell therapy." *Bone Marrow Transplantation* (2020): 1-11. https://www.nature.com/articles/s41409-020-01060-5 (I.F.: 3.570).

A dynamic COVID-19 immune signature includes associations with poor prognosis

Abstract

Improved understanding and management of COVID-19, a potentially life-threatening disease, could greatly reduce the threat posed by its etiologic agent, SARS-CoV-2. Toward this end, it was identified a core peripheral blood immune signature across 63 hospital-treated patients with COVID-19 who were otherwise highly heterogeneous. The signature includes discrete changes in B and myelomonocytic cell composition, profoundly altered T cell phenotypes, selective cytokine/chemokine upregulation and SARS-CoV-2-specific antibodies. Some signature traits identify links with other settings of immunoprotection and immunopathology; others, including basophil and plasmacytoid dendritic cell depletion, correlate strongly with disease severity; while a third set of traits, including a triad of IP-10, interleukin-10 and interleukin-6, anticipate subsequent clinical progression. Hence, contingent upon independent validation in other COVID-19 cohorts, individual traits within this signature may collectively and individually guide treatment

options; offer insights into COVID-19 pathogenesis; and aid early, risk-based patient stratification that is particularly beneficial in phasic diseases such as COVID-19.

Reference

Laing, Adam G., Anna Lorenc, Irene Del Molino Del Barrio, Abhishek Das, Matthew Fish, Leticia Monin, Miguel Muñoz-Ruiz et al. "A dynamic COVID-19 immune signature includes associations with poor prognosis." *Nature medicine* (2020): 1-13. https://www.nature.com/articles/s41591-020-1038-6 (I.F.: 36.130).

Clinical characterization and risk factors associated with cytokine release syndrome induced by COVID-19 and chimeric antigen receptor T-cell therapy

Abstract

An excessive immune response during coronavirus disease (COVID-19) can induce cytokine release syndrome (CRS), which is associated with life-threatening complications and disease progression. This retrospective study evaluated the clinical characteristics of severe CRS (sCRS, grade 3–4) induced by severe COVID-19 (40 patients) or chimeric antigen receptor T-cell (CAR-T) therapy as a comparator (41 patients). Grade 4 CRS was significantly more common in the COVID-19 group (15/40 (35.7%) vs. 5/41 (12.2%), P = 0.008). The CAR-T group had more dramatic increase in cytokines, including IL-2, IL-6, IL-10, and IFN-γ. Interestingly, COVID-19 group had significantly higher levels for TNF-α (31.1 pg/ml (16.1–70.0) vs. 3.3 (1.8–9.6), P < 0.001) and lg viral loads were correlated with lg IL-6 (R2 = 0.101; P < 0.001) and lg IL-10 (R2 = 0.105; P < 0.001). The independent risk factor for COVID-19-related sCRS was hypertension history (OR: 4.876, 95% CI: 2.038–11.668; P < 0.001). Our study demonstrated that there were similar processes but different intensity of inflammatory responses of sCRS in COVID-19 and CAR-T group. The diagnose and management of severe COVID-19-related sCRS can learn lessons from treatment of sCRS induced by CAR-T therapy.

Reference

Hong, Ruimin, Houli Zhao, Yiyun Wang, Yu Chen, Hongliu Cai, Yongxian Hu, Guoqing Wei, and He Huang. "Clinical characterization and risk factors associated with cytokine release syndrome induced by COVID-19 and chimeric antigen receptor T-cell therapy."

Bone Marrow Transplantation (2020): 1-11. https://www.nature.com/articles/s41409-020-01060-5 (I.F.: 3.570).

Environmental effects of COVID-19 pandemic and potential strategies of sustainability

Abstract

The global outbreak of coronavirus disease 2019 (COVID-19) is affecting every part of human lives, including the physical world. The measures taken to control the spread of the virus and the slowdown of economic activities have significant effects on the environment. Therefore, this study intends to explore the positive and negative environmental impacts of the COVID-19 pandemic, by reviewing the available scientific literatures. This study indicates that, the pandemic situation significantly improves air quality in different cities across the world, reduces GHGs emission, lessens water pollution and noise, and reduces the pressure on the tourist destinations, which may assist with the restoration of the ecological system. In addition, there are also some negative consequences of COVID-19, such as increase of medical waste, haphazard use and disposal of disinfectants, mask, and gloves; and burden of untreated wastes continuously endangering the environment. It seems that, economic activities will return soon after the pandemic, and the situation might change. Hence, this study also outlines possible ways to achieve long-term environmental benefits. It is expected that the proper implementation of the proposed strategies might be helpful for the global environmental sustainability.

Reference

Rume, Tanjena, and SM Didar-Ul Islam. "Environmental effects of COVID-19 pandemic and potential strategies of sustainability." *Heliyon* (2020): e04965. https://www.cell.com/heliyon/fulltext/S2405-8440(20)31808-9 (I.F.: 1.650).

Trends in clinical presentation of children with COVID-19: A systematic review of individual participant data

Abstract

Background: There are sparse patient-level data available for children with novel coronavirus disease (COVID-19). Therefore, there is an urgent need for an updated systematic literature review that analyzes individual children rather than aggregated data in broad age groups.

Methods: Six databases (MEDLINE, Scopus, Web of Science, CINAHL, Google Scholar, medRxiv) were searched for studies indexed from January 1 to May 15, 2020, with MeSH terms: children, pediatrics, COVID-19, SARS-CoV-2. 1241 records were identified, of which only unique papers in English with individual patient information and documented COVID-19 testing were included. This review of 22 eligible studies followed Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data guidelines.

Results: A total of 123 patients from five countries were identified. 46% were females. The median age was 5 years (IQR = 8). At presentation, 62% had a fever, 32% had a cough, 58% had a single symptom, and 21% were asymptomatic. Abnormal chest imaging was seen in 62% (65/105) of imaged and 76.9% (20/26) of asymptomatic children. A minority of children had elevated platelets, CRP, lactate dehydrogenase, and D-dimer.

Conclusion: Data from this independent participant data systematic review revealed that the majority of children with COVID-19 presented with either no symptoms or a single, non-respiratory symptom.

Reference

Christophers, Briana, Benjamin Gallo Marin, Rocío Oliva, Weston T. Powell, Timothy J. Savage, and Ian C. Michelow. "Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data." *Pediatric Research* (2020): 1-10. https://www.nature.com/articles/s41390-020-01161-3 (I. F.: 2.88).

SARS-CoV-2 seroprevalence and neutralizing activity in donor and patient blood

Abstract

Given the limited availability of serological testing to date, the seroprevalence of SARS-CoV-2-specific antibodies in different populations has remained unclear. Here, we report very low SARS-CoV-2 seroprevalence in two San Francisco Bay Area populations. Seroreactivity was 0.26% in 387 hospitalized patients admitted for non-respiratory indications and 0.1% in 1,000 blood donors in early April 2020. We additionally describe the longitudinal dynamics of immunoglobulin-G (IgG), immunoglobulin-M (IgM), and in vitro neutralizing antibody titers in COVID-19 patients. The median time to seroconversion ranged from 10.3–11.0 days for these 3 assays. Neutralizing antibodies rose in tandem with immunoglobulin titers following symptom onset, and positive percent agreement between detection of IgG and neutralizing titers was >93%. These findings emphasize the importance of using highly accurate tests for surveillance studies in low-prevalence populations, and provide evidence that seroreactivity using SARS-CoV-2 anti-nucleocapsid protein IgG and anti-spike IgM assays are generally predictive of in vitro neutralizing capacity.

Reference

Ng, Dianna L., Gregory M. Goldgof, Brian R. Shy, Andrew G. Levine, Joanna Balcerek, Sagar P. Bapat, John Prostko et al. "SARS-CoV-2 seroprevalence and neutralizing activity in donor and patient blood." *Nature Communications* 11, no. 1 (2020): 1-7. https://www.nature.com/articles/s41467-020-18468-8. (I. F.: 12.121).

Publication Date: Sep 22, 2020

COVID research updates: Good timing might help the immune system to control COVID-19

Nature wades through the literature on the new coronavirus — and summarizes key papers as they appear.

Good timing might help the immune system to control COVID-19 (September 22, 2020):

People aged 65 and older who are infected with the new coronavirus tend to mount a disorganized immune response — a response that is also associated with severe COVID-19. This could help to explain why the disease strikes older people particularly hard.

The immune system's 'adaptive' branch, which targets specific invaders, has three principle components: antibodies, CD4+ T cells and CD8+ T cells. Alessandro Sette and Shane Crotty at the La Jolla Institute for Immunology in California studied the adaptive immune response in 24 people whose COVID-19 symptoms ranged from mild to fatal (C. R. Moderbacher et al. Cell https://doi.org/ghbwh7; 2020). The team found that people whose immune systems failed to rapidly launch the entire adaptive immune system tended to have more severe disease than did people in whom all three arms ramped up production simultaneously. An uncoordinated response was particularly common among older people, and could indicate that both antibodies and T cells are important weapons against the coronavirus.

Musicians and a monk are tied to superspreading in Hong Kong (September 18, 2020):

An estimated 19% of SARS-CoV-2 infections in Hong Kong seeded 80% of the local transmission of the virus from one person to another, according to an analysis of the virus's early spread. The analysis also found that viral spread in social settings caused more infections than spread within family households.

Musicians who performed at four Hong Kong bars are thought to have triggered the biggest cluster, which led to 106 cases. Another 19 cases were linked to a temple; one

monk there had no symptoms but was found to be infected. The analysis also showed that more downstream cases were linked to spread in social settings such as weddings and restaurants than to household spread.

Immunity to common-cold coronaviruses is short-lived (September 17, 2020):

Previous studies have suggested that immune responses to common-cold coronaviruses protect against reinfection for only a matter of months, although symptoms are often reduced during the second infection. Lia van der Hoek at the University of Amsterdam and her colleagues looked for coronavirus antibodies in blood samples taken every few months from ten individuals, starting in the mid-1980s (A. W. D. Edridge *et al.* Nature Med. https://doi.org/ghbm79; 2020). The team used a rise in antibody levels as an indicator of infection. Infections with coronaviruses were least common from June to September, a seasonal pattern that the authors suggest SARS-CoV-2 might follow. The authors found reinfections occurring as early as 6 months after the first infection, and most often at 12 months.

Reference

https://www.nature.com/articles/d41586-020-00502-w

CORRESPONDANCE

Publication Date: Sep 17, 2020

Tocilizumab in COVID-19: Finding the optimal route and dose

The Tocilizumab in Patients with Severe COVID-19 Pneumonia (TESEO) study by Giovanni Guaraldi and colleagues provides vital information regarding the benefits of tocilizumab in severe pneumonia due to COVID-19. However, certain aspects of the study warrant deliberation in greater detail.

By contrast with the pharmacokinetic and pharmacodynamic bioequivalence data available from non-COVID settings, use of 324 mg of subcutaneous tocilizumab in patients with COVID-19 was found to be as efficacious as intravenous tocilizumab at a cumulative dose of 16 mg/kg. The difference in the therapy costs resulting from these cumulative doses (and the consumables involved in intravenous administration) could have substantial implications from a pharmacoeconomic point of view. Anecdotal signals of efficacy in COVID-19 have been reported previously with a single 162 mg dose of subcutaneous tocilizumab. Dose optimisation of subcutaneous tocilizumab could thus be explored in future studies, as it has the potential to further reduce the cost of therapy.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30334-9/fulltext

PERSPECTIVE

Publication Date: Sep 23, 2020

COVID-19 can affect the heart

The family of seven known human coronaviruses are known for their impact on the respiratory tract, not the heart. However, the most recent coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has marked tropism for the heart and can lead to myocarditis (inflammation of the heart), necrosis of its cells, mimicking of a heart attack, arrhythmias, and acute or protracted heart failure (muscle dysfunction). These complications, which at times are the only features of coronavirus disease 2019 (COVID-19) clinical presentation, have occurred even in cases with mild symptoms and in people who did not experience any symptoms. Recent findings of heart involvement in young athletes, including sudden death, have raised concerns about the current limits of our knowledge and potentially high risk and occult prevalence of COVID-19 heart manifestations. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/early/2020/09/23/science.abe2813?rss=1

REPORT

Publication Date: Sep 21, 2020

Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein

COVID-19, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), represents a global crisis. Key to SARS-CoV-2 therapeutic development is unraveling the mechanisms driving high infectivity, broad tissue tropism and severe pathology. Our 2.85 Å cryo-EM structure of SARS-CoV-2 spike (S) glycoprotein reveals that the receptor binding domains (RBDs) tightly bind the essential free fatty acid (FFA) linoleic acid (LA) in three composite binding pockets. The pocket also appears to be present in the highly pathogenic coronaviruses SARS-CoV and MERS-CoV. LA binding stabilizes a locked S conformation giving rise to reduced ACE2 interaction in vitro. In human cells, LA supplementation synergizes with the COVID-19 drug remdesivir, suppressing SARS-CoV-2 replication. Our structure directly links LA and S, setting the stage for intervention strategies targeting LA binding by SARS-CoV-2. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/early/2020/09/18/science.abd3255?rss=1

Publication Date: Sep 17, 2020

A case for inspiratory muscle training in SCI: Potential role as a preventative tool in infectious respiratory diseases like COVID-19

Introduction: Respiratory complications (RC) are a leading cause of death after spinal cord injury (SCI) due to compromised immune function and respiratory muscle weakness. Thus, individuals with SCI are at high risk of developing COVID-19 related RC. Results of a SCI clinical trial showed a supervised respiratory muscle training (RMT) program decreased risk of developing RC. The feasibility of conducting unsupervised RMT is not well documented. Four publications (n = 117) were identified in which unsupervised RMT was performed. Significant improvements in respiratory outcomes were reported in two studies: Maximal Inspiratory and Expiratory Pressure (MIP40% and MEP25%,

respectively), Peak Expiratory Flow (PEF9%), seated and supine Forced Vital Capacity (FVC23% and 26%, respectively), and Peak Cough Flow (28%). This review and case report will attempt to show that an inspiratory muscle training (IMT) home exercise program (HEP) is feasible and may prepare the respiratory system for RC associated with COVID-19 in patients with SCI.

Case presentation: A 23-year-old with tetraplegia (P1), history of mechanical ventilation, and hospitalization for RC, completed 27 IMT HEP sessions in one month. MIP and sustained MIP (SMIP) increased from baseline by 28% and 26.5%, respectively. Expiratory volumes and rates also improved (FVC, FEV1, and PEF: 11.7%, 8.3%, and 14.2%, respectively).

Discussion: The effects of COVID-19 on patients with SCI remains inconclusive, but recent literature and the results of this case suggest that unsupervised IMT is feasible and may limit the severity of RC in patients with SCI who contract COVID-19.

Reference

https://www.nature.com/articles/s41394-020-00337-7

COMMENT

Publication Date: Sep 23, 2020

The complexities of SARS-CoV-2 serology

Diagnosing previous infection with respiratory viruses is challenging. Our understanding of individual and population-level immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains incomplete and developing reliable serological assays to detect previous infection has been an intense focus of the global scientific effort. For public health planning we need scalable assays validated against large banks of samples from individuals who had proven seasonal (non-severe acute respiratory syndrome) coronaviruses and those who had well characterised symptomatic and asymptomatic confirmed SARS-CoV-2 infection. False-positive results, due to cross-reactivity with seasonal coronaviruses, are important to avoid, particularly if seropositive-individuals consider themselves immune. In *The Lancet Infectious Diseases,* the National SARS-CoV-2 Serology Assay Evaluation Group provide the first large comparative investigation of the performance of four widely available commercial assays and a single in-house assay.

Antibody responses to SARS-CoV-2 are predominantly directed at the spike glycoprotein, which the virus requires for entry, and the nucleocapsid protein, which binds the viral RNA genome. The SARS-CoV-2 IgG assay (Abbott, Chicago, IL, USA) and Elecsys Anti-SARS-CoV-2 assay (Roche, Basel, Switzerland) assays detect antibody to the nucleoprotein, whereas the LIAISON SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Saluggia, Italy), and SARS-CoV-2 Total assay (Siemens, Munich, Germany) detect antibodies to the spike glycoprotein. The Abbott and Diasorin assays detect IgG only, whereas Roche and Siemens detect total antibody. The diverse approaches taken by the four commercial assays highlight the challenge of choice posed to laboratories: all manufacturers report similarly high sensitivity and specificity. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30699-X/fulltext

Publication Date: Sep 22, 2020

COVID-19: Clinching the climate opportunity

The coronavirus disease 2019 (COVID-19) pandemic has triggered the largest drop in greenhouse gas emissions since World War II. Evolving mobility patterns, in particular, have shown the short-term mitigation potential of behavioral change. Sustaining such changes could abate 15% of all transportation emissions with limited net impacts on societal well-being.

This pandemic is to mark a historic peak in anthropogenic GHG emissions, we need to leverage such lessons and turn them into guardrails against a return to pre-pandemic emission growth. For more details, read the link given below.

Reference

https://www.cell.com/one-earth/fulltext/S2590-3322(20)30472-3

Publication Date: Sep 21, 2020

What can we expect from first-generation COVID-19 vaccines?

A first generation of COVID-19 vaccines is expected to gain approval as soon as the end of 2020 or early 2021. A popular assumption is that these vaccines will provide population immunity that can reduce transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and lead to a resumption of pre-COVID-19 “normalcy”. Given an initial reproduction number of around 2·2, which has since been revised to as high as about 4, and taking into account overdispersion of infections, perhaps about 25–50% of the population would have to be immune to the virus to achieve suppression of community transmission. Multiple COVID-19 vaccines are currently in phase 3 trials with efficacy assessed as prevention of virologically confirmed disease. WHO recommends that successful vaccines should show disease risk reduction of at least 50%, with 95% CI that true vaccine efficacy exceeds 30%. However, the impact of these COVID-19 vaccines on infection and thus transmission is not being assessed. Even if vaccines were able to confer protection from disease, they might not reduce transmission similarly. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31976-0/fulltext

The contribution of the observational research design to COVID-19 research

As the COVID-19 pandemic continues to influence global health, the search for effective therapies has been vigorous. An analysis published early during the pandemic suggested that hydroxychloroquine, with or without azithromycin, might improve nasopharyngeal viral clearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19. Despite the low quality of this study due to poor handling of confounders and participants lost to follow-up who had poor outcomes, a surge of prescriptions for the therapeutic and prophylactic use of hydroxychloroquine created shortages for patients with systemic lupus erythematosus and other rheumatic diseases who rely on this medication to treat their disease. Subsequently, an increased incidence of cardiac arrhythmias was observed in patients with COVID-19 treated with hydroxychloroquine. Thus, there is a need to determine whether the benefits of hydroxychloroquine for COVID-19 outweigh the risk of harms. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30336-2/fulltext