COVID-19

Aug 20-26, 2020

RESEARCH PUBLICATIONS

Publication Date: Aug 26, 2020

A drug screening toolkit based on the –1 ribosomal frameshifting of SARS-CoV-2

Abstract

The –1 ribosomal frameshifting is vital for the translation of the open reading frame (ORF)1b in SARS-CoV-2. The products of ORF1b participate in viral replication. Therefore, changing the frameshift frequency reduces the survival of the virus. This study aimed to successfully develop a toolkit for screening antiviral drugs. Finally, the FDA-approved drug library was screened, revealing that ivacaftor and (–)-Huperzine A worked well in changing the –1 ribosomal frameshifting of SARS-CoV-2 *in vitro*.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)31636-4

SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: An analysis of Cleveland clinic's COVID-19 registry

Abstract

Background: We sought to determine whether COPD conferred a higher risk for healthcare utilization in terms of hospitalization and clinical outcomes due to COVID-19.

Methods: A cohort study with covariate adjustment using multivariate logistic regression was conducted at the Cleveland Clinic Health System in Ohio and Florida. Symptomatic patients aged 35 years and older who were tested for SARS-CoV-2 between March 8 and May 13, 2020 were included.

Findings: 15,586 individuals tested for COVID-19 at the Cleveland Clinic between March 8, 2020 and May 13, 2020 met our inclusion criteria. 12.4% of COPD patients (164/1319) tested positive for COVID-19 compared to 16.6% (2363/14,267) of the non-COPD population. 48.2% (79/164) of COVID-19 positive COPD patients required hospitalization and 45.6% (36/79) required ICU admission. After adjustment for covariates, rates of COVID-19 infection were not significantly different than the non-COPD population (adj OR 0.97; CI: 0.89–1.05), but COPD patients had increased healthcare utilization as demonstrated by risk for hospitalization (adj OR 1.36; CI: 1.15–1.60), ICU admission (OR 1.20; CI: 1.02–1.40), and need for invasive mechanical ventilation (adj OR 1.49; CI: 1.28–1.73). Unadjusted risk for in-hospital mortality was higher in the COPD population (OR 1.51; CI: 1.14–1.96). After adjusting for covariates however, the risk for in-hospital mortality was not significantly different than the non-COPD population (adj OR 1.08: CI: 0.81–1.42).

Interpretation: Our analysis demonstrated that COPD patients with COVID-19 had a higher risk for healthcare utilization, although adjusted in-hospital mortality risk was not different than the non-COPD patients with COVID-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30259-5/fulltext

Population-scale longitudinal mapping of COVID-19 symptoms, behaviour and testing

Abstract

Despite the widespread implementation of public health measures, coronavirus disease 2019 (COVID-19) continues to spread in the United States. To facilitate an agile response to the pandemic, we developed How We Feel, a web and mobile application that collects longitudinal self-reported survey responses on health, behaviour and demographics. Here, we report results from over 500,000 users in the United States from 2 April 2020 to 12 May 2020. We show that self-reported surveys can be used to build predictive models to identify likely COVID-19-positive individuals. Evidence was found among our users for asymptomatic or presymptomatic presentation; show a variety of exposure, occupational and demographic risk factors for COVID-19 beyond

symptoms; reveal factors for which users have been SARS-CoV-2 PCR tested; and highlight the temporal dynamics of symptoms and self-isolation behaviour. These results highlight the utility of collecting a diverse set of symptomatic, demographic, exposure and behavioural self-reported data to fight the COVID-19 pandemic.

Reference

https://www.nature.com/articles/s41562-020-00944-2

Publication Date: Aug 25, 2020

Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients

Abstract

Coronavirus disease-2019 (COVID-19) is associated with severe inflammation in mainly the lung, and kidney. Reports suggest a beneficial effect of the use of heparin/low molecular weight heparin (LMWH) on mortality in COVID-19. In part, this beneficial effect could be explained by the anticoagulant properties of heparin/LMWH. Here, we summarise potential beneficial, non-anticoagulant mechanisms underlying treatment of COVID-19 patients with heparin/LMWH, which include: (i) Inhibition of heparanase activity, responsible for endothelial leakage; (ii) Neutralisation of chemokines, and cytokines; (iii) Interference with leukocyte trafficking; (iv) Reducing viral cellular entry, and (v) Neutralisation of extracellular cytotoxic histones. Considering the multiple inflammatory and pathogenic mechanisms targeted by heparin/LMWH, it is warranted to conduct clinical studies that evaluate therapeutic doses of heparin/LMWH in COVID-19 patients. In addition, identification of specific heparin-derived sequences that are functional in targeting non-anticoagulant mechanisms may have even higher therapeutic potential for COVID-19 patients, and patients suffering from other inflammatory diseases.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30345-5/fulltext

Clinical features, diagnostics, and outcomes of patients presenting with acute respiratory illness: A retrospective cohort study of patients with and without COVID-19

Abstract

Background: Most data on the clinical presentation, diagnostics, and outcomes of patients with COVID-19 have been presented as case series without comparison to patients with other acute respiratory illnesses.

Methods: We examined emergency department patients between February 3 and March 31, 2020 with an acute respiratory illness who were tested for SARS-CoV-2. We determined COVID-19 status by PCR and metagenomic next generation sequencing (mNGS). We compared clinical presentation, diagnostics, treatment, and outcomes.

Findings: Among 316 patients, 33 tested positive for SARS-CoV-2; 31 without COVID-19 tested positive for another respiratory virus. Among patients with additional viral testing (27/33), no SARS-CoV-2 co-infections were identified. Compared to those who tested negative, patients with COVID-19 reported longer symptoms duration (median 7d vs. 3d, $p < 0.001$). Patients with COVID-19 were more often hospitalized (79% vs. 56%, $p = 0.014$). When hospitalized, patients with COVID-19 had longer hospitalizations (median 10.7d vs. 4.7d, $p < 0.001$) and more often developed ARDS (23% vs. 3%, $p < 0.001$). Most comorbidities, medications, symptoms, vital signs, laboratories, treatments, and outcomes did not differ by COVID-19 status.

Interpretation: While differences were found in clinical features of COVID-19 compared to other acute respiratory illnesses, there was significant overlap in presentation and comorbidities. Patients with COVID-19 were more likely to be admitted to the hospital, have longer hospitalizations and develop ARDS, and were unlikely to have co-existent viral infections.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30262-5/fulltext

An inflammatory cytokine signature predicts COVID-19 severity and survival

Abstract

Several studies have revealed that the hyper-inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major cause of disease severity and death. However, predictive biomarkers of pathogenic inflammation to help guide targetable immune pathways are critically lacking. We implemented a rapid multiplex cytokine assay to measure serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and IL-1β in hospitalized patients with coronavirus disease 2019 (COVID-19) upon admission to the Mount Sinai Health System in New York. Patients ($n = 1,484$) were followed up to 41 d after admission (median, 8 d), and clinical information, laboratory test results and patient outcomes were collected. We found that high serum IL-6, IL-8 and TNF-α levels at the time of hospitalization were strong and independent predictors of patient survival ($P < 0.0001$, $P = 0.0205$ and $P = 0.0140$, respectively). Notably, when adjusting for disease severity, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of comorbidities, IL-6 and TNF-α serum levels remained independent and significant predictors of disease severity and death. These findings were validated in a second cohort of patients ($n = 231$). We propose that serum IL-6 and TNF-α levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options.

Reference

https://www.nature.com/articles/s41591-020-1051-9

Clinical, immunological and virological characterization of COVID-19 patients that test re-positive for SARS-CoV-2 by RT-PCR

Abstract

Background: Some COVID-19 cases test positive again for SARS-CoV-2 RNA following negative test results and discharge, raising questions about the meaning of virus detection. Better characterization of re-positive cases is urgently needed.

Methods: Clinical data were obtained through Guangdong's COVID-19 surveillance network. Neutralization antibody titre was determined using microneutralization assays. Potential infectivity of clinical samples was evaluated by cell inoculation. SARS-CoV-2 RNA was detected using three different RT-PCR kits and multiplex PCR with nanopore sequencing.

Findings: Among 619 discharged COVID-19 cases, 87 re-tested as SARS-CoV-2 positive in circumstances of social isolation. All re-positive cases had mild or moderate symptoms at initial diagnosis and were younger on average (median, 28). Re-positive cases (n = 59) exhibited similar neutralization antibodies (NAbs) titre distributions to other COVID-19 cases (n = 218) tested here. No infectious strain could be obtained by culture and no full-length viral genomes could be sequenced from re-positive cases.

Interpretation: Re-positive SARS-CoV-2 cases do not appear to be caused by active reinfection and were identified in ~14% of discharged cases. A robust NAb response and potential virus genome degradation were detected in almost all re-positive cases, suggesting a substantially lower transmission risk, especially through respiratory routes.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30336-4/fulltext

Association between renin–angiotensin–aldosterone system inhibitor treatment, neutrophil–lymphocyte ratio, D-Dimer and clinical severity of COVID-19 in hospitalized patients: A multicenter, observational study

Abstract

The aim of this study was to investigate the possible relationship between worse clinical outcomes and the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in hospitalized COVID-19 patients. A total of 247 adult patients (154 males, 93 females; mean age: 51.3 ± 14.2 years) hospitalized for COVID-19 as confirmed by polymerase chain reaction (PCR) were retrospectively reviewed. Demographic and clinical characteristics and laboratory parameters were analyzed using various statistical modeling. Primary outcomes were defined as the need for intensive care unit (ICU), mechanical ventilation, or occurrence of death. Of the patients, 48 were treated in the ICU with a high flow oxygen/noninvasive mechanical ventilation (NIMV, n = 12) or mechanical ventilation (n = 36). Median length of ICU stay was 13 (range, 7–18) days. Mortality was seen in four of the ICU patients. Other patients were followed in the COVID-19 services for a median of 7 days. There was no significant correlation between the primary outcomes and use of ACEIs/ARBs (frequentist OR = 0.82, 95% confidence interval (CI) 0.29–2.34, p = 0.715 and Bayesian posterior median OR = 0.80, 95% CI 0.31–2.02) and presence of hypertension (frequentist OR = 1.23, 95% CI 0.52–2.92, p = 0.631 and Bayesian posterior median OR = 1.25, 95% CI 0.58–2.60). Neutrophil-to-lymphocyte ratio (NLR) and D-dimer levels were strongly associated with primary outcomes. In conclusion, the presence of hypertension and use of ACEIs/ARBs were not significantly associated with poor primary clinical outcomes; however, NLR and D-dimer levels were strong predictors of clinical worsening.

Reference

https://www.nature.com/articles/s41371-020-00405-3

Process Analytical Technologies and data analytics for the manufacture of monoclonal antibodies

Abstract

Monoclonal Antibodies (mAbs) have evolved from being scientific tools derived from murine hybridomas in 1975 to biotherapeutic molecules based on humanized antibodies (see Glossary). The first mAb for therapeutic use in humans was approved in 1986 and the first bispecific mAb (bsAb; catumaxomab) was approved in 2009. Humanized antibodies include IgG1s, 2s, and 4s grafted onto the Fc and Fv regions, which comprise human sequences. Currently, there are ~570 antibody therapeutics at various clinical phases, with 62 in late-stage trials. Global mAb sales have grown from US $18.5 billion in 2010 to US $98 billion in 2017 with 57 mAbs and 11 biosimilars in clinical use as of the end of 2017'. Of these, 93% are produced in USA and Europe and half are based on fully human genetic sequences. Over time, several classes of mAb have evolved. Early products (Erbitux, Remicade, and rituximab) were obtained by grafting antigen-specific variable domains of mouse antibodies onto constant domains of a human antibody. Humanized mAbs (*e.g.,* Avastin, Mylotarg, and Herceptin), based on a murine hypervariable region grafted onto a human antibody framework, resulted in decreased immunogenic properties and reduced formation of antidrug antibodies. Ultimately, human mAbs emerged from research that utilized phage display technology and transgenic mouse strains that express human variable domains (*i.e*., Humira, Simponi, and Yervoy).

Approximately 20 bsAbs for non-oncology indications have entered various stages of testing since 2000. Candidates have the potential to attack Pseudomonas aeruginosa, treat type 2 diabetes mellitus, or provide postexposure protection against Ebola viruses. Approximately 500 fully human antibodies have been identified in the blood of a survivor of coronavirus disease 2019 (COVID-19), and are being assessed for effectiveness against COVID-19 with the goal of rapidly developing a therapeutic antibodyi. Both Biogen and GlaxoSmithKline have separately partnered with Vir to produce mAbs found capable of binding to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Administration of biologics at concentrations of 150 mg/ml or higher in formulated

matrices suitable for injection opens the possibility of subcutaneous home self-administration as the number of biotherapeutic mAbs increases. Dosages range from 50 to 1000 mg per patient per treatment. The patient's need for the therapeutic may last from months to years, and some mAbs or biosimilars will apply to a large population of patients. These combined requirements will necessitate total global production of metric ton quantities annually. PAT will be an important component of achieving enhanced productivity.

PAT is a framework for ensuring the quality of a pharmaceutical product by monitoring process streams and unit operations, thereby providing a real-time understanding of the manufacturing process. Determining the sources of variability in a process, how the variability is managed by the process, and whether the product quality may be predicted from process parameters is central to PAT. This knowledge is used to decide which material and process attributes need to be measured and controlled during manufacturing. Implementation of PAT tools (*e.g*., multivariate analytics, process analyzers, process controllers, and continuous improvement tools) for these critical attributes helps to ensure product quality. The FDA introduced the PAT framework in their Guidance to the Industry document in 2004. Since its introduction, the PAT framework has been implemented for the development of small-molecule active pharmaceutical ingredients (APIs) to improve the understanding of process chemistry, as highlighted by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium). Implementation of PAT for the development and manufacture of mAbs is now gaining momentum with pilot-scale demonstrations of multiattribute monitoring and potential for process control. The need for reliable scalable manufacturing of mAbs (and other biologics) continues to increase (*e.g*., antibody-based therapies for the COVID-19 pandemic). In this review, we highlight the current status of mAb manufacturing, associated challenges, and how PAT and data analytics can help overcome these challenges to develop a new therapeutic product.

Reference

Maruthamuthu, Murali K., Scott R. Rudge, Arezoo M. Ardekani, Michael R. Ladisch, and Mohit S. Verma. "Process Analytical Technologies and Data Analytics for the Manufacture of Monoclonal Antibodies." *Trends in Biotechnology* (2020) (I.F.: 14.343).

Renin–angiotensin system inhibitors and the severity of coronavirus disease 2019 in Kanagawa, Japan: A retrospective cohort study

Abstract

Since the beginning of the coronavirus disease 2019 (COVID-19) outbreak initiated on the Diamond Princess Cruise Ship at Yokohama harbor in February 2020, we have been doing our best to treat COVID-19 patients. In animal experiments, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) are reported to suppress the downregulation of angiotensin converting enzyme 2 (ACE2), and they may inhibit the worsening of pathological conditions. We aimed to examine whether preceding use of ACEIs and ARBs affected the clinical manifestations and prognosis of COVID-19 patients. One hundred fifty-one consecutive patients (mean age 60 ± 19 years) with polymerase-chain-reaction proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were admitted to six hospitals in Kanagawa Prefecture, Japan, were analyzed in this multicenter retrospective observational study. Among all COVID-19 patients, in the multiple regression analysis, older age (age ≥ 65 years) was significantly associated with the primary composite outcome (odds ratio (OR) 6.63, 95% confidence interval (CI) 2.28–22.78, $P < 0.001$), which consisted of (i) in-hospital death, (ii) extracorporeal membrane oxygenation, (iii) mechanical ventilation, including invasive and noninvasive methods, and (iv) admission to the intensive care unit. In COVID-19 patients with hypertension, preceding ACEI/ARB use was significantly associated with a lower occurrence of new-onset or worsening mental confusion (OR 0.06, 95% CI 0.002–0.69, $P = 0.02$), which was defined by the confusion criterion, which included mild disorientation or hallucination with an estimation of medical history of mental status, after adjustment for age, sex, and diabetes. In conclusion, older age was a significant contributor to a worse prognosis in COVID-19 patients, and ACEIs/ARBs could be beneficial for the prevention of confusion in COVID-19 patients with hypertension.

Reference

Matsuzawa, Yasushi, Hisao Ogawa, Kazuo Kimura, Masaaki Konishi, Jin Kirigaya, Kazuki Fukui, Kengo Tsukahara et al. "Renin–angiotensin system inhibitors and the

severity of coronavirus disease 2019 in Kanagawa, Japan: a retrospective cohort study." *Hypertension Research* (2020): 1-10.

Publication Date: Aug 20, 2020

Metformin use is associated with increased incidence of acidosis but not mortality in individuals with COVID-19 and pre-existing Type 2 Diabetes

Abstract

The safety and efficacy of anti-diabetic drugs are critical for maximizing the benefical impacts of well-controlled blood glucose on the prognosis of individuals with COVID-19 and pre-existing type 2 diabetes (T2D). Metformin is the most commonly prescribed first-line medication for T2D, but its impact on the outcomes of individuals with COVID-19 and T2D remains to be clarified. Our current retrospective study in a cohort of 1,213 hospitalized individuals with COVID-19 and pre-existing T2D indicated that metformin use was significantly associated with a higher incidence of acidosis, particularly in cases with severe COVID-19, but not with 28-day COVID-19-related mortality. Furthermore, metformin use was significantly associated with reduced heart failure and inflammation. Our findings provide clinical evidence in support of continuing metformin treatment in individuals with COVID-19 and pre-existing T2D, but acidosis and kidney function should be carefully monitored in individuals with severe COVID-19.

Reference

Cheng, Xu, Ye-Mao Liu, Haomiao Li, Xin Zhang, Fang Lei, Juan-Juan Qin, Ze Chen *et al.* "Metformin Use Is Associated with Increased Incidence of Acidosis but not Mortality in Individuals with COVID-19 and Pre-existing Type 2 Diabetes." *Cell Metabolism (*2020) (I.F.: 21.567).

Resilience, COVID-19-related stress, anxiety and depression during the pandemic in a large population enriched for healthcare providers

Abstract

COVID-19 pandemic is a global calamity posing an unprecedented opportunity to study resilience. We developed a brief resilience survey probing self-reliance, emotion-

regulation, interpersonal-relationship patterns and neighborhood-environment, and applied it online during the acute COVID-19 outbreak (April 6–15, 2020), on a crowdsourcing research website (www.covid19resilience.org) advertised through social media. We evaluated level of stress (worries) regarding COVID-19: (1) contracting, (2) dying from, (3) currently having, (4) family member contracting, (5) unknowingly infecting others with (6) experiencing significant financial burden following. Anxiety (GAD7) and depression (PHQ2) were measured. Totally, 3042 participants ($n = 1964$ females, age range 18–79, mean age = 39) completed the resilience and COVID-19-related stress survey and 1350 of them (mean age = 41, $SD = 13$; $n = 997$ females) completed GAD7 and PHQ2. Participants significantly endorsed more distress about family contracting COVID-19 (48.5%) and unknowingly infecting others (36%), than getting COVID-19 themselves (19.9%), $p < 0.0005$ covarying for demographics and proxy COVID-19 exposures like getting tested and knowing infected individuals. Patterns of COVID-19 related worries, rates of anxiety (GAD7 > 10, 22.2%) and depression (PHQ2 > 2, 16.1%) did not differ between healthcare providers and non-healthcare providers. Higher resilience scores were associated with lower COVID-19 related worries (main effect $F1,3054 = 134.9$; $p < 0.00001$, covarying for confounders). Increase in 1 SD on resilience score was associated with reduced rate of anxiety (65%) and depression (69%), across healthcare and non-healthcare professionals. Findings provide empirical evidence on mental health associated with COVID-19 outbreak in a large convenience sample, setting a stage for longitudinal studies evaluating mental health trajectories following COVID-19 pandemic.

Reference

Barzilay, Ran, Tyler M. Moore, David M. Greenberg, Grace E. DiDomenico, Lily A. Brown, Lauren K. White, Ruben C. Gur, and Raquel E. Gur. "Resilience, COVID-19-related stress, anxiety and depression during the pandemic in a large population enriched for healthcare providers." *Translational Psychiatry* 10, no. 1 (2020): 1-8 (I.F.: 5.28).

Integrative analyses of SARS-CoV-2 genomes from different geographical locations reveal unique features potentially consequential to host-virus interaction, pathogenesis and clues for novel therapies

Abstract

An integrative analysis of SARS-CoV-2 genome sequences has been performefrom different countries. Apart from mutational analysis, host antiviral miRNAs targeting virus genes, PTMs in the virus proteins and antiviral peptides have been predicted. A comparison of the analyses with other coronavirus genomes has been performed, wherever possible. The analysis confirms unique features in the SARS-CoV-2 genomes absent in other evolutionarily related coronavirus family genomes, which presumably confer unique infection, transmission and virulence capabilities to the virus. For understanding the crucial factors involved in host-virus interactions, Bioinformatics aided analysis integrated with experimental data related to other corona viruses have been performed. 42 Conserved miRNAs have been identified that can potentially target SARS-CoV-2 genomes. Interestingly, out of these, 3 are previously reported to exhibit antiviral activity against other respiratory viruses. Gene expression analysis of known host antiviral factors reveals significant over-expression of IFITM3 and down regulation of cathepsins during SARS-CoV-2 infection, suggesting its active role in pathogenesis and delayed immune response. Antiviral peptides have been also predicted which can be used in designing peptide-based drugs against SARS-CoV-2. The analysis explores the functional impact of the virus mutations on its proteins and interaction of its genes with host antiviral mechanisms.

Reference

Sardar, Rahila, Deepshikha Satish, Shweta Birla, and Dinesh Gupta. "Integrative analyses of SARS-CoV-2 genomes from different geographical locations reveal unique features potentially consequential to host-virus interaction, pathogenesis and clues for novel therapies." *Heliyon* (2020): e04658 (I.F.: 1.650).

Leptin levels in SARS-CoV-2 infection related respiratory failure: A cross-sectional study and a pathophysiological framework on the role of fat tissue

Abstract

Obesity is a risk factor for SARS-CoV-2 infected patients to develop respiratory failure. Leptin produced in visceral fat might play a role in the deterioration to mechanical ventilation. A cross sectional study was performed. The mean BMI was 31 kg/m^2 (range 24.8–48.4) for the 31 SARS-CoV-2 ventilated patients and 26 kg/m^2 (range 22.4–33.5) for 8 critically ill non-infected control patients. SARS-CoV-2 infected patients with a similar BMI as control patients appear to have significantly higher levels of serum leptin. The mean leptin level was 21.2 (6.0–85.2) vs 5.6 (2.4–8.2) ug/L for SARS-CoV-2 and controls respectively ($p = 0.0007$). With these findings we describe a clinical and biological framework that may explain these clinical observations. The ACE2 utilization by the virus leads to local pulmonary inflammation due to ACE2-ATII disbalance. This might be enhanced by an increase in leptin production induced by SARS-CoV-2 infection of visceral fat. Leptin receptors in the lungs are now more activated to enhance local pulmonary inflammation. This adds to the pre-existent chronic inflammation in obese patients. Visceral fat, lung tissue and leptin production play an interconnecting role. This insight can lead the way to further research and treatment.

Reference

van der Voort, Peter HJ, Jill Moser, Durk F. Zandstra, Anneke C. Muller Kobold, Marjolein Knoester, Cornelis F. Calkhoven, Inge Hamming, and Matijs van Meurs. "Leptin levels in SARS-CoV-2 infection related respiratory failure: a cross-sectional study and a pathophysiological framework on the role of fat tissue." *Heliyon* (2020): e04696 (I.F.: 1.650).

PERSPECTIVE

Publication Date: Aug 25, 2020

Lung innervation in the eye of a cytokine storm: Neuroimmune interactions and COVID-19

Abstract

COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2, which was first reported in Wuhan, China, in December 2019 and has caused a global pandemic. Acute respiratory distress syndrome (ARDS) is a common feature of severe forms of COVID-19 and can lead to respiratory failure, especially in older individuals. The increasing recognition of the neurotropic potential of SARS-CoV-2 has sparked interest in the role of the nervous system in respiratory failure in people with COVID-19. However, the neuroimmune interactions in the lung in the context of ARDS are poorly understood. In this Perspectives article, we propose the concept of the neuroimmune unit as a critical determinant of lung function in the context of COVID-19, inflammatory conditions and ageing, focusing particularly on the involvement of the vagus nerve. We discuss approaches such as neurostimulation and pharmacological neuromodulation to reduce tissue inflammation with the aim of preventing respiratory failure. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41582-020-0402-y

Publication Date: Aug 24, 2020

Lifting the mask on neurological manifestations of COVID-19

Abstract

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic spreads, it is becoming increasingly evident that coronavirus disease 2019 (COVID-19) is not limited to the respiratory system, and that other organs can be affected. In

particular, virus-related neurological manifestations are being reported more and more frequently in the scientific literature. In this article, we review the literature on the association between COVID-19 and neurological manifestations, present evidence from preclinical research suggesting that SARS-CoV-2 could be responsible for many of these manifestations, and summarize the biological pathways that could underlie each neurological symptom. Understanding the mechanisms that lead to neurological manifestations in patients with COVID-19 and how these manifestations correlate with clinical outcomes will be instrumental in guiding the optimal use of targeted therapeutic strategies.

Reference

https://www.nature.com/articles/s41582-020-0398-3

Publication Date: Aug 20, 2020

COVID-19 and possible links with Parkinson's disease and parkinsonism: From bench to bedside

Abstract

This Viewpoint discusses insights from basic science and clinical perspectives on coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection in the brain, with a particular focus on Parkinson's disease. Major points include that neuropathology studies have not answered the central issue of whether the virus enters central nervous system neurons, astrocytes or microglia, and the brain vascular cell types that express virus have not yet been identified. Currently, there is no clear evidence for human neuronal or astrocyte expression of angiotensin-converting enzyme 2 (ACE2), the major receptor for viral entry, but ACE2 expression may be activated by inflammation, and a comparison of healthy and infected brains is important. In contrast to the 1918 influenza pandemic and avian flu, reports of encephalopathy in COVID-19 have been slow to emerge, and there are so far no documented reports of parkinsonism apart from a single case report. We recommend consensus guidelines for the clinical treatment of Parkinson's patients with COVID-19. While a role for the virus in causing or exacerbating Parkinson's disease appears unlikely at this time, aggravation of specific motor and non-motor symptoms has been

reported, and it will be important to monitor subjects after recovery, particularly for those with persisting hyposmia.

Reference

Sulzer, David, Angelo Antonini, Valentina Leta, Anna Nordvig, Richard J. Smeyne, James E. Goldman, Osama Al-Dalahmah et al. "COVID-19 and possible links with Parkinson's disease and parkinsonism: from bench to bedside." *npj Parkinson's Disease* 6, no. 1 (2020): 1-10 (I.F.: 5.178).

NEWS LETTER

Publication Date: Aug 26, 2020

CKD is a key risk factor for COVID-19 mortality

A new study uses the OpenSAFELY health analytics platform to identify risk factors for COVID-19 mortality. This analysis, which includes data for more than 17 million people in the UK, suggests that patients with chronic kidney disease are at higher risk than those with other known risk factors, including chronic heart and lung disease. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41581-020-00349-4

Publication Date: Aug 25, 2020

Coronavirus research updates: Reinfection with SAR-CoV-2 is confirmed for the first time with genetic evidence

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

Reinfection with SARS-CoV-2 is confirmed for the first time with genetic evidence (August 25, 2020):

A man in Hong Kong, who was ill with COVID-19 in March was infected by a different variant of the new coronavirus several months later — the first evidence for reinfection that is supported by genetic analysis.

People infected with SARS-CoV-2 mount an immune response, which scientists think probably prevents most reinfections. The durability of this protection is unclear, and a documented case of reinfection would signal that immunity can wane. But previously reported reinfections have been found to relate instead to prolonged shedding of the virus or its genetic material. Kwok-Yung Yuen and his colleagues at the University of Hong Kong identified a 33-year-old man who recovered from COVID-19 in April and

tested positive again more than 4 months later, after returning from Spain via the United Kingdom (K. K.-W. To *et al.* Clin. Infect. Dis. http://doi.org/d7ds; 2020). Genetic sequencing suggested that the second infection was caused by a virus that was genetically distinct from the one responsible for his initial bout. The man never developed symptoms from the second infection, but his immune system responded by producing a fresh batch of antibodies.

Vaccines given through the nose could protect against infection (August 21, 2020):

A man Studies in mice and monkeys show that nasal vaccinations can shield the animals from the new coronavirus — and that such vaccinations might be more effective than an injected form of the same vaccine.

David Curiel and Michael Diamond at Washington University School of Medicine in St Louis, Missouri, and their colleagues created a candidate vaccine encoding the SARS-CoV-2 spike protein, which the virus uses to invade cells (A. O. Hassan et al. Cell http://doi.org/d63k; 2020). The researchers then gave the vaccine to bioengineered mice that had human receptors for the protein.

After being injected with the vaccine and then exposed to SARS-CoV-2, mice showed no infectious virus in their lungs — but their lungs did harbour small amounts of viral RNA. By contrast, mice that had the vaccine inserted up their noses before exposure had no measurable viral RNA in their lungs. This and other evidence suggests that the nasal vaccine entirely warded off infection, the authors say. Ling Chen at the First Affiliated Hospital of Guangzhou Medical University in China and colleagues developed another vaccine encoding the spike protein (L. Feng et al. Nature Commun. 11, 4207; 2020). The researchers found that both nasal and injected forms of the vaccine protected rhesus macaques (Macaca mulatta) from infection. The authors say that a vaccine that can be given by nose might allow people to vaccinate themselves.

A coronavirus mutation is tied to less severe illness (August 20, 2020):

A SARS-CoV-2 mutation that appeared in East Asia early in the pandemic is linked to symptoms milder than those caused by the unmutated version of the virus. In early 2020, researchers in Singapore identified a cluster of COVID-19 cases caused by a SARS-CoV-2 variant missing a chunk of DNA that spanned two genes, ORF7b and

ORF8. To determine the consequences of this change, called a deletion, Lisa Ng at the Singapore Immunology Network and colleagues compared people infected with viruses carrying the deletion with those infected by normal viruses (B. E. Young et al. Lancet http://doi.org/d6x7; 2020). None of the 29 people whose viruses had the mutation needed supplemental oxygen, but 26 of the 92 people whose viruses lacked the mutation did. Viruses carrying the deletion haven't been detected since March — possibly owing to infection-control measures.

The virus responsible for the 2002–04 outbreak of severe acute respiratory syndrome (SARS) acquired a similar deletion in the ORF8 gene, suggesting that this might be an important adaption to infecting humans, the authors say.

Reference

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

The coronavirus may shut down the immune system's vital classrooms

At the top of the long list of uncertainties about COVID-19 is whether people who recover will develop durable immune responses to the coronavirus that causes it. A research team that has autopsied people who died from COVID-19 has now discovered they lack so-called germinal centers, classrooms in the spleen and lymph nodes in which immune cells learn to mount a long-lasting antibody response to a pathogen. Although the finding may not apply to people who have mild or asymptomatic coronavirus infections, it may help explain COVID-19 progression in the sickest cases and provide important insights to vaccine developers.

The study, led by immunologist Shiv Pillai of the Ragon Institute of MGH, MIT and Harvard and published last week in Cell, may take on increased importance as a report out yesterday provided the first compelling evidence that a person can become reinfected with SARS-CoV-2, suggesting antibody protection could be fleeting in some people. A "storm" of cytokines, biochemicals that send messages to B cells and other immune system actors, occurs in response to some SARS-CoV-2 infections, contributing to inflammation and severe disease. Pillai's team found that lymph nodes in the COVID-19 deaths had a large increase in the amount of one of these cytokines, tumor necrosis factor alpha (TNF-α), in comparison with the control autopsies. The

researchers also found a lack of a type of T cell that plays a central role in forming the germinal centers and they propose the excessive TNF-α blocks its creation, as found in some mouse studies.

But Pillai agrees with many immunologists who believe SARS-CoV-2 does not appear to be a particularly difficult virus to stop with a vaccine. He is even confident that a properly designed vaccine could lead to durable antibody responses to SARS-CoV-2. But he hopes vaccine developers take note of his group's findings. "If you are making too much TNF-α in the lymph nodes, maybe your vaccination won't last that long," he says.

Reference

https://www.sciencemag.org/news/2020/08/coronavirus-may-shut-down-immune-system-s-vital-classrooms

Publication Date: Aug 24, 2020

New drool-based tests are replacing the dreaded coronavirus nasal swab

When SARS-CoV-2, the respiratory virus that causes COVID-19, emerged in December 2019, researchers scrambled to develop tests to detect the virus. Initially, they turned to a long-trusted technique for diagnosing respiratory infections: looking for viral genetic material in mucosal fluid, thought to be the best hunting ground for a respiratory virus, collected from deep in a patient's nasal passages. That's where the 15-centimeter swab comes in. The swab goes into a plastic tube with a chemical mixture that stabilizes the virus during transport to a diagnostics lab. There, technicians extract its genetic material and load it into a machine to carry out the polymerase chain reaction (PCR), which amplifies snippets of genetic material unique to the virus. The procedure accurately identifies infections about 95% of the time. But the test is uncomfortable and, because collecting the swab requires close contact with patients, it puts medical personnel at risk of contracting the virus.

A new saliva test for RNA viruses, such as Zika and SARS-CoV-2, was reported last week in Science Advances by researchers at the University at Albany. It could be even faster and cheaper because it does not need expensive lab equipment such as PCR

machines. Rather than amplifying RNA to identify the virus, the approach uses snippets of DNA that bind to short, unique sections of RNA and change them from linear strands to loops. That alters how the RNA behaves in a common lab procedure known as gel electrophoresis, making it easy to detect. For more details, read the link given below.

Reference

https://www.sciencemag.org/news/2020/08/new-drool-based-tests-are-replacing-dreaded-coronavirus-nasal-swab

COMMENT

Publication Date: Aug 25, 2020

Delirium: A suggestive sign of COVID-19 in dementia

Approximately 40% - 60% of people with dementia in residential care facilities experience behavioral and psychological symptoms (BPSD), such as agitation, psychosis, or apathy. During the COVID-19, older adults with dementia were likely to develop behavioral changes. Among multiple factors contributing to the behavioral disturbances in unprecedented times, delirium was not well recognized in dementia, especially among those without respiratory failure. In the EClinicalMedicine, Tino Emanuele Poloni and colleagues report a retrospective study of delirium superimposed on dementia during the COVID-19 outbreak peak in a dementia facility in Italy. Based on a review of the medical charts of 57 residents with positive SARS-CoV-2 infection in the residential care facility, Poloni *et al*. found that delirium occurred as the initial presentation in about 38.7% of the subjects. Hypoactive (52.4%) delirium was slightly more prevalent than hyperactive (47.6%) delirium. The prevalence of delirium increased with age. Persons with moderate and severe dementia had a higher prevalence of delirium than those in the advanced dementia stage. In the study facility, residents with delirium-onset COVID-19 had higher mortality than those who did not manifest delirium at onset (mortality rate: 52.4% vs. 8.3%, OR=17.0, 95% CI: 2.8–102.7). Besides, the male gender and multiple comorbidities increased the risk of COVID-19 mortality.

Delirium in older people with dementia may represent a prodromal phase of COVID-19. Therefore, in clinical practice, it is particularly important to increase access to the CAM screening and encourage prompt pharyngeal swab testing in high-risk settings, such as dementia care facilities. Further investigations on the mechanism of the COVID-19 on CNS are warranted. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30268-6/fulltext

Differentiating diagnosis of COVID-19 or influenza in patients based on laboratory data during flu season

Both coronaviruses and influenza A viruses (IAVs) are general pathogens which are responsible for the seasonal cold. However, a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is pulling the world into the torment of the COVID-19 pandemic. As the SARS-CoV-2 is still circulating in almost every continent with its ability for airborne and asymptomatic transmission, it would be very likely that the COVID-19 pandemic will overlap with the influenza epidemic in the coming winter. COVID-19 shares many clinical symptoms with pneumonia caused by IAVs, but its fatality rate is much higher than that of seasonal flu. Therefore, to precisely treat patients with respiratory diseases during the epidemic season, it would be very important that doctors are able to differentiate COVID-19 from seasonal influenza based on laboratory data as early as possible.

Currently published clinical and laboratory data on COVID-19 are limited to studies with small sample sizes mostly originating from China. In the study, Ji *et al.* in Northwestern University reveals significant differences in laboratory parameters between hospitalized COVID-19 and influenza patients in the US, with a sample size of more than 1000 cases. Instead of comparing clinical endpoints to evaluate risks, they compiled and temporally tracked all available laboratory results of the hospitalized patients from the day of presentation to day 14. Compared to influenza patients, the most significant differences over the course of 14 days of hospitalization in COVID-19 patients were faster worsening anemia and leukocytosis, and a more rapid increase in D-dimer, BUN, and ALT. The level of lactate dehydrogenase (LDH) was significantly higher in patients with influenza. However, the most commonly reported laboratory abnormalities in COVID-19 include lymphopenia, prolonged prothrombin time (PT), and elevated LDH.

It would be interesting to further investigate whether the different risk clusters of COVID-19 correlate with the pathophysiology in these patients. Future studies on specific organ systems in correlation with other clinical manifestations, including the level of inflammatory cytokines, may be useful to confirm the underlying pathology in patients in these clusters. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30255-8/fulltext

EDITORIAL

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Growth factors and SARS-CoV-2

There is an urgent need to better understand the molecular mechanisms underlying infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that has caused the coronavirus disease 2019 (COVID-19) pandemic, so that effective therapies can be developed. Klann et al., performed phosphoproteomics analysis of a colonic epithelial cell line infected with SARS-CoV-2 in vitro to determine changes in the relative abundances (compared to those in mock-infected cells) of phosphorylated proteins 24 hours after infection. The authors first identified phosphorylation sites in six viral proteins expressed in the infected cells, many of which are targeted by kinases of CMGC family, which includes casein kinase II (CK2). Protein-protein coregulation analysis revealed three clusters of phosphorylated proteins that were affected by SARS-CoV-2 infection. One such cluster included proteins in signaling pathways activated by the growth factor receptors EGFR and PDGFR. The authors tested clinically approved anticancer drugs that inhibit the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, both of which are downstream of growth factor receptors, and found five such drugs that inhibited SARS-CoV-2 replication in two different cell lines at clinically relevant concentrations. Together, these data provide a useful resource for the analysis of the signaling pathways affected by viral infection and indicate approved drugs that should be further investigated in other models of SARS-CoV-2 infection to determine whether they can be repurposed as antiviral agents.

Reference

https://stke.sciencemag.org/content/13/646/eabe4450