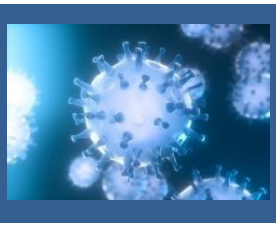
COVID-19

Aug 26 - Sep 01, 2021



RESEARCH PUBLICATIONS

Publication Date: Sep 01, 2021

Label-free SARS-CoV-2 detection and classification using phase imaging with computational specificity

Abstract

Efforts to mitigate the COVID-19 crisis revealed that fast, accurate, and scalable testing is crucial for curbing the current impact and that of future pandemics. An optical method was proposed for directly imaging unlabeled viral particles and using deep learning for detection and classification. An ultrasensitive interferometric method was used to image four virus types with nanoscale optical path-length sensitivity. Pairing these data with fluorescence images for ground truth, we trained semantic segmentation models based on U-Net, a particular type of convolutional neural network. The trained network was applied to classify the viruses from the interferometric images only, containing simultaneously SARS-CoV-2, H1N1 (influenza-A virus), HAdV (adenovirus), and ZIKV (Zika virus). Remarkably, due to the nanoscale sensitivity in the input data, the neural network was able to identify SARS-CoV-2 vs. the other viruses with 96% accuracy. The inference time for each image is 60 ms, on a common graphic-processing unit. This approach of directly imaging unlabeled viral particles may provide an extremely fast test, of less than a minute per patient. As the imaging instrument operates on regular glass slides, we envision this method as potentially testing on patient breath condensates. The necessary high throughput can be achieved by translating concepts from digital pathology, where a microscope can scan hundreds of slides automatically.

Reference

https://www.nature.com/articles/s41377-021-00620-8

Targeting SARS-CoV-2 receptor-binding domain to cells expressing CD40 improves protection to infection in convalescent macaques

Abstract

Achieving sufficient worldwide vaccination coverage against SARS-CoV-2 will require additional approaches to currently approved viral vector and mRNA vaccines. Subunit vaccines may have distinct advantages when immunizing vulnerable individuals, children and pregnant women. Here, a new generation of subunit vaccines targeting viral antigens was presented to CD40-expressing antigen-presenting cells. It was demonstrated that targeting the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein to CD40 (αCD40.RBD) induces significant levels of specific T and B cells, with long-term memory phenotypes, in a humanized mouse model. Additionally, it was demonstrated that a single dose of the αCD40.RBD vaccine, injected without adjuvant, is sufficient to boost a rapid increase in neutralizing antibodies in convalescent non-human primates (NHPs) exposed six months previously to SARS-CoV-2. Vaccine-elicited antibodies cross-neutralize different SARS-CoV-2 variants, including D614G, B1.1.7 and to a lesser extent B1.351. Such vaccination significantly improves protection against a new high-dose virulent challenge versus that in non-vaccinated convalescent animals.

Reference

https://www.nature.com/articles/s41467-021-25382-0

A dual-role of SARS-CoV-2 nucleocapsid protein in regulating innate immune response

Abstract

The recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the causative agent of ongoing global pandemic of COVID-19, may trigger immunosuppression in the early stage and overactive immune response in the late stage of infection; However, the underlying mechanisms are not well understood. Here we demonstrated that the SARS-CoV-2 nucleocapsid (N) protein dually regulated innate immune responses, i.e., the low-dose N protein suppressed type I interferon (IFN-I) signaling and inflammatory cytokines, whereas high-dose N protein promoted IFN-I

signaling and inflammatory cytokines. Mechanistically, the SARS-CoV-2 N protein dually regulated the phosphorylation and nuclear translocation of IRF3, STAT1, and STAT2. Additionally, low-dose N protein combined with TRIM25 could suppress the ubiquitination and activation of retinoic acid-inducible gene I (RIG-I). The findings revealed a regulatory mechanism of innate immune responses by the SARS-CoV-2 N protein, which would contribute to understanding the pathogenesis of SARS-CoV-2 and other SARS-like coronaviruses, and development of more effective strategies for controlling COVID-19.

Reference

https://www.nature.com/articles/s41392-021-00742-w

Cellular host factors for SARS-CoV-2 infection

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has claimed millions of lives and caused a global economic crisis. No effective antiviral drugs are currently available to treat infections of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The medical need imposed by the pandemic has spurred unprecedented research efforts to study coronavirus biology. Every virus depends on cellular host factors and pathways for successful replication. These proviral host factors represent attractive targets for antiviral therapy as they are genetically more stable than viral targets and may be shared among related viruses. The application of various ‘omics’ technologies, has led to the rapid discovery of proviral host factors that are required for the completion of the SARS-CoV-2 life cycle. In this Review, we summarize insights into the proviral host factors that are required for SARS-CoV-2 infection that were mainly obtained using functional genetic and interactome screens. Cellular processes were discussed that are important for the SARS-CoV-2 life cycle, as well as parallels with non-coronaviruses. Finally, we highlight host factors that could be targeted by clinically approved molecules and molecules in clinical trials as potential antiviral therapies for COVID-19.

Reference

https://www.nature.com/articles/s41564-021-00958-0

Pro-inflammatory microenvironment and systemic accumulation of CXCR3$^+$ cell exacerbate lung pathology of old rhesus macaques infected with SARS-CoV-2

Abstract

Understanding the pathological features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in an animal model is crucial for the treatment of coronavirus disease 2019 (COVID-19). Here, immunopathological changes were compared in young and old rhesus macaques (RMs) before and after SARS-CoV-2 infection at the tissue level. Quantitative analysis of multiplex immunofluorescence staining images of formalin-fixed paraffin-embedded (FFPE) sections showed that SARS-CoV-2 infection specifically induced elevated levels of apoptosis, autophagy, and nuclear factor kappa-B (NF-κB) activation of angiotensin-converting enzyme 2 (ACE2)+ cells, and increased interferon α (IFN-α)- and interleukin 6 (IL-6)-secreting cells and C-X-C motif chemokine receptor 3 (CXCR3)+ cells in lung tissue of old RMs. This pathological pattern, which may be related to the age-related pro-inflammatory microenvironment in both lungs and spleens, was significantly correlated with the systemic accumulation of CXCR3+ cells in lungs, spleens, and peripheral blood. Furthermore, the ratio of CXCR3+ to T-box protein expression in T cell (T-bet)+ (CXCR3+/T-bet+ ratio) in CD8+ cells may be used as a predictor of severe COVID-19. These findings uncovered the impact of aging on the immunopathology of early SARS-CoV-2 infection and demonstrated the potential application of CXCR3+ cells in predicting severe COVID-19.

Reference

https://www.nature.com/articles/s41392-021-00734-w

SARS-CoV-2-specific T cells in infection and vaccination

Abstract

During viral infections, antibodies and T cells act together to prevent pathogen spread and remove virus-infected cells. Virus-specific adaptive immunity can, however, also trigger pathological processes characterized by localized or systemic inflammatory events. The protective and/or pathological role of virus-specific T cells in SARS-CoV-2 infection has been the focus of many studies in COVID-19 patients and in vaccinated individuals. Here, the works were reviewed that have elucidated the function of SARS-

CoV-2-specific T cells in patients and in vaccinated individuals. Understanding whether SARS-CoV-2-specific T cells are more linked to protection or pathogenesis is pivotal to define future therapeutic and prophylactic strategies to manage the current pandemic.

Reference

https://www.nature.com/articles/s41423-021-00743-3

Distinct systemic and mucosal immune responses during acute SARS-CoV-2 infection

Abstract

Coordinated local mucosal and systemic immune responses following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection either protect against coronavirus disease 2019 (COVID-19) pathologies or fail, leading to severe clinical outcomes. To understand this process, an integrated analysis of SARS-CoV-2 spike-specific antibodies, cytokines, viral load and bacterial communities was performed in paired nasopharyngeal swabs and plasma samples from a cohort of clinically distinct patients with COVID-19 during acute infection. Plasma viral load was associated with systemic inflammatory cytokines that were elevated in severe COVID-19, and also with spike-specific neutralizing antibodies. By contrast, nasopharyngeal viral load correlated with SARS-CoV-2 humoral responses but inversely with interferon responses, the latter associating with protective microbial communities. Potential pathogenic microorganisms, often implicated in secondary respiratory infections, were associated with mucosal inflammation and elevated in severe COVID-19. The results demonstrate distinct tissue compartmentalization of SARS-CoV-2 immune responses and highlight a role for the nasopharyngeal microbiome in regulating local and systemic immunity that determines COVID-19 clinical outcomes.

Reference

https://www.nature.com/articles/s41590-021-01028-7

Multiomics: Unraveling the panoramic landscapes of SARS-CoV-2 infection

Abstract

In response to emerging infectious diseases, such as the recent pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it is critical to quickly identify and understand responsible pathogens, risk factors, host immune responses, and pathogenic mechanisms at both the molecular and cellular levels. The recent development of multiomic technologies, including genomics, proteomics, metabolomics, and single-cell transcriptomics, has enabled a fast and panoramic grasp of the pathogen and the disease. Here, the major advances in the virology, immunology, and pathogenic mechanisms of SARS-CoV-2 infection were systematically reviewed that have been achieved *via* multiomic technologies. Based on well-established cohorts, omics-based methods can greatly enhance the mechanistic understanding of diseases, contributing to the development of new diagnostics, drugs, and vaccines for emerging infectious diseases, such as COVID-19.

Reference

https://www.nature.com/articles/s41423-021-00754-0

Assessing the extent and timing of chemosensory impairments during COVID-19 pandemic

Abstract

Chemosensory impairments have been established as a specific indicator of COVID-19. They affect most patients and may persist long past the resolution of respiratory symptoms, representing an unprecedented medical challenge. Since the SARS-CoV-2 pandemic started, it was now known much more about smell, taste, and chemesthesis loss associated with COVID-19. However, the temporal dynamics and characteristics of recovery are still unknown. Here, capitalizing on data from the Global Consortium for Chemosensory Research (GCCR) crowdsourced survey, chemosensory abilities were assessed after the resolution of respiratory symptoms in participants diagnosed with COVID-19 during the first wave of the pandemic in Italy. This analysis led to the identification of two patterns of chemosensory recovery, partial and substantial, which

were found to be associated with differential age, degrees of chemosensory loss, and regional patterns. Uncovering the self-reported phenomenology of recovery from smell, taste, and chemesthetic disorders is the first, yet essential step, to provide healthcare professionals with the tools to take purposeful and targeted action to address chemosensory disorders and their severe discomfort.

Reference

https://www.nature.com/articles/s41598-021-96987-0

A virus-free cellular model recapitulates several features of severe COVID-19

Abstract

As for all newly-emergent pathogens, SARS-CoV-2 presents with a relative paucity of clinical information and experimental models, a situation hampering both the development of new effective treatments and the prediction of future outbreaks. Here, it was found that a simple virus-free model, based on publicly available transcriptional data from human cell lines, is surprisingly able to recapitulate several features of the clinically relevant infections. By segregating cell lines (n = 1305) from the CCLE project on the base of their sole angiotensin-converting enzyme 2 (ACE2) mRNA content, we found that overexpressing cells present with molecular features resembling those of at-risk patients, including senescence, impairment of antibody production, epigenetic regulation, DNA repair and apoptosis, neutralization of the interferon response, proneness to an overemphasized innate immune activity, hyperinflammation by IL-1, diabetes, hypercoagulation and hypogonadism. Likewise, several pathways were found to display a differential expression between sexes, with males being in the least advantageous position, thus suggesting that the model could reproduce even the sex-related disparities observed in the clinical outcome of patients with COVID-19. Overall, besides validating a new disease model, our data suggest that, in patients with severe COVID-19, a baseline ground could be already present and, as a consequence, the viral infection might simply exacerbate a variety of latent (or inherent) pre-existing conditions, representing therefore a tipping point at which they become clinically significant.

Reference

https://www.nature.com/articles/s41598-021-96875-7

Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: A substudy of two randomised controlled trials (COV001 and COV002)

Abstract

Background: COVID-19 vaccine supply shortages are causing concerns about compromised immunity in some countries as the interval between the first and second dose becomes longer. Conversely, countries with no supply constraints are considering administering a third dose. The persistence of immunogenicity was assessed after a single dose of ChAdOx1 nCoV-19 (AZD1222), immunity after an extended interval (44–45 weeks) between the first and second dose, and response to a third dose as a booster given 28–38 weeks after the second dose.

Methods: In this substudy, volunteers aged 18–55 years who were enrolled in the phase 1/2 (COV001) controlled trial in the UK and had received either a single dose or two doses of 5 × 1010 viral particles were invited back for vaccination. Here the reactogenicity and immunogenicity of a delayed second dose (44–45 weeks after first dose) or a third dose of the vaccine (28–38 weeks after second dose), were reported. Data from volunteers aged 18–55 years who were enrolled in either the phase 1/2 (COV001) or phase 2/3 (COV002), single-blinded, randomised controlled trials of ChAdOx1 nCoV-19 and who had previously received a single dose or two doses of 5 × 1010 viral particles are used for comparison purposes. COV001 is registered with ClinicalTrials.gov, NCT04324606, and ISRCTN, 15281137, and COV002 is registered with ClinicalTrials.gov, NCT04400838, and ISRCTN, 15281137, and both are continuing but not recruiting.

Findings: Between March 11 and 21, 2021, 90 participants were enrolled in the third-dose boost substudy, of whom 80 (89%) were assessable for reactogenicity, 75 (83%) were assessable for evaluation of antibodies, and 15 (17%) were assessable for T-cells responses. The two-dose cohort comprised 321 participants who had reactogenicity data (with prime-boost interval of 8–12 weeks: 267 [83%] of 321; 15–25 weeks: 24 [7%]; or 44–45 weeks: 30 [9%]) and 261 who had immunogenicity data (interval of 8–12

weeks: 115 [44%] of 261; 15–25 weeks: 116 [44%]; and 44–45 weeks: 30 [11%]). 480 participants from the single-dose cohort were assessable for immunogenicity up to 44–45 weeks after vaccination. Antibody titres after a single dose measured approximately 320 days after vaccination remained higher than the titres measured at baseline (geometric mean titre of 66·00 ELISA units [EUs; 95% CI 47·83–91·08] vs 1·75 EUs [1·60–1·93]). 32 participants received a late second dose of vaccine 44–45 weeks after the first dose, of whom 30 were included in immunogenicity and reactogenicity analyses. Antibody titres were higher 28 days after vaccination in those with a longer interval between first and second dose than for those with a short interval (median total IgG titre: 923 EUs [IQR 525–1764] with an 8–12 week interval; 1860 EUs [917–4934] with a 15–25 week interval; and 3738 EUs [1824–6625] with a 44–45 week interval). Among participants who received a third dose of vaccine, antibody titres (measured in 73 [81%] participants for whom samples were available) were significantly higher 28 days after a third dose (median total IgG titre: 3746 EUs [IQR 2047–6420]) than 28 days after a second dose (median 1792 EUs [IQR 899–4634]; Wilcoxon signed rank test p=0·0043). T-cell responses were also boosted after a third dose (median response increased from 200 spot forming units [SFUs] per million peripheral blood mononuclear cells [PBMCs; IQR 127–389] immediately before the third dose to 399 SFUs per milion PBMCs [314–662] by day 28 after the third dose; Wilcoxon signed rank test p=0·012). Reactogenicity after a late second dose or a third dose was lower than reactogenicity after a first dose.

Interpretation: An extended interval before the second dose of ChAdOx1 nCoV-19 leads to increased antibody titres. A third dose of ChAdOx1 nCoV-19 induces antibodies to a level that correlates with high efficacy after second dose and boosts T-cell responses.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01699-8/fulltext

Automated processing of thermal imaging to detect COVID-19

Abstract

Rapid and sensitive screening tools for SARS-CoV-2 infection are essential to limit the spread of COVID-19 and to properly allocate national resources. Here, a new point-of-care, non-contact thermal imaging tool was developed to detect COVID-19, based on

advanced image processing algorithms. Thermal images of the backs of individuals were captured with and without COVID-19 using a portable thermal camera that connects directly to smartphones. The novel image processing algorithms automatically extracted multiple texture and shape features of the thermal images and achieved an area under the curve (AUC) of 0.85 in COVID-19 detection with up to 92% sensitivity. Thermal imaging scores were inversely correlated with clinical variables associated with COVID-19 disease progression. In summary, it was shown, for the first time, that a hand-held thermal imaging device can be used to detect COVID-19. Non-invasive thermal imaging could be used to screen for COVID-19 in out-of-hospital settings, especially in low-income regions with limited imaging resources.

Reference

https://www.nature.com/articles/s41598-021-96900-9

Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: A prospective, community-based, nested, case-control study

Abstract

Background: COVID-19 vaccines show excellent efficacy in clinical trials and effectiveness in real-world data, but some people still become infected with SARS-CoV-2 after vaccination. This study aimed to identify risk factors for post-vaccination SARS-CoV-2 infection and describe the characteristics of post-vaccination illness.

Methods: This prospective, community-based, nested, case-control study used self-reported data (eg, on demographics, geographical location, health risk factors, and COVID-19 test results, symptoms, and vaccinations) from UK-based, adult (≥18 years) users of the COVID Symptom Study mobile phone app. For the risk factor analysis, cases had received a first or second dose of a COVID-19 vaccine between Dec 8, 2020, and July 4, 2021; had either a positive COVID-19 test at least 14 days after their first vaccination (but before their second; cases 1) or a positive test at least 7 days after their second vaccination (cases 2); and had no positive test before vaccination. Two control groups were selected (who also had not tested positive for SARS-CoV-2 before vaccination): users reporting a negative test at least 14 days after their first vaccination but before their second (controls 1) and users reporting a negative test at least 7 days

after their second vaccination (controls 2). Controls 1 and controls 2 were matched (1:1) with cases 1 and cases 2, respectively, by the date of the post-vaccination test, health-care worker status, and sex. In the disease profile analysis, we sub-selected participants from cases 1 and cases 2 who had used the app for at least 14 consecutive days after testing positive for SARS-CoV-2 (cases 3 and cases 4, respectively). Controls 3 and controls 4 were unvaccinated participants reporting a positive SARS-CoV-2 test who had used the app for at least 14 consecutive days after the test, and were matched (1:1) with cases 3 and 4, respectively, by the date of the positive test, health-care worker status, sex, body-mass index (BMI), and age. We used univariate logistic regression models (adjusted for age, BMI, and sex) to analyse the associations between risk factors and post-vaccination infection, and the associations of individual symptoms, overall disease duration, and disease severity with vaccination status.

Findings: Between Dec 8, 2020, and July 4, 2021, 1 240 009 COVID Symptom Study app users reported a first vaccine dose, of whom 6030 (0·5%) subsequently tested positive for SARS-CoV-2 (cases 1), and 971 504 reported a second dose, of whom 2370 (0·2%) subsequently tested positive for SARS-CoV-2 (cases 2). In the risk factor analysis, frailty was associated with post-vaccination infection in older adults (≥60 years) after their first vaccine dose (odds ratio [OR] 1·93, 95% CI 1·50–2·48; p<0·0001), and individuals living in highly deprived areas had increased odds of post-vaccination infection following their first vaccine dose (OR 1·11, 95% CI 1·01–1·23; p=0·039). Individuals without obesity (BMI <30 kg/m2) had lower odds of infection following their first vaccine dose (OR 0·84, 95% CI 0·75–0·94; p=0·0030). For the disease profile analysis, 3825 users from cases 1 were included in cases 3 and 906 users from cases 2 were included in cases 4. Vaccination (compared with no vaccination) was associated with reduced odds of hospitalisation or having more than five symptoms in the first week of illness following the first or second dose, and long-duration (≥28 days) symptoms following the second dose. Almost all symptoms were reported less frequently in infected vaccinated individuals than in infected unvaccinated individuals, and vaccinated participants were more likely to be completely asymptomatic, especially if they were 60 years or older.

Interpretation: To minimise SARS-CoV-2 infection, at-risk populations must be targeted in efforts to boost vaccine effectiveness and infection control measures. The findings

might support caution around relaxing physical distancing and other personal protective measures in the post-vaccination era, particularly around frail older adults and individuals living in more deprived areas, even if these individuals are vaccinated, and might have implications for strategies such as booster vaccinations.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00460-6/fulltext

Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): A randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

Abstract

Background: Baricitinib is an oral selective Janus kinase 1/2 inhibitor with known anti-inflammatory properties. This study evaluates the efficacy and safety of baricitinib in combination with standard of care for the treatment of hospitalised adults with COVID-19.

Methods: In this phase 3, double-blind, randomised, placebo-controlled trial, participants were enrolled from 101 centres across 12 countries in Asia, Europe, North America, and South America. Hospitalised adults with COVID-19 receiving standard of care were randomly assigned (1:1) to receive once-daily baricitinib (4 mg) or matched placebo for up to 14 days. Standard of care included systemic corticosteroids, such as dexamethasone, and antivirals, including remdesivir. The composite primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28, assessed in the intention-to-treat population. All-cause mortality by day 28 was a key secondary endpoint, and all-cause mortality by day 60 was an exploratory endpoint; both were assessed in the intention-to-treat population. Safety analyses were done in the safety population defined as all randomly allocated participants who received at least one dose of study drug and who were not lost to follow-up before the first post-baseline visit. This study is registered with ClinicalTrials.gov, NCT04421027.

Findings: Between June 11, 2020, and Jan 15, 2021, 1525 participants were randomly assigned to the baricitinib group (n=764) or the placebo group (n=761). 1204 (79·3%) of

1518 participants with available data were receiving systemic corticosteroids at baseline, of whom 1099 (91·3%) were on dexamethasone; 287 (18·9%) participants were receiving remdesivir. Overall, 27·8% of participants receiving baricitinib and 30·5% receiving placebo progressed to meet the primary endpoint (odds ratio 0·85 [95% CI 0·67 to 1·08], p=0·18), with an absolute risk difference of −2·7 percentage points (95% CI −7·3 to 1·9). The 28-day all-cause mortality was 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0·57 [95% CI 0·41–0·78]; nominal p=0·0018), a 38·2% relative reduction in mortality; one additional death was prevented per 20 baricitinib-treated participants. The 60-day all-cause mortality was 10% (n=79) for baricitinib and 15% (n=116) for placebo (HR 0·62 [95% CI 0·47–0·83]; p=0·0050). The frequencies of serious adverse events (110 [15%] of 750 in the baricitinib group vs 135 [18%] of 752 in the placebo group), serious infections (64 [9%] vs 74 [10%]), and venous thromboembolic events (20 [3%] vs 19 [3%]) were similar between the two groups.

Interpretation: Although there was no significant reduction in the frequency of disease progression overall, treatment with baricitinib in addition to standard of care (including dexamethasone) had a similar safety profile to that of standard of care alone, and was associated with reduced mortality in hospitalised adults with COVID-19.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00331-3/fulltext

Increased risk of severe clinical course of COVID-19 in carriers of HLA-C*04:01

Abstract

Background: Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, there has been increasing urgency to identify pathophysiological characteristics leading to severe clinical course in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Human leukocyte antigen alleles (HLA) have been suggested as potential genetic host factors that affect individual immune response to SARS-CoV-2. It was sought to evaluate this hypothesis by conducting a multicenter study using HLA sequencing.

Methods: It was analyzed the association between COVID-19 severity and HLAs in 435 individuals from Germany (n = 135), Spain (n = 133), Switzerland (n = 20) and the United States (n = 147), who had been enrolled from March 2020 to August 2020. This study included patients older than 18 years, diagnosed with COVID-19 and representing the full spectrum of the disease. Finally, we tested our results by meta-analysing data from prior genome-wide association studies (GWAS).

Findings: A potential association of HLA-C*04:01 was described with severe clinical course of COVID-19. Carriers of HLA-C*04:01 had twice the risk of intubation when infected with SARS-CoV-2 (risk ratio 1.5 [95% CI 1.1–2.1], odds ratio 3.5 [95% CI 1.9–6.6], adjusted p-value = 0.0074). These findings are based on data from four countries and corroborated by independent results from GWAS. The findings are biologically plausible, as HLA-C*04:01 has fewer predicted bindings sites for relevant SARS-CoV-2 peptides compared to other HLA alleles.

Interpretation: HLA-C*04:01 carrier state is associated with severe clinical course in SARS-CoV-2. Our findings suggest that HLA class I alleles have a relevant role in immune defense against SARS-CoV-2.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00379-5/fulltext

Age-stratified transmission model of COVID-19 in Ontario with human mobility during pandemic's first wave

Abstract

In this work, a data-fitted compartmental model was employed to visualize the progression and behavioural response to COVID-19 that match provincial case data in Ontario, Canada from February to June of 2020. This is a “rear-view mirror” glance at how this region has responded to the 1st wave of the pandemic, when testing was sparse and NPI measures were the only remedy to stave off the pandemic. An SEIR-type model was used with age-stratified subpopulations and their corresponding contact rates and asymptomatic rates in order to incorporate heterogeneity in the population and to calibrate the time-dependent reduction of Ontario-specific contact rates to reflect intervention measures in the province throughout lockdown and various stages of

social-distancing measures. Cell phone mobility data taken from Google, combining several mobility categories, allows us to investigate the effects of mobility reduction and other NPI measures on the evolution of the pandemic. Of interest here is our quantification of the effectiveness of Ontario's response to COVID-19 before and after provincial measures and our conclusion that the sharp decrease in mobility has had a pronounced effect in the first few weeks of the lockdown, while its effect is harder to infer once other NPI measures took hold.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)02008-9

Development of humoral and cellular immunological memory against SARS-CoV-2 despite B-cell depleting treatment in multiple sclerosis

Abstract

B-cell depleting therapies (BCDTs) are widely used as immunomodulating agents for autoimmune diseases such as multiple sclerosis. Their possible impact on development of immunity to SARS-CoV-2 has raised concerns with the COVID-19 pandemic. We here evaluated the frequency of COVID-19-like symptoms and determined immunological responses in participants of an observational trial comprising several multiple sclerosis disease modulatory drugs, (COMBAT-MS; NCT03193866) and in eleven patients after vaccination, with a focus on BCDT. Almost all seropositive and 17.9% of seronegative patients on BCDT, enriched for a history of COVID-19-like symptoms, developed anti-SARS-CoV-2 T-cell memory and T-cells displayed functional similarity to controls producing IFN-γ and TNF. Following vaccination, vaccine-specific humoral memory was impaired, while all patients developed a specific T-cell response. These results indicate that BCDTs do not abrogate SARS-CoV-2 cellular memory and provide a possible explanation as to why the majority of patients on BCDTs recover from COVID-19.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)01046-4

Predicting hosts based on early SARS-CoV-2 samples and analyzing the 2020 pandemic

Abstract

The SARS-CoV-2 pandemic has raised concerns in the identification of the hosts of the virus since the early stages of the outbreak. To address this problem, a deep learning method, DeepHoF, was proposed based on extracting viral genomic features automatically, to predict the host likelihood scores on five host types, including plant, germ, invertebrate, non-human vertebrate and human, for novel viruses. DeepHoF made up for the lack of an accurate tool, reaching a satisfactory AUC of 0.975 in the five-classification, and could make a reliable prediction for the novel viruses without close neighbors in phylogeny. Additionally, to fill the gap in the efficient inference of host species for SARS-CoV-2 using existing tools, we conducted a deep analysis on the host likelihood profile calculated by DeepHoF. Using the isolates sequenced in the earliest stage of the COVID-19 pandemic, it was inferred that minks, bats, dogs and cats were potential hosts of SARS-CoV-2, while minks might be one of the most noteworthy hosts. Several genes of SARS-CoV-2 demonstrated their significance in determining the host range. Furthermore, a large-scale genome analysis, based on DeepHoF's computation for the later pandemic in 2020, disclosed the uniformity of host range among SARS-CoV-2 samples and the strong association of SARS-CoV-2 between humans and minks.

Reference

https://www.nature.com/articles/s41598-021-96903-6

Mechanical activation of spike fosters SARS-CoV-2 viral infection

Abstract

The outbreak of SARS-CoV-2 (SARS2) has caused a global COVID-19 pandemic. The spike protein of SARS2 (SARS2-S) recognizes host receptors, including ACE2, to initiate viral entry in a complex biomechanical environment. Here, it was revealed that tensile force, generated by bending of the host cell membrane, strengthens spike recognition of ACE2 and accelerates the detachment of spike's S1 subunit from the S2

subunit to rapidly prime the viral fusion machinery. Mechanistically, such mechano-activation is fulfilled by force-induced opening and rotation of spike's receptor-binding domain to prolong the bond lifetime of spike/ACE2 binding, up to 4 times longer than that of SARS-S binding with ACE2 under 10 pN force application, and subsequently by force-accelerated S1/S2 detachment which is up to ~10^3 times faster than that in the no-force condition. Interestingly, the SARS2-S D614G mutant, a more infectious variant, shows 3-time stronger force-dependent ACE2 binding and 35-time faster force-induced S1/S2 detachment. It was also revealed that an anti-S1/S2 non-RBD-blocking antibody that was derived from convalescent COVID-19 patients with potent neutralizing capability can reduce S1/S2 detachment by 3×10^6 times under force. Our study sheds light on the mechano-chemistry of spike activation and on developing a non-RBD-blocking but S1/S2-locking therapeutic strategy to prevent SARS2 invasion.

Reference

https://www.nature.com/articles/s41422-021-00558-x

Trans-ethnic genome-wide association study of severe COVID-19

Abstract

COVID-19 has caused numerous infections with diverse clinical symptoms. To identify human genetic variants contributing to the clinical development of COVID-19, 1457 (598/859 with severe/mild symptoms) patients of Chinese ancestry were genotyped and 1141 (severe/mild: 474/667) were sequenced. It was further incorporated that 1401 genotyped and 948 sequenced ancestry-matched population controls, and tested genome-wide association on 1072 severe cases versus 3875 mild or population controls, followed by trans-ethnic meta-analysis with summary statistics of 3199 hospitalized cases and 897,488 population controls from the COVID-19 Host Genetics Initiative. It was identified that three significant signals outside the well-established 3p21.31 locus: an intronic variant in *FOXP4-AS1* (rs1853837, odds ratio OR = 1.28, $P = 2.51 \times 10^{-10}$, allele frequencies in Chinese/European AF = 0.345/0.105), a frameshift insertion in *ABO* (rs8176719, OR = 1.19, $P = 8.98 \times 10^{-9}$, AF = 0.422/0.395) and a Chinese-specific intronic variant in *MEF2B* (rs74490654, OR = 8.73, $P = 1.22 \times 10^{-8}$, AF = 0.004/0). These findings highlight an important role of

the adaptive immunity and the ABO blood-group system in protection from developing severe COVID-19.

Reference

https://www.nature.com/articles/s42003-021-02549-5

Microbial signatures in the lower airways of mechanically ventilated COVID-19 patients associated with poor clinical outcome

Abstract

Respiratory failure is associated with increased mortality in COVID-19 patients. There are no validated lower airway biomarkers to predict clinical outcome. It was investigated whether bacterial respiratory infections were associated with poor clinical outcome of COVID-19 in a prospective, observational cohort of 589 critically ill adults, all of whom required mechanical ventilation. For a subset of 142 patients who underwent bronchoscopy, we quantified SARS-CoV-2 viral load, analysed the lower respiratory tract microbiome using metagenomics and metatranscriptomics and profiled the host immune response. Acquisition of a hospital-acquired respiratory pathogen was not associated with fatal outcome. Poor clinical outcome was associated with lower airway enrichment with an oral commensal (Mycoplasma salivarium). Increased SARS-CoV-2 abundance, low anti-SARS-CoV-2 antibody response and a distinct host transcriptome profile of the lower airways were most predictive of mortality. Our data provide evidence that secondary respiratory infections do not drive mortality in COVID-19 and clinical management strategies should prioritize reducing viral replication and maximizing host responses to SARS-CoV-2.

Reference

https://www.nature.com/articles/s41564-021-00961-5

The association of community mobility with the time-varying reproduction number (R) of SARS-CoV-2: A modelling study across 330 local UK authorities

Abstract

Background: Community mobility data have been used to assess adherence to non-pharmaceutical interventions and its impact on SARS-CoV-2 transmission. The

association was assessed between location-specific community mobility and the reproduction number (R) of SARS-CoV-2 across UK local authorities.

Methods: In this modelling study, data was linked on community mobility from Google with data on R from 330 UK local authorities, for the period June 1, 2020, to Feb 13, 2021. Six mobility metrics are available in the Google community mobility dataset: visits to retail and recreation places, visits to grocery and pharmacy stores, visits to transit stations, visits to parks, visits to workplaces, and length of stay in residential places. For each local authority, we modelled the weekly change in R (the R ratio) per a rescaled weekly percentage change in each location-specific mobility metric relative to a pre-pandemic baseline period (Jan 3–Feb 6, 2020), with results synthesised across local authorities using a random-effects meta-analysis.

Findings: On a weekly basis, increased visits to retail and recreation places were associated with a substantial increase in R (R ratio 1·053 [99·2% CI 1·041–1·065] per 15% weekly increase compared with baseline visits) as were increased visits to workplaces (R ratio 1·060 [1·046–1·074] per 10% increase compared with baseline visits). By comparison, increased visits to grocery and pharmacy stores were associated with a small but still statistically significant increase in R (R ratio 1·011 [1·005–1·017] per 5% weekly increase compared with baseline visits). Increased visits to parks were associated with a decreased R (R ratio 0·972 [0·965–0·980]), as were longer stays at residential areas (R ratio 0·952 [0·928–0·976]). Increased visits to transit stations were not associated with R nationally, but were associated with a substantial increase in R in cities. An increasing trend was observed for the first 6 weeks of 2021 in the effect of visits to retail and recreation places and workplaces on R.

Interpretation: Increased visits to retail and recreation places, workplaces, and transit stations in cities are important drivers of increased SARS-CoV-2 transmission; the increasing trend in the effects of these drivers in the first 6 weeks of 2021 was possibly associated with the emerging alpha (B.1.1.7) variant. These findings provide important evidence for the management of current and future mobility restrictions.

Reference

https://www.thelancet.com/journals/landig/article/PIIS2589-7500(21)00144-8/fulltext

Cross-reactive $CD4^+$ T cells enhance SARS-CoV-2 immune responses upon infection and vaccination

Abstract

The functional relevance of pre-existing cross-immunity to SARS-CoV-2 is a subject of intense debate. Here, it was shown that human endemic coronavirus (HCoV)-reactive and SARS-CoV-2-cross-reactive $CD4^+$ T cells are ubiquitous but decrease with age. A universal immunodominant coronavirus-specific spike peptide (S816-830) was identified and demonstrated that pre-existing spike- and S816-830-reactive T cells were recruited into immune responses to SARS-CoV-2 infection and their frequency correlated with anti-SARS-CoV-2-S1-IgG antibodies. Spike-cross-reactive T cells were also activated after primary BNT162b2 COVID-19 mRNA vaccination displaying kinetics similar to secondary immune responses. The results highlight the functional contribution of pre-existing spike-cross-reactive T cells in SARS-CoV-2 infection and vaccination. Cross-reactive immunity may account for the unexpectedly rapid induction of immunity following primary SARS-CoV-2 immunization and the high rate of asymptomatic/mild COVID-19 disease courses.

Reference

https://www.science.org/doi/10.1126/science.abh1823

Antihypertensive drug treatment and susceptibility to SARS-CoV-2 infection in human PSC-derived cardiomyocytes and primary endothelial cells

Abstract

The pathogenicity of SARS-CoV-2 has been attributed to its ability to enter through the membrane-bound angiotensin-converting enzyme 2 (ACE2) receptor. Therefore, it has been heavily speculated that angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy may modulate SARS-CoV-2 infection. In this study, exposure of human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) and primary endothelial cells (hECs) to SARS-CoV-2 identified significant differences in protein coding genes involved in immunity, viral response, and cardiomyocyte/endothelial structure. Specifically, transcriptome changes were identified in the TNF, Interferon α/β, and MAPK (hPSC-CMs) as well as NF-kappaB (hECs)

signalling pathways. However, pre-treatment of hPSC-CMs or hECs with two widely prescribed antihypertensive medications, losartan and lisinopril, did not affect the susceptibility of either cell type to SARS-CoV-2 infection. These findings demonstrate the toxic effects of SARS-CoV-2 in hPSC-CMs/hECs and taken together with newly emerging multicenter trials, suggest that antihypertensive drug treatment alone does not alter SARS-CoV-2 infection.

Reference

https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(21)00436-7

Publication Date: Aug 30, 2021

Durability of antibody response to vaccination and surrogate neutralization of emerging variants based on SARS-CoV-2 exposure history

Abstract

Two-dose messenger RNA vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are highly effective in preventing symptomatic COVID-19 infection. However, the durability of protection is not known, nor is the effectiveness against emerging viral variants. Additionally, vaccine responses may differ based on prior SARS-CoV-2 exposure history. To investigate protection against SARS-CoV-2 variants we measured binding and neutralizing antibody responses following both vaccine doses. It was documented that significant declines in antibody levels three months post-vaccination, and reduced neutralization of emerging variants, highlighting the need to identify correlates of clinical protection to inform the timing of and indications for booster vaccination.

Reference

https://www.nature.com/articles/s41598-021-96879-3

Durable tracking anti-SARS-CoV-2 antibodies in cancer patients recovered from COVID-19

Abstract

Cancer patients are more susceptible to SARS-CoV-2 infection and generally have higher mortality rate. Anti-SARS-CoV-2 IgG is an important consideration for the patients in this COVID-19 pandemic. Recent researches suggested the rapid decay of anti-SARS-CoV-2 antibodies in the general population, but the decline rate of the antibodies in cancer patients was unknown. In this observational study, we reported the clinical features of the 53 cancer patients infected by SARS-CoV-2 from Wuhan, China and tracked the presence of anti-SARS-CoV-2 antibodies in the patients for more than 12 months. It was found that the duration (days) of anti-SARS-CoV-2 IgG in the patients was significant longer in chemotherapy (mean: 175; range: 75 to 315) and radiotherapy groups (mean: 168; range: 85 to 265) than in non-chemo- or radio-therapy group (mean: 58; range: 21 to 123) after their recovery from COVID-19. We also used single-cell RNA sequencing to track the immunologic changes in a representative patient recovered from COVID-19 and found that $CD8^+$ effective T cells, memory B cells and plasma cells were persistently activated in the patient undergoing chemotherapy. Together, the findings show that chemotherapy and radiotherapy might be beneficial to extend the duration of anti-SARS-CoV-2 IgG.

Reference

https://www.nature.com/articles/s41598-021-96195-w

Data-driven clustering identifies features distinguishing multisystem inflammatory syndrome from acute COVID-19 in children and adolescents

Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) consensus criteria were designed for maximal sensitivity and therefore capture patients with acute COVID-19 pneumonia.

Methods: Unsupervised clustering was performed on data from 1,526 patients (684 labeled MIS-C by clinicians) <21 years old hospitalized with COVID-19-related illness admitted between 15 March 2020 and 31 December 2020. Prevalence of assigned MIS-

C labels and clinical features were compared among clusters, followed by recursive feature elimination to identify characteristics of potentially misclassified MIS-C-labeled patients.

Findings: Of 94 clinical features tested, 46 were retained for clustering. Cluster 1 patients (N = 498; 92% labeled MIS-C) were mostly previously healthy (71%), with mean age 7·2 ± 0·4 years, predominant cardiovascular (77%) and/or mucocutaneous (82%) involvement, high inflammatory biomarkers, and mostly SARS-CoV-2 PCR negative (60%). Cluster 2 patients (N = 445; 27% labeled MIS-C) frequently had pre-existing conditions (79%, with 39% respiratory), were similarly 7·4 ± 2·1 years old, and commonly had chest radiograph infiltrates (79%) and positive PCR testing (90%). Cluster 3 patients (N = 583; 19% labeled MIS-C) were younger (2·8 ± 2·0 y), PCR positive (86%), with less inflammation. Radiographic findings of pulmonary infiltrates and positive SARS-CoV-2 PCR accurately distinguished cluster 2 MIS-C labeled patients from cluster 1 patients.

Interpretation: Using a data driven, unsupervised approach, we identified features that cluster patients into a group with high likelihood of having MIS-C. Other features identified a cluster of patients more likely to have acute severe COVID-19 pulmonary disease, and patients in this cluster labeled by clinicians as MIS-C may be misclassified. These data driven phenotypes may help refine the diagnosis of MIS-C.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00392-8/fulltext

Casirivimab–Imdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19

Abstract

Background: Real-world clinical data to support the use of casirivimab–imdevimab for the treatment of outpatients with mild to moderate coronavirus disease-19 (COVID-19) is needed. This study aimed to assess the outcomes of casirivimab–imdevimab treatment of mild to moderate COVID-19.

Methods: A retrospective cohort of 696 patients who received casirivimab–imdevimab between December 4, 2020 and April 9, 2021 was compared to a propensity-matched control of 696 untreated patients with mild to moderate COVID-19 at Mayo Clinic sites in Arizona, Florida, Minnesota, and Wisconsin. Primary outcome was rate of hospitalization at days 14, 21 and 28 after infusion.

Findings: The median age of the antibody-treated cohort was 63 years (interquartile range, 52–71); 45·5% were ≥65 years old; 51.4% were female. High-risk characteristics were hypertension (52.4%), body mass index ≥35 (31.0%), diabetes mellitus (24.6%), chronic lung disease (22.1%), chronic renal disease (11.4%), congestive heart failure (6.6%), and compromised immune function (6.7%). Compared to the propensity-matched untreated control, patients who received casirivimab–imdevimab had significantly lower all-cause hospitalization rates at day 14 (1.3% vs 3.3%; Absolute Difference: 2.0%; 95% confidence interval (CI): 0.5–3.7%), day 21 (1.3% vs 4.2%; Absolute Difference: 2.9%; 95% CI: 1.2–4.7%), and day 28 (1.6% vs 4.8%; Absolute Difference: 3.2%; 95% CI: 1.4–5.1%). Rates of intensive care unit admission and mortality at days 14, 21 and 28 were similarly low for antibody-treated and untreated groups.

Interpretation: Among high-risk patients with mild to moderate COVID-19, casirivimab–imdevimab treatment was associated with a significantly lower rate of hospitalization.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00382-5/fulltext

Host-specific asymmetric accumulation of mutation types reveals that the origin of SARS-CoV-2 is consistent with a natural process

Abstract

The capacity of RNA viruses to adapt to new hosts and rapidly escape the host immune system is largely attributable to *de novo* genetic diversity that emerges through mutations in RNA. Although the molecular spectrum of de novo mutations—the relative rates at which various base substitutions occur—are widely recognized as informative towards understanding the evolution of a viral genome, little attention has been paid to the possibility of using molecular spectra to infer the host origins of a virus. Here, the

molecular spectrum of *de novo* mutations was characterized for SARS-CoV-2 from transcriptomic data obtained from virus-infected cell lines, enabled by the use of sporadic junctions formed during discontinuous transcription as molecular barcodes. We find that de novo mutations are generated in a replication-independent manner, typically on the genomic strand, and highly dependent on mutagenic mechanisms specific to the host cellular environment. *De novo* mutations will then strongly influence the types of base substitutions accumulated during SARS-CoV-2 evolution, in an asymmetric manner favoring specific mutation types. Consequently, similarities between the mutation spectra of SARS-CoV-2 and the bat coronavirus RaTG13 which have accumulated since their divergence strongly suggest that SARS-CoV-2 evolved in a host cellular environment highly similar to that of bats before its zoonotic transfer into humans. Collectively, our findings provide data-driven support for the natural origin of SARS-CoV-2.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758(21)00084-9

Fab and Fc contribute to maximal protection against SARS-CoV-2 following NVX-CoV2373 subunit vaccine with Matrix-M™ vaccination

Abstract

Recently approved vaccines have shown remarkable efficacy in limiting SARS-CoV-2 associated disease. However, with the variety of vaccines, immunization strategies, and waning antibody titers, defining correlates of immunity across a spectrum of antibody titers is urgently required. Thus, the humoral immune response was profiled in a cohort of non-human primates immunized with a recombinant SARS-CoV-2 spike glycoprotein (NVX-CoV2373) at two doses, administered as a single or two-dose regimen. Both antigen dose and boosting significantly altered neutralization titers and Fc-effector profiles, driving unique vaccine-induced antibody fingerprints Combined differences in antibody effector functions and neutralization were associated with distinct levels of protection in the upper and lower respiratory tract. Moreover, NVX-CoV2373 elicited antibodies that functionally targeted emerging SARS-CoV-2 variants. Collectively, the data presented here suggest that a single dose may prevent disease via combined

Fc/Fab functions, but that two doses may be essential to block further transmission of SARS-CoV-2 and emerging variants.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00263-9

A comparative recombination analysis of human coronaviruses and implications for the SARS-CoV-2 pandemic

Abstract

The SARS-CoV-2 pandemic prompts evaluation of recombination in human coronavirus (hCoV) evolution. Recombination analyses of 158,118 public seasonal hCoV, SARS-CoV-1, SARS-CoV-2 and MERS-CoV genome sequences were undertook using the RDP4 software. It was found that moderate evidence for 8 SARS-CoV-2 recombination events, two of which involved the spike gene, and low evidence for one SARS-CoV-1 recombination event. Within MERS-CoV, 229E, OC43, NL63 and HKU1 datasets, we noted 7, 1, 9, 14, and 1 high-confidence recombination events, respectively. There was propensity for recombination breakpoints in the non-ORF1 region of the genome containing structural genes, and recombination severely skewed the temporal structure of these data, especially for NL63 and OC43. Bayesian time-scaled analyses on recombinant-free data indicated the sampled diversity of seasonal CoVs emerged in the last 70 years, with 229E displaying continuous lineage replacements. These findings emphasize the importance of genomic based surveillance to detect recombination in SARS-CoV-2, particularly if recombination may lead to immune evasion.

Reference

https://www.nature.com/articles/s41598-021-96626-8

Diagnostic performance of a colorimetric RT -LAMP for the identification of SARS-CoV-2: A multicenter prospective clinical evaluation in sub-Saharan Africa

Abstract

Background: Management and control of the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus SARS-CoV-2 is critically dependent on quick and reliable identification of the virus in clinical specimens. Detection of viral RNA by a colorimetric reverse transcription loop-mediated isothermal amplification (RT-LAMP) is a simple, reliable and cost-effective assay, deployable in resource-limited settings (RLS). The objective was to evaluate the intrinsic and extrinsic performances of RT-LAMP in RLS.

Methods: This is a multicenter prospective observational study of diagnostic accuracy, conducted from October 2020 to February 2021 in four African Countries: Cameroon, Ethiopia, Kenya and Nigeria; and in Italy. We enroled 1657 individuals who were either COVID-19 suspect cases, or asymptomatic and presented for screening. RNA extracted from pharyngeal swabs was tested in parallel by a colorimetric RT-LAMP and by a standard real time polymerase chain reaction (RT-PCR).

Findings: The sensitivity and specificity of index RT LAMP compared to standard RT-PCR on 1657 prospective specimens from infected individuals was determined. For a subset of 1292 specimens, which underwent exactly the same procedures in different countries, we obtained very high specificity (98%) and positive predictive value (PPV = 99%), while the sensitivity was 87%, with a negative predictive value NPV = 70%, Stratification of RT-PCR data showed superior sensitivity achieved with an RT-PCR cycle threshold (Ct) below 35 (97%), which decreased to 60% above 35.

Interpretation: In this field trial, RT-LAMP appears to be a reliable assay, comparable to RT-PCR, particularly with medium-high viral loads (Ct < 35). Hence, RT-LAMP can be deployed in RLS for timely management and prevention of COVID-19, without compromising the quality of output.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00381-3/fulltext

Outcomes among patients with breakthrough SARS-CoV-2 infection after vaccination in a high-risk national population

Abstract

Background: Breakthrough infections after SARS-CoV-2 infection have been reported. Clinical outcomes among persons with breakthrough infection are not known.

Methods: All Veterans were retrospectively identified with a confirmed SARS-CoV-2 infection >14 days after the second dose of either Pfizer-BNT-162b2 or Moderna-mRNA-1273 vaccine between December 15, 2020 and March 30, 2021, and age, race, sex, body mass index, Charlson comorbidity index, geographical location, and date of positive test matched unvaccinated controls with SARS-CoV-2 infection. The primary endpoint was the rate or severe disease defined as hospitalization, mechanical ventilation, or death in both groups.

Findings: Among 258,716 persons with both doses of vaccines and 756,150 without any vaccination, we identified 271 (0.1%) vaccinated persons with breakthrough infection and 48,114 (6.4%) unvaccinated matched controls with infection between December 15, 2020 and March 30, 2021. Among 213 matched pairs, symptoms were present in 33.3% of those with breakthrough infection and 42.2% of the controls. A total of 79 persons met the definition of severe disease or death (42 in the breakthrough infection group and 37 in the control group). Rate of severe disease or death per 1,000 person-days (95% CI) was 4.08 (2.64,5.31) among those with breakthrough infection and 3.6 (2.53,4.73) among the controls (P = 0.58). Rate was similar among both groups regardless of age-group, race, BMI or presence of comorbidities. Among persons with breakthrough infection and matched controls with infection, vaccination was not associated with a lower risk of severe disease or death in the main analyses but was associated with a lower risk when matching did not include geographic location (HR 0.62, 95% CI 0.43,0.91).

Interpretation: Demographic or clinical factors are not associated with a lower risk of severe disease or death in persons with breakthrough SARS-CoV-2 infection.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00397-7/fulltext

1-Year outcomes in hospital survivors with COVID-19: A longitudinal cohort study

Abstract

Background: The full range of long-term health consequences of COVID-19 in patients who are discharged from hospital is largely unclear. The aim of our study was to comprehensively compare consequences between 6 months and 12 months after symptom onset among hospital survivors with COVID-19.

Methods: An ambidirectional cohort study of COVID-19 survivors was undertook who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7 and May 29, 2020. At 6-month and 12-month follow-up visit, survivors were interviewed with questionnaires on symptoms and health-related quality of life (HRQoL), and received a physical examination, a 6-min walking test, and laboratory tests. They were required to report their health-care use after discharge and work status at the 12-month visit. Survivors who had completed pulmonary function tests or had lung radiographic abnormality at 6 months were given the corresponding tests at 12 months. Non-COVID-19 participants (controls) matched for age, sex, and comorbidities were interviewed and completed questionnaires to assess prevalent symptoms and HRQoL. The primary outcomes were symptoms, modified British Medical Research Council (mMRC) score, HRQoL, and distance walked in 6 min (6MWD). Multivariable adjusted logistic regression models were used to evaluate the risk factors of 12-month outcomes.

Findings: 1276 COVID-19 survivors completed both visits. The median age of patients was 59·0 years (IQR 49·0–67·0) and 681 (53%) were men. The median follow-up time was 185·0 days (IQR 175·0–198·0) for the 6-month visit and 349·0 days (337·0–361·0) for the 12-month visit after symptom onset. The proportion of patients with at least one sequelae symptom decreased from 68% (831/1227) at 6 months to 49% (620/1272) at 12 months ($p<0·0001$). The proportion of patients with dyspnoea, characterised by mMRC score of 1 or more, slightly increased from 26% (313/1185) at 6-month visit to 30% (380/1271) at 12-month visit ($p=0·014$). Additionally, more patients had anxiety or depression at 12-month visit (26% [331/1271] at 12-month visit vs 23% [274/1187] at 6-month visit; $p=0·015$). No significant difference on 6MWD was observed between 6 months and 12 months. 88% (422/479) of patients who were employed before COVID-19 had returned to their original work at 12 months. Compared with men, women had an

odds ratio of 1·43 (95% CI 1·04–1·96) for fatigue or muscle weakness, 2·00 (1·48–2·69) for anxiety or depression, and 2·97 (1·50–5·88) for diffusion impairment. Matched COVID-19 survivors at 12 months had more problems with mobility, pain or discomfort, and anxiety or depression, and had more prevalent symptoms than did controls.

Interpretation: Most COVID-19 survivors had a good physical and functional recovery during 1-year follow-up, and had returned to their original work and life. The health status in our cohort of COVID-19 survivors at 12 months was still lower than that in the control population.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01755-4/fulltext

Efficacy and safety of hydroxychloroquine as pre-and post-exposure prophylaxis and treatment of COVID-19: A systematic review and meta-analysis of blinded, placebo-controlled, randomized clinical trials

Abstract

Background: Hydroxychloroquine (HCQ) is an anti-malarial and immunomodulatory drug considered a potential candidate for drug repurposing in COVID-19 due to their in vitro antiviral activity against SARS-CoV-2. Despite the potential antiviral effects and anti-inflammatory profile, the results based on clinical studies are contradictory. Therefore, the quality of the decision-making process from meta-analyses summarizing the available evidence selecting studies with different designs and unblinded trials is limited. The aim of this study was to synthesize the best evidence on the efficacy and safety of HCQ as pre-and post-exposure prophylaxis and treatment of non-hospitalized and hospitalized patients with COVID-19.

Methods: Searches were performed in PubMed, Web of Science, Embase, Lilacs, the website ClinicalTrials.gov and the preprint server medRxiv from January 1, 2020 to May 17, 2021. The following elements were used to define eligibility criteria: (1) Population: individuals at high-risk of exposure to SARS-CoV-2 (pre-exposure), individuals who had close contact with a positive or probable case of COVID-19 (post-exposure), non-hospitalized patients with COVID-19 and hospitalized patients with COVID-19; (2) Intervention: HCQ; (3) Comparison: placebo; (4) Outcomes: incidence of SARS-CoV-2

infection, need for hospitalization, length of hospital stay, need for invasive mechanical ventilation (MV), death, and adverse events; and (5) Study type: blinded, placebo-controlled, randomized clinical trials (RCTs). Risk of bias was judged according to the Cochrane guidelines for RCTs. Treatment effects were reported as relative risk (RR) for dichotomous variables and mean difference (MD) for continuous variables with 95% confidence intervals (CI). We used either a fixed or random-effects model to pool the results of individual studies depending on the presence of heterogeneity. The GRADE system was used to evaluate the strength of evidence between use of HCQ and the outcomes of interest.

Findings: Fourteen blinded, placebo-controlled RCTs were included in this meta-analysis. Four trials (1942 patients: HCQ = 1271; placebo = 671) used HCQ as a prophylactic medication pre-exposure to COVID-19, two (1650 patients: HCQ = 821; placebo = 829) as a prophylactic medication post-exposure to COVID-19, three (1018 patients: HCQ = 497; placebo = 521) as treatment for non-hospitalized patients, and five (1138 patients: HCQ = 572; placebo = 566) as treatment for hospitalized patients with COVID-19. We found no decreased risk of SARS-CoV-2 infection among individuals receiving HCQ as pre-exposure (RR = 0.90; 95% CI 0.46 to 1.77) or post-exposure (RR = 0.96; 95% CI 0.72 to 1.29) prophylaxis to prevent COVID-19. There was no significant decreased risk of hospitalization for outpatients with SARS-CoV-2 infection (RR = 0.64; 95% CI 0.33 to 1.23) and no decreased risk of MV (RR = 0.81; 95% CI 0.49 to 1.34) and death (RR = 1.05; 95% CI 0.62 to 1.78) among hospitalized patients with COVID-19 receiving HCQ. The certainty of the results on the lack of clinical benefit for HCQ was rated as moderate. Moreover, our results demonstrated an increased risk for any adverse events and gastrointestinal symptoms among those using HCQ.

Interpretation: Available evidence based on the results of blinded, placebo-controlled RCTs showed no clinical benefits of HCQ as pre-and post-exposure prophylaxis and treatment of non-hospitalized and hospitalized patients with COVID-19.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00058-2/fulltext

Exercise performance in patients with post-acute sequelae of SARS-CoV-2 infection compared to patients with unexplained dyspnea

Abstract

Background: Dyspnea and exercise intolerance are commonly reported post-acute sequelae of SARS-CoV-2 infection (PASC), but routine diagnostic testing is often normal. Cardiopulmonary exercise testing (CPET) offers comprehensive assessment of dyspnea to characterize pulmonary PASC.

Methods: We performed a retrospective cohort study of CPET performed on patients reporting dyspnea and/or exercise intolerance following confirmed COVID-19 between August 1, 2020 and March 1, 2021, and compared them to age- and sex-matched patients with unexplained dyspnea referred for CPET at the same center in the pre-COVID-19 era.

Findings: Compared to matched unexplained dyspnea comparators, PASC patients shared similar medical comorbidities and subjective dyspnea at referral (mMRC score 1.6 ± 0.9 vs. 1.4 ± 0.9, P = 0.5). Fifteen (83.3%) PASC patients underwent high resolution computed tomography of the chest, of which half (46.7%) were normal, and 17 (94.4%) patients had pulmonary function testing, of which the majority (76.5%) were normal. All patients underwent CPET, and 12 (67%) had normal findings. Compared to matched comparators, PASC patients had similar peak oxygen consumption, oxygen consumption at ventilatory anaerobic threshold, and ventilatory efficiency measured by the minute ventilation to carbon dioxide production (VE/VCO2) slope.

Interpretation: Despite prominent dyspnea, physiological abnormalities on CPET were mild across a range of initial Covid-19 severity and similar to matched comparators referred for dyspnea without antecedent SARS-CoV-2.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00346-1/fulltext

Mutational spectrum of SARS-CoV-2 during the global pandemic

Abstract

Viruses accumulate mutations under the influence of natural selection and host–virus interactions. Through a systematic comparison of 351,525 full viral genome sequences collected during the recent COVID-19 pandemic, we reveal the spectrum of SARS-CoV-2 mutations. Unlike those of other viruses, the mutational spectrum of SARS-CoV-2 exhibits extreme asymmetry, with a much higher rate of C>U than U>C substitutions, as well as a higher rate of G>U than U>G substitutions. This suggests directional genome sequence evolution during transmission. The substantial asymmetry and directionality of the mutational spectrum enable pseudotemporal tracing of SARS-CoV-2 without prior information about the root sequence, collection time, and sampling region. This shows that the viral genome sequences collected in Asia are similar to the original genome sequence. Adjusted estimation of the d*N*/d*S* ratio accounting for the asymmetrical mutational spectrum also shows evidence of negative selection on viral genes, consistent with previous reports. The findings provide deep insights into the mutational processes in SARS-CoV-2 viral infection and advance the understanding of the history and future evolution of the virus.

Reference

https://www.nature.com/articles/s12276-021-00658-z

Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: A cohort study

Abstract

Background: The SARS-CoV-2 delta (B.1.617.2) variant was first detected in England in March, 2021. It has since rapidly become the predominant lineage, owing to high transmissibility. It is suspected that the delta variant is associated with more severe disease than the previously dominant alpha (B.1.1.7) variant. It was aimed to characterise the severity of the delta variant compared with the alpha variant by determining the relative risk of hospital attendance outcomes.

Methods: This cohort study was done among all patients with COVID-19 in England between March 29 and May 23, 2021, who were identified as being infected with either the alpha or delta SARS-CoV-2 variant through whole-genome sequencing. Individual-level data on these patients were linked to routine health-care datasets on vaccination, emergency care attendance, hospital admission, and mortality (data from Public Health England's Second Generation Surveillance System and COVID-19-associated deaths dataset; the National Immunisation Management System; and NHS Digital Secondary Uses Services and Emergency Care Data Set). The risk for hospital admission and emergency care attendance were compared between patients with sequencing-confirmed delta and alpha variants for the whole cohort and by vaccination status subgroups. Stratified Cox regression was used to adjust for age, sex, ethnicity, deprivation, recent international travel, area of residence, calendar week, and vaccination status.

Findings: Individual-level data on 43 338 COVID-19-positive patients (8682 with the delta variant, 34 656 with the alpha variant; median age 31 years [IQR 17–43]) were included in the analysis. 196 (2·3%) patients with the delta variant versus 764 (2·2%) patients with the alpha variant were admitted to hospital within 14 days after the specimen was taken (adjusted hazard ratio [HR] 2·26 [95% CI 1·32–3·89]). 498 (5·7%) patients with the delta variant versus 1448 (4·2%) patients with the alpha variant were admitted to hospital or attended emergency care within 14 days (adjusted HR 1·45 [1·08–1·95]). Most patients were unvaccinated (32 078 [74·0%] across both groups). The HRs for vaccinated patients with the delta variant versus the alpha variant (adjusted HR for hospital admission 1·94 [95% CI 0·47–8·05] and for hospital admission or emergency care attendance 1·58 [0·69–3·61]) were similar to the HRs for unvaccinated patients (2·32 [1·29–4·16] and 1·43 [1·04–1·97]; p=0·82 for both) but the precision for the vaccinated subgroup was low.

Interpretation: This large national study found a higher hospital admission or emergency care attendance risk for patients with COVID-19 infected with the delta variant compared with the alpha variant. Results suggest that outbreaks of the delta variant in unvaccinated populations might lead to a greater burden on health-care services than the alpha variant.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00475-8/fulltext

COVID-19 and immune-mediated inflammatory diseases: Effect of disease and treatment on COVID-19 outcomes and vaccine responses

Abstract

At the beginning of the COVID-19 pandemic, patients with immune-mediated inflammatory diseases were considered to be at high risk for SARS-CoV-2 infection and the development of severe COVID-19. Data collected over the past year, however, suggest that a diagnosis of inflammatory arthritis, psoriasis, or inflammatory bowel diseases does not increase risk for SARS-CoV-2 infection or severe COVID-19 compared with people without these diseases. Furthermore, substantial data suggest that certain medications frequently used in patients with immune-mediated inflammatory diseases, in particular cytokine inhibitors, might even lower the risk for severe COVID-19. Conversely, glucocorticoids and potentially B-cell-depleting treatments seem to worsen COVID-19 outcomes. Additionally, the first data on SARS-CoV-2 vaccination in patients with these diseases suggest that tolerability of vaccination in patients with immune-mediated inflammatory diseases is good, although the immune response to vaccination can be somewhat reduced in this patient group, particularly those taking methotrexate or CD20-targeted treatment.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00247-2/fulltext

COVID-19 vaccination intention during early vaccine rollout in Canada: A nationwide online survey

Abstract

Background: Understanding vaccination intention during early vaccination rollout in Canada can help the government's efforts in vaccination education and outreach.

Method: Panel members age 18 and over from the nationally representative Angus Reid Forum were invited to complete an online survey about their experience with COVID-19, including their intention to get vaccinated. Respondents were asked “When a vaccine

against the coronavirus becomes available to you, will you get vaccinated or not?" Having no intention to vaccinate was defined as choosing "No – I will not get a coronavirus vaccination" as a response. Odds ratios and predicted probabilities are reported for no vaccine intentionality in demographic groups.

Findings: 14,621 panel members completed the survey. Having no intention to vaccinate against COVID-19 is relatively low overall (9%) with substantial variation among demographic groups. Being a resident of Alberta (predicted probability = 15%; OR 0.58 [95%CI 0.14-2.24]), aged 40-59 (predicted probability = 12%; OR 0.87 [0.78-0.97]), identifying as a visible minority (predicted probability = 15%; OR 0.56 [0.37-0.84]), having some college level education or lower (predicted probability = 14%) and living in households of at least five members (predicted probability = 13%; OR 0.82 [0.76-0.88]) are related to lower vaccination intention.

Interpretation: The study identifies population groups with greater and lesser intention to vaccinate in Canada. As the Canadian COVID-19 vaccination effort continues, policymakers may use this information to focus outreach, education, and other efforts on the latter groups, which also have had higher risks for contracting and dying from COVID-19.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00047-8/fulltext

SARS-CoV-2 infection of the central nervous system in a 14-month-old child: A case report of a complete autopsy

Abstract

Background: Neurological and other systemic complications occur in adults with severe COVID-19. Here SARS-CoV-2 infection was described as complicated by neuroinvasion in the post-mortem tissues of a child.

Methods: A complete autopsy of a 14-month-old child was performed who died of COVID-19 pneumonitis. Histological sections of multiple organs were stained with haematoxylin and eosin. Luxol fast blue staining for myelin and immunohistochemistry were performed in selected areas of the brain. The presence of SARS-CoV-2 was investigated by immunostaining with anti-spike protein antibody and by RT-qPCR.

Findings: Lesions included microthrombosis, pulmonary congestion, interstitial oedema, lymphocytic infiltrates, bronchiolar injury, collapsed alveolar spaces, cortical atrophy, and severe neuronal loss. SARS-CoV-2 staining was observed along the apical region of the choroid plexus (ChP) epithelium and in ependymal cells of the lateral ventricle, but was restricted to ChP capillaries and vessels in some regions. SARS-CoV-2 infection of brain tissue was confirmed by RT-qPCR in fragments of the ChP, lateral ventricle, and cortex.

Interpretation: The results show multisystemic histopathological alterations caused by SARS-CoV-2 infection and contribute to knowledge regarding the course of fatal COVID-19 in children. Furthermore, our findings of ChP infection and viral neurotropism suggest that SARS-CoV-2 may invade the central nervous system by blood-cerebrospinal fluid barrier disruption.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00038-7/fulltext

Airborne transmission of respiratory viruses

Abstract

The COVID-19 pandemic has revealed critical knowledge gaps in our understanding of and a need to update the traditional view of transmission pathways for respiratory viruses. The long-standing definitions of droplet and airborne transmission do not account for the mechanisms by which virus-laden respiratory droplets and aerosols travel through the air and lead to infection. In this Review, current evidence was discussed regarding the transmission of respiratory viruses by aerosols—how they are generated, transported, and deposited, as well as the factors affecting the relative contributions of droplet-spray deposition versus aerosol inhalation as modes of transmission. Improved understanding of aerosol transmission brought about by studies of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requires a reevaluation of the major transmission pathways for other respiratory viruses, which will allow better-informed controls to reduce airborne transmission.

Reference

https://www.science.org/doi/10.1126/science.abd9149

Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum

Abstract

SARS-CoV-2 and its variants continue to infect hundreds of thousands every day despite the rollout of effective vaccines. Therefore, it is essential to understand the levels of protection that these vaccines provide in the face of emerging variants. Here, we report two demographically balanced cohorts of BNT162b2 vaccine recipients and COVID-19 patients, from which we evaluate neutralizing antibody titers against SARS-CoV-2 as well as the B.1.1.7 (alpha) and B.1.351 (beta) variants. We show that both B.1.1.7 and B.1.351 are less well neutralized by serum from vaccinated individuals, and that B.1.351, but not B.1.1.7, is less well neutralized by convalescent serum. We also find that the levels of variant-specific anti-spike antibodies are proportional to neutralizing activities. Together, our results demonstrate the escape of the emerging SARS-CoV-2 variants from neutralization by serum antibodies, which may lead to reduced protection from re-infection or increased risk of vaccine breakthrough.

Reference

https://www.nature.com/articles/s41467-021-25479-6

AHR signaling is induced by infection with coronaviruses

Abstract

Coronavirus infection in humans is usually associated to respiratory tract illnesses, ranging in severity from mild to life-threatening respiratory failure. The aryl hydrocarbon receptor (AHR) was recently identified as a host factor for Zika and dengue viruses; AHR antagonists boost antiviral immunity, decrease viral titers and ameliorate Zika-induced pathology *in vivo*. Here it was reported that AHR is activated by infection with different coronaviruses, potentially impacting antiviral immunity and lung epithelial cells. Indeed, the analysis of single-cell RNA-seq from lung tissue detected increased expression of AHR and AHR transcriptional targets, suggesting AHR signaling activation in SARS-CoV-2-infected epithelial cells from COVID-19 patients. Moreover,

an association was detected between AHR expression and viral load in SARS-CoV-2 infected patients. Finally, we found that the pharmacological inhibition of AHR suppressed the replication *in vitro* of one of the causative agents of the common cold, HCoV-229E, and the causative agent of the COVID-19 pandemic, SARS-CoV-2. Taken together, these findings suggest that AHR activation is a common strategy used by coronaviruses to evade antiviral immunity and promote viral replication, which may also contribute to lung pathology. Future studies should further evaluate the potential of AHR as a target for host-directed antiviral therapy.

Reference

https://www.nature.com/articles/s41467-021-25412-x

Tracheal aspirate RNA sequencing identifies distinct immunological features of COVID-19 ARDS

Abstract

The immunological features that distinguish COVID-19-associated acute respiratory distress syndrome (ARDS) from other causes of ARDS are incompletely understood. Here, we report the results of comparative lower respiratory tract transcriptional profiling of tracheal aspirate from 52 critically ill patients with ARDS from COVID-19 or from other etiologies, as well as controls without ARDS. In contrast to a “cytokine storm,” we observe reduced proinflammatory gene expression in COVID-19 ARDS when compared to ARDS due to other causes. COVID-19 ARDS is characterized by a dysregulated host response with increased PTEN signaling and elevated expression of genes with non-canonical roles in inflammation and immunity. In silico analysis of gene expression identifies several candidate drugs that may modulate gene expression in COVID-19 ARDS, including dexamethasone and granulocyte colony stimulating factor. Compared to ARDS due to other types of viral pneumonia, COVID-19 is characterized by impaired interferon-stimulated gene (ISG) expression. The relationship between SARS-CoV-2 viral load and expression of ISGs is decoupled in patients with COVID-19 ARDS when compared to patients with mild COVID-19. In summary, assessment of host gene expression in the lower airways of patients reveals distinct immunological features of COVID-19 ARDS.

Reference

https://www.nature.com/articles/s41467-021-25040-5

Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum

Abstract

SARS-CoV-2 and its variants continue to infect hundreds of thousands every day despite the rollout of effective vaccines. Therefore, it is essential to understand the levels of protection that these vaccines provide in the face of emerging variants. Here, we report two demographically balanced cohorts of BNT162b2 vaccine recipients and COVID-19 patients, from which neutralizing antibody titers were evaluated against SARS-CoV-2 as well as the B.1.1.7 (alpha) and B.1.351 (beta) variants. We show that both B.1.1.7 and B.1.351 are less well neutralized by serum from vaccinated individuals, and that B.1.351, but not B.1.1.7, is less well neutralized by convalescent serum. We also find that the levels of variant-specific anti-spike antibodies are proportional to neutralizing activities. Together, the results demonstrated the escape of the emerging SARS-CoV-2 variants from neutralization by serum antibodies, which may lead to reduced protection from re-infection or increased risk of vaccine breakthrough.

Reference

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Reference

https://www.nature.com/articles/s41467-021-25040-5

Therapeutic targets and interventional strategies in COVID-19: Mechanisms and clinical studies

Abstract

Owing to the limitations of the present efforts on drug discovery against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the lack of the understanding of the biological regulation mechanisms underlying COVID-19, alternative or novel therapeutic targets for COVID-19 treatment are still urgently required. SARS-CoV-2 infection and immunity dysfunction are the two main courses driving the pathogenesis of COVID-19. Both the virus and host factors are potential targets for antiviral therapy. Hence, in this study, the current therapeutic strategies of COVID-19 have been classified into “target virus” and “target host” categories. Repurposing drugs, emerging approaches, and promising potential targets are the implementations of the above two strategies. First, a comprehensive review of the highly acclaimed old drugs was performed according to evidence-based medicine to provide recommendations for clinicians. Additionally, their unavailability in the fight against COVID-19 was analyzed. Next, a profound analysis of the emerging approaches was conducted, particularly all licensed vaccines and monoclonal antibodies (mAbs) enrolled in clinical trials against primary SARS-CoV-2 and mutant strains. Furthermore, the pros and cons of the present licensed vaccines were compared from different perspectives. Finally, the most

promising potential targets were reviewed, and the update of the progress of treatments has been summarized based on these reviews.

Reference

https://www.nature.com/articles/s41392-021-00733-x

Radiomics-based machine learning differentiates “ground-glass” opacities due to COVID-19 from acute non-COVID-19 lung disease

Abstract

Ground-glass opacities (GGOs) are a non-specific high-resolution computed tomography (HRCT) finding tipically observed in early Coronavirus disesase 19 (COVID-19) pneumonia. However, GGOs are also seen in other acute lung diseases, thus making challenging the differential diagnosis. To this aim, we investigated the performance of a radiomics-based machine learning method to discriminate GGOs due to COVID-19 from those due to other acute lung diseases. Two sets of patients were included: a first set of 28 patients (COVID) diagnosed with COVID-19 infection confirmed by real-time polymerase chain reaction (RT-PCR) between March and April 2020 having (a) baseline HRCT at hospital admission and (b) predominant GGOs pattern on HRCT; a second set of 30 patients (nCOVID) showing (a) predominant GGOs pattern on HRCT performed between August 2019 and April 2020 and (b) availability of final diagnosis. Two readers independently segmented GGOs on HRCTs using a semi-automated approach, and radiomics features were extracted using a standard open source software (PyRadiomics). Partial least square (PLS) regression was used as the multivariate machine-learning algorithm. A leave-one-out nested cross-validation was implemented. PLS β-weights of radiomics features, including the 5% features with the largest β-weights in magnitude (top 5%), were obtained. The diagnostic performance of the radiomics model was assessed through receiver operating characteristic (ROC) analysis. The Youden’s test assessed sensitivity and specificity of the classification. A null hypothesis probability threshold of 5% was chosen ($p < 0.05$). The predictive model delivered an AUC of 0.868 (Youden’s index = 0.68, sensitivity = 93%, specificity 75%, $p = 4.2 \times 10–7$). Of the seven features included in the top 5% features, five were texture-related. A radiomics-based machine learning signature showed the potential to accurately differentiate GGOs due to COVID-19

pneumonia from those due to other acute lung diseases. Most of the discriminant radiomics features were texture-related. This approach may assist clinician to adopt the appropriate management early, while improving the triage of patients.

Reference

https://www.nature.com/articles/s41598-021-96755-0

Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): A cohort study

Abstract

Background: Previous studies have shown that children and adolescents with COVID-19 generally have mild disease. Children and adolescents with cancer, however, can have severe disease when infected with respiratory viruses. In this study, we aimed to understand the clinical course and outcomes of SARS-CoV-2 infection in children and adolescents with cancer.

Methods: A cohort study was done with data from 131 institutions in 45 countries. We created the Global Registry of COVID-19 in Childhood Cancer to capture de-identified data pertaining to laboratory-confirmed SARS-CoV-2 infections in children and adolescents (<19 years) with cancer or having received a haematopoietic stem-cell transplantation. There were no centre-specific exclusion criteria. The registry was disseminated through professional networks through email and conferences and health-care providers were invited to submit all qualifying cases. Data for demographics, oncological diagnosis, clinical course, and cancer therapy details were collected. Primary outcomes were disease severity and modification to cancer-directed therapy. The registry remains open to data collection.

Findings: Of 1520 submitted episodes, 1500 patients were included in the study between April 15, 2020, and Feb 1, 2021. 1319 patients had complete 30-day follow-up. 259 (19·9%) of 1301 patients had a severe or critical infection, and 50 (3·8%) of 1319 died with the cause attributed to COVID-19 infection. Modifications to cancer-directed therapy occurred in 609 (55·8%) of 1092 patients receiving active oncological treatment. Multivariable analysis revealed several factors associated with severe or critical illness, including World Bank low-income or lower-middle-income (odds ratio [OR] 5·8 [95% CI

3·8–8·8]; p<0·0001) and upper-middle-income (1·6 [1·2–2·2]; p=0·0024) country status; age 15–18 years (1·6 [1·1–2·2]; p=0·013); absolute lymphocyte count of 300 or less cells per mm3 (2·5 [1·8–3·4]; p<0·0001), absolute neutrophil count of 500 or less cells per mm3 (1·8 [1·3–2·4]; p=0·0001), and intensive treatment (1·8 [1·3–2·3]; p=0·0005). Factors associated with treatment modification included upper-middle-income country status (OR 0·5 [95% CI 0·3–0·7]; p=0·0004), primary diagnosis of other haematological malignancies (0·5 [0·3–0·8]; p=0·0088), the presence of one of more COVID-19 symptoms at the time of presentation (1·8 [1·3–2·4]; p=0·0002), and the presence of one or more comorbidities (1·6 [1·1–2·3]; p=0·020).

Interpretation: In this global cohort of children and adolescents with cancer and COVID-19, severe and critical illness occurred in one fifth of patients and deaths occurred in a higher proportion than is reported in the literature in the general paediatric population. Additionally, it was found that variables associated with treatment modification were not the same as those associated with greater disease severity. These data could inform clinical practice guidelines and raise awareness globally that children and adolescents with cancer are at high-risk of developing severe COVID-19 illness.

Reference

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00454-X/fulltext

Evolution of antibody responses up to 13 months after SARS-CoV-2 infection and risk of reinfection

Abstract

Background: Assessment of the kinetics of SARS-CoV-2 antibodies is essential in predicting risk of reinfection and durability of vaccine protection.

Methods: This is a prospective, monocentric, longitudinal, cohort clinical study. Healthcare workers (HCW) from Strasbourg University Hospital were enrolled between April 6th and May 7th, 2020 and followed up to 422 days. Serial serum samples were tested for antibodies against the Receptor Binding Domain (RBD) of the spike protein and nucleocapsid protein (N) to characterize the kinetics of SARS-CoV-2 antibodies and the incidence of reinfection. Live-neutralization assays were performed for a subset of samples before and after vaccination to analyze sensitivity to SARS-CoV-2 variants.

Findings: A total of 4290 samples from 393 convalescent COVID-19 and 916 COVID-19 negative individuals were analyzed. In convalescent individuals, SARS-CoV-2 antibodies followed a triphasic kinetic model with half-lives at month (M) 11–13 of 283 days (95% CI 231–349) for anti-N and 725 days (95% CI 623–921) for anti-RBD IgG, which stabilized at a median of 1.54 log BAU/mL (95% CI 1.42–1.67). The incidence of SARS-CoV-2 infections was 12.22 and 0.40 per 100 person-years in COVID-19-negative and COVID-19-positive HCW, respectively, indicating a relative reduction in the incidence of SARS-CoV-2 reinfection of 96.7%. Live-virus neutralization assay revealed that after one year, variants D614G and B.1.1.7, but less so B.1.351, were sensitive to anti-RBD antibodies at 1.4 log BAU/mL, while IgG ≥ 2.0 log BAU/mL strongly neutralized all three variants. These latter anti-RBD IgG titers were reached by all vaccinated HCW regardless of pre-vaccination IgG levels and type of vaccine.

Interpretation: The study demonstrates a long-term persistence of anti-RBD antibodies that may reduce risk of reinfection. By significantly increasing cross-neutralizing antibody titers, a single-dose vaccination strengthens protection against variants.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00354-6/fulltext

A randomized trial of icosapent ethyl in ambulatory patients with COVID-19

Abstract

The coronavirus disease 2019 (COVID-19) pandemic remains a source of considerable morbidity and mortality throughout the world. Therapeutic options to reduce symptoms, inflammatory response, or disease progression are limited. This randomized open-label trial enrolled 100 ambulatory patients with symptomatic COVID-19 in Toronto, Canada. Results indicate that icosapent ethyl (8g daily for 3 days followed by 4g daily for 11 days) significantly reduced high-sensitivity C-reactive protein (hs-CRP) and improved symptomatology compared with patients assigned to usual care. Specifically, the primary biomarker endpoint, change in hs-CRP, was significantly reduced by 25% among treated patients (-0.5mg/L, IQR[-6.9,0.4], within-group P=0.011). Conversely, a non-significant 5.6% reduction was observed among usual care patients (-0.1mg/L, IQR[-3.2,1.7], within-group P=0.51). An unadjusted between-group primary biomarker analysis was non-significant (P=0.082). Overall, this report provides evidence of an

early anti-inflammatory effect of icosapent ethyl in a modest sample, including an initial well-tolerated loading dose, in symptomatic COVID-19 outpatients. ClinicalTrials.gov Identifier: NCT04412018.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)01008-7

Single-dose intranasal vaccination elicits systemic and mucosal immunity against SARS-CoV-2

Abstract

Despite remarkable progress in the development and authorization of vaccines against SARS-CoV-2, there is a need to validate vaccine platforms for broader application. The current intramuscular vaccines are designed to elicit systemic immunity without conferring mucosal immunity in the nasal compartment, which is the first barrier that SARS-CoV-2 virus breaches before dissemination to the lung. The development of an intranasal subunit vaccine was reported that uses lyophilized spike protein and liposomal STING agonist as an adjuvant. This vaccine induces systemic neutralizing antibodies, IgA in the lung and nasal compartments, and T-cell responses in the lung of mice. Single-cell RNA-sequencing confirmed the coordinated activation of T/ B cell responses in a germinal center-like manner within the nasal-associated lymphoid tissues, confirming its role as an inductive site to enable durable immunity. The ability to elicit immunity in the respiratory tract can prevent the establishment of infection in individuals and prevent disease transmission.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)01005-1

Profiling $CD8^+$ T Cell Epitopes of COVID-19 Convalescents Reveals Reduced Cellular Immune Responses to SARS-CoV-2 Variants

Abstract

Cellular immunity is important in determining disease severity of COVID-19 patients. However, current understanding of SARS-CoV-2 epitopes mediating cellular immunity is limited. Here we apply T-Scan, a recently developed method to identify $CD8^+$ T cell

epitopes from COVID-19 patients of four major HLA-A alleles. Several identified epitopes are conserved across human coronaviruses, which might mediate preexisting cellular immunity to SARS-CoV-2. In addition, we identify and validate four epitopes that were mutated in the newly circulating variants including the Delta variant. The mutations significantly reduce T cell responses to the epitope peptides in convalescent and vaccinated samples. It was further determined that the crystal structure of HLA-A∗02:01/HLA-A∗24:02 in complex with the epitope KIA_S/NYN_S respectively, which reveal the importance of K417 and L452 of the spike protein for binding to HLA. The data suggest that evading cellular immunity might contribute to the increased transmissibility and disease severity associated with the new SARS-CoV-2 variants.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01155-4

PERSPECTIVE

Publication Date: Aug 27, 2021

The animal origin of SARS-CoV-2

Abstract

To understand the origin of the COVID-19 pandemic, it is necessary to go back to 2002. At that time a novel respiratory coronavirus appeared in Foshan, Guangdong province, China, and spread to 29 countries. Altogether ~8000 people were infected with severe acute respiratory syndrome coronavirus (SARS-CoV) before public health measures controlled its spread in 2003. The zoonotic origin of SARS-CoV was subsequently linked to live animals available at markets. Further sporadic spill-over events of SARS-CoV from animals took place in Guangzhou, Guangdong, and some researchers working with cultured virus were infected in laboratory accidents (3), but ultimately SARS-CoV was removed from the human population. Trading of susceptible host animals is an important common theme in the emergence of SARS and COVID-19. For more details, read the link below.

Reference

https://www.science.org/doi/10.1126/science.abh0117