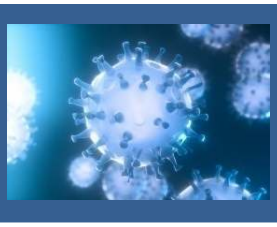
COVID-19

Jun 03 - 09, 2021



RESEARCH PUBLICATIONS

Publication Date: June 09, 2021

Single-cell epigenomic landscape of peripheral immune cells reveals establishment of trained immunity in individuals convalescing from COVID-19

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection often causes severe complications and even death. However, asymptomatic infection has also been reported, highlighting the difference in immune responses among individuals. Here we performed single-cell chromatin accessibility and T cell-receptor analyses of peripheral blood mononuclear cells collected from individuals convalescing from COVID-19 and healthy donors. Chromatin remodelling was observed in both innate and adaptive immune cells in the individuals convalescing from COVID-19. Compared with healthy donors, recovered individuals contained abundant TBET-enriched CD16+ and IRF1-enriched CD14+ monocytes with sequential trained and activated epigenomic states. The B-cell lineage in recovered individuals exhibited an accelerated developmental programme from immature B cells to antibody-producing plasma cells. Finally, an integrated analysis of single-cell T cell-receptor clonality with the chromatin accessibility landscape revealed the expansion of putative SARS-CoV-2-specific CD8+ T cells with epigenomic profiles that promote the differentiation of effector or memory cells. Overall, our data suggest that immune cells of individuals convalescing from COVID-19 exhibit global remodelling of the chromatin accessibility landscape, indicative of the establishment of immunological memory.

Reference

https://www.nature.com/articles/s41556-021-00690-1

A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: A retrospective observational matched-cohort study

Abstract

Background: Effective home treatment algorithms implemented based on a pathophysiologic and pharmacologic rationale to accelerate recovery and prevent hospitalisation of patients with early coronavirus disease 2019 (COVID-19) would have major implications for patients and health system.

Methods: This academic, matched-cohort study compared outcomes of 90 consecutive consenting patients with mild COVID-19 treated at home by their family physicians between October 2020 and January 2021 in Northern and Central Italy, according to the proposed recommendation algorithm, with outcomes for 90 age-, sex-, and comorbidities-matched patients who received other therapeutic regimens. Primary outcome was time to resolution of major symptoms. Secondary outcomes included prevention of hospitalisation. Analyses were by intention-to-treat.

Findings: All patients achieved complete remission. The median [IQR] time to resolution of major symptoms was 18 [14–23] days in the 'recommended schedule' cohort and 14 [7–30] days in the matched 'control' cohort (p = 0·033). Other symptoms persisted in a lower percentage of patients in the 'recommended' than in the 'control' cohort (23·3% versus 73·3%, respectively, p<0·0001) and for a shorter period (p = 0·0107). Two patients in the 'recommended' cohort were hospitalised compared to 13 (14·4%) controls (p = 0·0103). The prevention algorithm reduced the days and cumulative costs of hospitalisation by >90%.

Interpretation: Implementation of an early home treatment algorithm failed to accelerate recovery from major symptoms of COVID-19, but reduced the risk of hospitalisation and related treatment costs. Given the study design, additional research would be required to consolidate the proposed treatment recommendations.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00221-2/fulltext

Structural basis for accommodation of emerging B.1.351 and B.1.1.7 variants by two potent SARS-CoV-2 neutralizing antibodies

Abstract

Emerging SARS-CoV-2 strains, B.1.1.7 and B.1.351, from the UK and South Africa, respectively, show decreased neutralization by monoclonal antibodies and convalescent or vaccinee sera raised against the original wild-type virus, and are thus of clinical concern. However, the neutralization potency of two antibodies, 1–57 and 2–7, which target the receptor-binding domain (RBD) of the spike, was unaffected by these emerging strains. Here, we report cryo-EM structures of 1–57 and 2–7 in complex with spike, revealing each of these antibodies to utilize a distinct mechanism to bypass or accommodate RBD mutations. Notably, each antibody represented an immune response with recognition distinct from those of frequent antibody classes. Moreover, many epitope residues recognized by 1–57 and 2–7 were outside hotspots of evolutionary pressure for ACE2 binding and neutralizing antibody escape. We suggest the therapeutic use of antibodies, such as 1–57 and 2–7, which target less prevalent epitopes, could ameliorate issues of monoclonal antibody escape.

Reference

https://www.cell.com/structure/fulltext/S0969-2126%2821%2900172-6

Anxiety, gender, and social media consumption predict COVID-19 emotional distress

Abstract

Fear and anxiety about COVID-19 have swept across the globe. Understanding the factors that contribute to increased emotional distress regarding the pandemic is paramount—especially as experts warn about rising cases. Despite large amounts of data, it remains unclear which variables are essential for predicting who will be most affected by the distress of future waves. Cross-sectional data was collected on a multitude of socio-psychological variables from a sample of 948 United States participants during the early stages of the pandemic. Using a cross-validated hybrid stepwise procedure, we developed a descriptive model of COVID-19 emotional distress. Results reveal that trait anxiety, gender, and social (but not government) media

consumption were the strongest predictors of increasing emotional distress. In contrast, commonly associated variables, such as age and political ideology, exhibited much less unique explanatory power. Together, these results can help public health officials identify which populations will be especially vulnerable to experiencing COVID-19-related emotional distress.

Reference

https://www.nature.com/articles/s41599-021-00816-8

First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland

Abstract

Reports of ChAdOx1 vaccine–associated thrombocytopenia and vascular adverse events have led to some countries restricting its use. Using a national prospective cohort, we estimated associations between exposure to first-dose ChAdOx1 or BNT162b2 vaccination and hematological and vascular adverse events using a nested incident-matched case-control study and a confirmatory self-controlled case series (SCCS) analysis. An association was found between ChAdOx1 vaccination and idiopathic thrombocytopenic purpura (ITP) (0–27 d after vaccination; adjusted rate ratio (aRR) = 5.77, 95% confidence interval (CI), 2.41–13.83), with an estimated incidence of 1.13 (0.62–1.63) cases per 100,000 doses. An SCCS analysis confirmed that this was unlikely due to bias (RR = 1.98 (1.29–3.02)). There was also an increased risk for arterial thromboembolic events (aRR = 1.22, 1.12–1.34) 0–27 d after vaccination, with an SCCS RR of 0.97 (0.93–1.02). For hemorrhagic events 0–27 d after vaccination, the aRR was 1.48 (1.12–1.96), with an SCCS RR of 0.95 (0.82–1.11). A first dose of ChAdOx1 was found to be associated with small increased risks of ITP, with suggestive evidence of an increased risk of arterial thromboembolic and hemorrhagic events. The attenuation of effect found in the SCCS analysis means that there is the potential for overestimation of the reported results, which might indicate the presence of some residual confounding or confounding by indication. Public health authorities should inform their jurisdictions of these relatively small increased risks associated with ChAdOx1. No positive associations were seen between BNT162b2 and thrombocytopenic, thromboembolic and hemorrhagic events.

Reference

https://www.nature.com/articles/s41591-021-01408-4

Clinical and molecular characteristics of COVID-19 patients with persistent SARS-CoV-2 infection

Abstract

The characteristics of COVID-19 patients with persistent SARS-CoV-2 infection are not yet well described. Here, we compare the clinical and molecular features of patients with long duration of viral shedding (LDs) with those from patients with short duration patients (SDs), and healthy donors (HDs). We find that several cytokines and chemokines, such as interleukin (IL)-2, tumor necrosis factor (TNF) and lymphotoxin α (LT-α) are present at lower levels in LDs than SDs. Single-cell RNA sequencing shows that natural killer (NK) cells and CD14+ monocytes are reduced, while regulatory T cells are increased in LDs; moreover, T and NK cells in LDs are less activated than in SDs. Importantly, most cells in LDs show reduced expression of ribosomal protein (RP) genes and related pathways, with this inversed correlation between RP levels and infection duration further validated in 103 independent patients. Our results thus indicate that immunosuppression and low RP expression may be related to the persistence of the viral infection in COVID-19 patients.

Reference

https://www.nature.com/articles/s41467-021-23621-y

Identification of novel bat coronaviruses sheds light on the evolutionary origins of SARS-CoV-2 and related viruses

Abstract

Despite the discovery of animal coronaviruses related to SARS-CoV-2, the evolutionary origins of this virus are elusive. A meta-transcriptomic study of 411 bat samples was described, which was collected from a small geographical region in Yunnan province, China, between May 2019 and November 2020. 24 Full-length coronavirus genomes were identified, including four novel SARS-CoV-2-related and three SARS-CoV-related viruses. Rhinolophus pusillus virus RpYN06 was the closest relative of SARS-CoV-2 in most of the genome, although it possessed a more divergent spike gene. The other

three SARS-CoV-2-related coronaviruses carried a genetically distinct spike gene that could weakly bind to the hACE2 receptor in vitro. Ecological modeling predicted the co-existence of up to 23 Rhinolophus bat species, with the largest contiguous hotspots extending from South Laos and Vietnam to southern China. The study highlights the remarkable diversity of bat coronaviruses at the local scale, including close relatives of both SARS-CoV-2 and SARS-CoV.

Reference

https://www.cell.com/cell/fulltext/S0092-8674%2821%2900709-1

CD177, a specific marker of neutrophil activation, is associated with coronavirus disease 2019 severity and death

Abstract

The identification of patients with coronavirus disease 2019 and high risk of severe disease is a challenge in routine care. Cell phenotypic, serum, and RNA sequencing gene expression analyses were performed in severe hospitalized patients (n = 61). Relative to healthy donors, results showed abnormalities of 27 cell populations and an elevation of 42 cytokines, neutrophil chemo-attractants, and inflammatory components in patients. Supervised and unsupervised analyses revealed a high abundance of CD177, a specific neutrophil activation marker, contributing to the clustering of severe patients. Gene abundance correlated with high serum levels of CD177 in severe patients. Higher levels were confirmed in a second cohort and in intensive care unit (ICU) than non-ICU patients ($P < 0.001$). Longitudinal measurements discriminated between patients with the worst prognosis, leading to death, and those who recovered ($P = 0.01$). These results highlight neutrophil activation as a hallmark of severe disease and CD177 assessment as a reliable prognostic marker for routine care.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042%2821%2900679-9

Deep spatial profiling of human COVID-19 brains reveals neuroinflammation with distinct microanatomical microglia-T-cell interactions

Abstract

COVID-19 can cause severe neurological symptoms, but the underlying pathophysiological mechanisms are unclear. Here, the brain stems and olfactory bulbs in postmortem patients were interrogated who had COVID-19 using imaging mass cytometry to understand the local immune response at a spatially resolved, high-dimensional, single-cell level and compared their immune map to non-COVID respiratory failure, multiple sclerosis, and control patients. Substantial immune activation was observed in the central nervous system with pronounced neuropathology (astrocytosis, axonal damage, and blood-brain-barrier leakage) and detected viral antigen in ACE2-receptor-positive cells enriched in the vascular compartment. Microglial nodules and the perivascular compartment represented COVID-19-specific, microanatomic-immune niches with context-specific cellular interactions enriched for activated CD8+ T cells. Altered brain T-cell-microglial interactions were linked to clinical measures of systemic inflammation and disturbed hemostasis. This study identifies profound neuroinflammation with activation of innate and adaptive immune cells as correlates of COVID-19 neuropathology, with implications for potential therapeutic strategies.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613%2821%2900246-6

Validation of a rapid antigen test as a screening tool for SARS-CoV-2 infection in asymptomatic populations. Sensitivity, specificity and predictive values

Abstract

Background: Early diagnosis of SARS-CoV-2 infection is essential to reduce disease spread. Rapid antigen tests have not been sufficiently evaluated in asymptomatic patients to be used as massive population screening tools.

Methods: Head-to-head evaluation of Roche SARS-CoV-2 Rapid Antigen Test and real-time reverse transcription polymerase chain reaction (RT-PCR) as SARS-CoV-2 screening tools performed in asymptomatic adults from a semi-closed community in

University of Navarra (Spain) from November 2020 to January 2021. Sensitivity, specificity and predictive values were calculated using RT-PCR as reference method.

Findings: Roche SARS-CoV-2 Rapid Antigen Test was performed on 2542 asymptomatic adults in a community with a SARS-CoV-2 incidence of 1·93%. It showed a sensitivity of 71·43% (CI 95%: 56·74 – 83·42) and a specificity of 99·68% (CI 95%: 99·37 - 99·86). Positive Predictive Value was 81·4 (CI 95% 66·6 – 91·61) and Negative Predictive Value was 99·44 (CI 95% 99·06 – 99·69). Test sensitivity was related to viral load, with higher sensitivity in RT-PCR cycle threshold (Ct) values under 25 (93·75%, CI 95%: 71·96 – 98·93), that dropped to 29·41% (CI 95%: 10·31- 55·96) in RT-PCR Ct values above 25.

Interpretation: This study suggests that rapid antigen tests are less effective in asymptomatic population, when compared with RT-PCR. Further studies are needed to evaluate different options to improve screenings based on rapid antigen test, such as the use of clinical questionnaires to select higher risk-participants, the confirmation of negative results with RT-PCR or the use of repetitive sequential testing.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00234-0/fulltext

Structural racism and risk of SARS-CoV-2 in pregnancy

Abstract

Background: Structural racism leads to adverse health outcomes, as highlighted by inequities in COVID-19 infections. Black/White disparities were characterized among pregnant women with SARS-CoV-2 in Cuyahoga County which has some of the most extreme health disparities in the U.S., such as a rate of Black infant mortality that is three times that of White counterparts.

Methods: This was a retrospective cohort study using data collected as part of public health surveillance between March 16, 2020 until October 1, 2020. This study aimed to compare Black and Non-Black pregnant women infected with SARS-CoV-2 to understand how the distribution of risk factors may differ by race. Outcomes included

age, gestational age at infection, medical co-morbidities, exposure history, socio-economic status, occupation, symptom severity and pregnancy complications.

Findings: One hundred and sixty-two women were included. 81 (50%) were Black, 67 (41%) White, 9 (0·05%) Hispanic, 2 (0·01%) Asian; and three did not self-identify with any particular race. More than half who supplied occupational information (n = 132) were essential workers as classified by the CDC definition (55%, n = 73). Black women were younger (p = 0·0062) and more likely to identify an occupational contact as exposing them to SARS-CoV-2 (p = 0·020). Non-Black women were more likely to work from home (p = 0·018) and indicate a personal or household contact as their exposure (p = 0·020). Occupation was a risk factor for severe symptoms (aOR 4·487, p = 0·037). Most Black women lived in areas with median income <$39,000 and Black women were more likely to have a preterm delivery (22·2% versus 0%, p = 0·026).

Interpretation: Many pregnant women infected by SARS-CoV-2 are essential workers. Black women are more likely than White counterparts to have occupational exposure as the presumed source for their infection. Limitations in occupational options and controlling risk in these positions could be related to lower socio-economic status, resulting from a long history of structural racism in Cuyahoga County as evidenced by redlining and other policies limiting opportunities for people of color.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00230-3/fulltext

A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: A retrospective observational matched-cohort study

Abstract

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Methods: This academic, matched-cohort study compared outcomes of 90 consecutive consenting patients with mild COVID-19 treated at home by their family physicians

between October 2020 and January 2021 in Northern and Central Italy, according to the proposed recommendation algorithm, with outcomes for 90 age-, sex-, and comorbidities-matched patients who received other therapeutic regimens. Primary outcome was time to resolution of major symptoms. Secondary outcomes included prevention of hospitalisation. Analyses were by intention-to-treat.

Findings: All patients achieved complete remission. The median [IQR] time to resolution of major symptoms was 18 [14–23] days in the 'recommended schedule' cohort and 14 [7–30] days in the matched 'control' cohort (p = 0·033). Other symptoms persisted in a lower percentage of patients in the 'recommended' than in the 'control' cohort (23·3% versus 73·3%, respectively, p<0·0001) and for a shorter period (p = 0·0107). Two patients in the 'recommended' cohort were hospitalised compared to 13 (14·4%) controls (p = 0·0103). The prevention algorithm reduced the days and cumulative costs of hospitalisation by >90%.

Interpretation: Implementation of an early home treatment algorithm failed to accelerate recovery from major symptoms of COVID-19, but reduced the risk of hospitalisation and related treatment costs. Given the study design, additional research would be required to consolidate the proposed treatment recommendations.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00221-2/fulltext

SARS-CoV-2 infection, antibody positivity and seroconversion rates in staff and students following full reopening of secondary schools in England: A prospective cohort study, September–December 2020

Abstract

Background: Older children have higher SARS-CoV-2 infection rates than younger children. We investigated SARS-CoV-2 infection, seroprevalence and seroconversion rates in staff and students following the full reopening of all secondary schools in England.

Methods: Public Health England (PHE) invited secondary schools in six regions (East and West London, Hertfordshire, Derbyshire, Manchester and Birmingham) to

participate in SARS-CoV-2 surveillance during the 2020/21 academic year. Participants had nasal swabs for RT-PCR and blood samples for SARS-CoV-2 antibodies at the beginning (September 2020) and end (December 2020) of the autumn term. Multivariable logistic regression was used to assess independent risk factors for seropositivity and seroconversion.

Findings: Eighteen schools in six regions enrolled 2,209 participants, including 1,189 (53.8%) students and 1,020 (46.2%) staff. SARS-CoV-2 infection rates were not significantly different between students and staff in round one (5/948; [0.53%] vs. 2/876 [0.23%]; p = 0.46) or round two (10/948 [1.05%] vs. 7/886 [0.79%]; p = 0.63), and similar to national prevalence. None of four and 7/15 (47%) sequenced strains in rounds 1 and 2 were the highly transmissible SARS-CoV-2 B.1.1.7 variant. In round 1, antibody seropositivity was higher in students than staff (114/893 [12.8%] vs. 79/861 [9.2%]; p = 0.016), but similar in round 2 (117/893 [13.1%] vs.117/872 [13.3%]; p = 0.85), comparable to local community seroprevalence. Between the two rounds, 8.7% (57/652) staff and 6.6% (36/549) students seroconverted (p = 0.16).

Interpretation: In secondary schools, SARS-CoV-2 infection, seropositivity and seroconversion rates were similar in staff and students, and comparable to local community rates. Ongoing surveillance will be important for monitoring the impact of new variants in educational settings.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00228-5/fulltext

Publication Date: June 08, 2021

Optimizing vaccine allocation for COVID-19 vaccines shows the potential role of single-dose vaccination

Abstract

Most COVID-19 vaccines require two doses, however with limited vaccine supply, policymakers are considering single-dose vaccination as an alternative strategy. Using a mathematical model combined with optimization algorithms, optimal allocation strategies were determined with one and two doses of vaccine under various degrees of

viral transmission. Under low transmission, we show that the optimal allocation of vaccine vitally depends on the single-dose efficacy. With high single-dose efficacy, single-dose vaccination is optimal, preventing up to 22% more deaths than a strategy prioritizing two-dose vaccination for older adults. With low or moderate single-dose efficacy, mixed vaccination campaigns with complete coverage of older adults are optimal. However, with modest or high transmission, vaccinating older adults first with two doses is best, preventing up to 41% more deaths than a single-dose vaccination given across all adult populations. Our work suggests that it is imperative to determine the efficacy and durability of single-dose vaccines, as mixed or single-dose vaccination campaigns may have the potential to contain the pandemic much more quickly.

Reference

https://www.nature.com/articles/s41467-021-23761-1

A novel mouse AAV6 hACE2 transduction model of wild-type SARS-CoV-2 infection studied using synDNA immunogens

Abstract

More than 100 million people have been infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Common laboratory mice are not susceptible to wild-type SARS-CoV-2 infection, challenging the development and testing of effective interventions. Here, we describe the development and testing of a mouse model for SARS-CoV-2 infection based on transduction of the respiratory tract of laboratory mice with an adeno-associated virus vector (AAV6) expressing human ACE-2 (AAV6.2FF-hACE2). We validated this model using a previously described synthetic DNA vaccine plasmid, INO-4800 (pS). Intranasal instillation of AAV6.2FF-hACE2 resulted in robust hACE2 expression in the respiratory tract. pS induced robust cellular and humoral responses. Vaccinated animals were challenged with 105 TCID50 SARS-CoV-2 (hCoV-19/Canada/ON-VIDO-01/2020) and euthanized four days post-challenge to assess viral load. One immunization resulted in 50% protection and two immunizations were completely protective. Overall, the AAV6.2FF-hACE2 mouse transduction model represents an easily accessible, genetically diverse mouse model for wild-type SARS-CoV-2 infection and preclinical evaluation of potential interventions.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042%2821%2900667-2

Analysis of SARS-CoV-2 variant mutations reveals neutralization escape mechanisms and the ability to use ACE2 receptors from additional species

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants continue to emerge during the global pandemic and may facilitate escape from current antibody therapies and vaccine protection. Here we showed that the South African variant B.1.351 was the most resistant to current monoclonal antibodies and convalescent plasma from coronavirus disease 2019 (COVID-19)-infected individuals, followed by the Brazilian variant P.1 and the United Kingdom variant B.1.1.7. This resistance hierarchy corresponded with Y144del and 242–244del mutations in the N-terminal domain and K417N/T, E484K, and N501Y mutations in the receptor-binding domain (RBD) of SARS-CoV-2. Crystal structure analysis of the B.1.351 triple mutant (417N-484K-501Y) RBD complexed with the monoclonal antibody P2C-1F11 revealed the molecular basis for antibody neutralization and escape. B.1.351 and P.1 also acquired the ability to use mouse and mink ACE2 receptors for entry. Our results demonstrate major antigenic shifts and potential broadening of the host range for B.1.351 and P.1 variants, which poses serious challenges to current antibody therapies and vaccine protection.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613%2821%2900247-8

Identification of presented SARS-CoV-2 HLA class I and HLA class II peptides using HLA peptidomics

Abstract

The human leukocyte antigen (HLA)-bound viral antigens serve as an immunological signature that can be selectively recognized by T cells. As viruses evolve by acquiring mutations, it is essential to identify a range of presented viral antigens. Using HLA peptidomics, we are able to identify severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-derived peptides presented by highly prevalent HLA class I (HLA-I)

molecules by using infected cells as well as overexpression of SARS-CoV-2 genes. We find 26 HLA-I peptides and 36 HLA class II (HLA-II) peptides. Among the identified peptides, some are shared between different cells and some are derived from out-of-frame open reading frames (ORFs). Seven of these peptides were previously shown to be immunogenic, and we identify two additional immunoreactive peptides by using HLA multimer staining. These results may aid the development of the next generation of SARS-CoV-2 vaccines based on presented viral-specific antigens that span several of the viral genes.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900681-1

Recurrent emergence of SARS-CoV-2 spike deletion H69/V70 and its role in the Alpha variant B.1.1.7

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike ΔH69/V70 was reported in multiple independent lineages, often occurring after acquisition of receptor binding motif replacements such as N439K and Y453F, known to increase binding affinity to the ACE2 receptor and confer antibody escape. In vitro, it was shown that, although ΔH69/V70 itself is not an antibody evasion mechanism, it increases infectivity associated with enhanced incorporation of cleaved spike into virions. ΔH69/V70 is able to partially rescue infectivity of spike proteins that have acquired N439K and Y453F escape mutations by increased spike incorporation. In addition, replacement of the H69 and V70 residues in the Alpha variant B.1.1.7 spike (where ΔH69/V70 occurs naturally) impairs spike incorporation and entry efficiency of the B.1.1.7 spike pseudotyped virus. Alpha variant B.1.1.7 spike mediates faster kinetics of cell-cell fusion than wild-type Wuhan-1 D614G, dependent on ΔH69/V70. Therefore, as ΔH69/V70 compensates for immune escape mutations that impair infectivity, continued surveillance for deletions with functional effects is warranted.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900663-X

SARS-CoV-2 mRNA vaccination induces functionally diverse antibodies to NTD, RBD, and S2

Abstract

In this study we profiled vaccine-induced polyclonal antibodies as well as plasmablast-derived mAbs from individuals who received SARS-CoV-2 spike mRNA vaccine. Polyclonal antibody responses in vaccinees were robust and comparable to or exceeded those seen after natural infection. However, the ratio of binding to neutralizing antibodies after vaccination was greater than that after natural infection and, at the monoclonal level, we found that the majority of vaccine-induced antibodies did not have neutralizing activity. A co-dominance of mAbs was also found, targeting the NTD and RBD of SARS-CoV-2 spike and an original antigenic-sin like backboost to spikes of seasonal human coronaviruses OC43 and HKU1. Neutralizing activity of NTD mAbs but not RBD mAbs against a clinical viral isolate carrying E484K as well as extensive changes in the NTD was abolished, suggesting that a proportion of vaccine-induced RBD binding antibodies may provide substantial protection against viral variants carrying single E484K RBD mutations.

Reference

https://www.cell.com/cell/fulltext/S0092-8674%2821%2900706-6

Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: A cohort study

Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) is a potentially life-threatening hyperinflammatory syndrome that occurs after primary SARS-CoV-2 infection. The pathogenesis of MIS-C remains undefined, and whether specific inflammatory biomarker patterns can distinguish MIS-C from other hyperinflammatory syndromes, including Kawasaki disease and macrophage activation syndrome (MAS), is unknown. Therefore, we aimed to investigate whether inflammatory biomarkers could be used to distinguish between these conditions.

Methods: A prospective cohort of patients was studied with MIS-C and Kawasaki disease and an established cohort of patients with new-onset systemic juvenile idiopathic arthritis (JIA) and MAS associated with systemic JIA (JIA-MAS), diagnosed according to established guidelines. The study was done at Cincinnati Children's Hospital Medical Center (Cincinnati, OH, USA). Clinical and laboratory features as well as S100A8/A9, S100A12, interleukin (IL)-18, chemokine (C-X-C motif) ligand 9 (CXCL9), and IL-6 concentrations were assessed by ELISA and compared using parametric and non-parametric tests and receiver operating characteristic curve analysis.

Findings: Between April 30, 2019, and Dec 14, 2020, we enrolled 19 patients with MIS-C (median age 9·0 years [IQR 4·5–15·0]; eight [42%] girls and 11 [58%] boys) and nine patients with Kawasaki disease (median age 2·0 years [2·0–4·0]); seven [78%] girls and two [22%] boys). Patients with MIS-C and Kawasaki disease had similar S100 proteins and IL-18 concentrations but patients with MIS-C were distinguished by significantly higher median concentrations of the IFNγ-induced CXCL9 (1730 pg/mL [IQR 604–6300] vs 278 pg/mL [54–477]; p=0·038). Stratifying patients with MIS-C by CXCL9 concentrations (high vs low) revealed differential severity of clinical and laboratory presentation. Compared with patients with MIS-C and low CXCL9 concentrations, more patients with high CXCL9 concentrations had acute kidney injury (six [60%] of ten vs none [0%] of five), altered mental status (four [40%] of ten vs none [0%] of five), shock (nine [90%] of ten vs two [40%] of five), and myocardial dysfunction (five [50%] of ten vs one [20%] of five); these patients also had higher concentrations of systemic inflammatory markers and increased severity of cytopenia and coagulopathy. By contrast, patients with MIS-C and low CXCL9 concentrations resembled patients with Kawasaki disease, including the frequency of coronary involvement. Elevated concentrations of S100A8/A9, S100A12, and IL-18 were also useful in distinguishing systemic JIA from Kawasaki disease with high sensitivity and specificity.

Interpretation: The findings show MIS-C is distinguishable from Kawasaki disease primarily by elevated CXCL9 concentrations. The stratification of patients with MIS-C by high or low CXCL9 concentrations provides support for MAS-like pathophysiology in patients with severe MIS-C, suggesting new approaches for diagnosis and management.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00139-9/fulltext

Senolytics reduce coronavirus-related mortality in old mice

Abstract

The COVID-19 pandemic has revealed the pronounced vulnerability of the elderly and chronically-ill to SARS-CoV-2-induced morbidity and mortality. Cellular senescence contributes to inflammation, multiple chronic diseases, and age-related dysfunction, but effects on responses to viral infection are unclear. Here, it was demonstrated that senescent cells (SnC) become hyper-inflammatory in response to pathogen-associated molecular patterns (PAMPs), including SARS-CoV-2 Spike protein-1, increasing expression of viral entry proteins and reducing anti-viral gene expression in non-SnCs through a paracrine mechanism. Old mice acutely infected with pathogens that included a SARS-CoV-2-related mouse β-coronavirus experienced increased senescence and inflammation with nearly 100% mortality. Targeting SnCs using senolytic drugs before or after pathogen exposure significantly reduced mortality, cellular senescence, and inflammatory markers and increased anti-viral antibodies. Thus, reducing the SnC burden in diseased or aged individuals should enhance resilience and reduce mortality following viral infection, including SARS-CoV-2.

Reference

https://science.sciencemag.org/content/early/2021/06/07/science.abe4832

Publication Date: June 07, 2021

SARS-CoV-2 RNAemia and proteomic trajectories inform prognostication in COVID-19 patients admitted to intensive care

Abstract

Prognostic characteristics inform risk stratification in intensive care unit (ICU) patients with coronavirus disease 2019 (COVID-19). Blood samples (n = 474) were obtained from hospitalized COVID-19 patients (n = 123), non-COVID-19 ICU sepsis patients (n = 25) and healthy controls (n = 30). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was detected in plasma or serum (RNAemia) of COVID-19 ICU

patients when neutralizing antibody response was low. RNAemia is associated with higher 28-day ICU mortality (hazard ratio [HR], 1.84 [95% CI, 1.22–2.77] adjusted for age and sex). RNAemia is comparable in performance to the best protein predictors. Mannose binding lectin 2 and pentraxin-3 (PTX3), two activators of the complement pathway of the innate immune system, are positively associated with mortality. Machine learning identified 'Age, RNAemia' and 'Age, PTX3' as the best binary signatures associated with 28-day ICU mortality. In longitudinal comparisons, COVID-19 ICU patients have a distinct proteomic trajectory associated with mortality, with recovery of many liver-derived proteins indicating survival. Finally, proteins of the complement system and galectin-3-binding protein (LGALS3BP) are identified as interaction partners of SARS-CoV-2 spike glycoprotein. LGALS3BP overexpression inhibits spike-pseudoparticle uptake and spike-induced cell-cell fusion *in vitro*.

Reference

https://www.nature.com/articles/s41467-021-23494-1

Cell entry by SARS-CoV-2

Abstract

Both severe acute respiratory syndrome virus 2 (SARS-CoV-2) and SARS-CoV mainly invade human lungs, although increasing evidence shows that SARS-CoV-2 can also infect many other tissues to develop systematic infection and multiple organ damage, and can also hijack T cells to directly paralyze host immunity. Angiotensin-converting enzyme 2 (ACE2) is the major receptor for SARS-CoV-2 infection and is a crucial determinant for cross-species transmission of the virus; SARS-CoV-2 can establish infections in a panel of domestic or wild animals *via* their ACE2 orthologs. Several proteins and non-protein molecules have been found to interact with SARS-CoV-2 S protein and serve as potential alternative/auxiliary attachment receptors/coreceptors to facilitate SARS-CoV-2 entry into specific types of host cells. Membrane fusion of SARS-CoV-2 requires two proteolytic events of S protein by host proteases, and the S1/S2 boundary of SARS-CoV-2 S protein harbors a polybasic insertion that expands the spectrum of available proteases and thus the tropism for different tissues. Severe acute respiratory syndrome virus 2 (SARS-CoV-2) invades host cells by interacting with receptors/coreceptors, as well as with other cofactors, via its spike (S) protein that

further mediates fusion between viral and cellular membranes. The host membrane protein, angiotensin-converting enzyme 2 (ACE2), is the major receptor for SARS-CoV-2 and is a crucial determinant for cross-species transmission. In addition, some auxiliary receptors and cofactors are also involved that expand the host/tissue tropism of SARS-CoV-2. After receptor engagement, specific proteases are required that cleave the S protein and trigger its fusogenic activity. Here the recent advances were discussed in understanding the molecular events during SARS-CoV-2 entry which will contribute to developing vaccines and therapeutics.

Reference

https://www.cell.com/trends/biochemical-sciences/fulltext/S0968-0004%2821%2900118-3

Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome

Abstract

In some people, the aftermath of acute coronavirus disease 2019 (COVID-19) is a lingering illness with fatigue and cognitive defects, known as post–COVID-19 syndrome or 'long COVID.' Post–COVID-19 syndrome is similar to postinfectious fatigue syndromes triggered by other infectious agents and to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a condition that patients often report is preceded by an infectious-like illness. ME/CFS is associated with underlying abnormalities of the central and autonomic nervous systems, immune dysregulation, disordered energy metabolism, and redox imbalance. It is currently unclear if the same abnormalities will be identified in post–COVID-19 syndrome. The USA and other developed nations have committed considerable support for research on post–COVID-19 illnesses.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause chronic and acute disease. Postacute sequelae of SARS-CoV-2 infection (PASC) include injury to the lungs, heart, kidneys, and brain that may produce a variety of symptoms. PASC also includes a post–coronavirus disease 2019 (COVID-19) syndrome ('long COVID') with features that can follow other acute infectious diseases and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Here what is known is

summarized about the pathogenesis of ME/CFS and of 'acute' COVID-19, and speculated that the pathogenesis of post–COVID-19 syndrome in some people may be similar to that of ME/CFS. Molecular mechanisms were proposed that might explain the fatigue and related symptoms in both illnesses, and a research agenda was suggested for both ME/CFS and post–COVID-19 syndrome.

Reference

https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914%2821%2900134-9

Trends in respiratory virus circulation following COVID-19-targeted nonpharmaceutical interventions in Germany, January - September 2020: Analysis of national surveillance data

Abstract

Background: During the initial COVID-19 response, Germany's Federal Government implemented several nonpharmaceutical interventions (NPIs) that were instrumental in suppressing early exponential spread of SARS-CoV-2. NPI effect on the transmission of other respiratory viruses has not been examined at the national level thus far.

Methods: Upper respiratory tract specimens from 3580 patients with acute respiratory infection (ARI), collected within the nationwide German ARI Sentinel, underwent RT-PCR diagnostics for multiple respiratory viruses. The observation period (weeks 1-38 of 2020) included the time before, during and after a far-reaching contact ban. Detection rates for different viruses were compared to 2017-2019 sentinel data (15350 samples; week 1-38, 11823 samples).

Findings: The March 2020 contact ban, which was followed by a mask mandate, was associated with an unprecedented and sustained decline of multiple respiratory viruses. Among these, rhinovirus was the single agent that resurged to levels equalling those of previous years. Rhinovirus rebound was first observed in children, after schools and daycares had reopened. By contrast, other nonenveloped viruses (i.e. gastroenteritis viruses reported at the national level) suppressed after the shutdown did not rebound.

Interpretation: Contact restrictions with a subsequent mask mandate in spring may substantially reduce respiratory virus circulation. This reduction appears sustained for most viruses, indicating that the activity of influenza and other respiratory viruses during

the subsequent winter season might be low,whereas rhinovirus resurgence, potentially driven by transmission in educational institutions in a setting of waning population immunity, might signal predominance of rhinovirus-related ARIs.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00089-2/fulltext

Excess deaths from COVID-19 and other causes by region, neighbourhood deprivation level and place of death during the first 30 weeks of the pandemic in England and Wales: A retrospective registry study

Abstract

Background: Excess deaths during the COVID-19 pandemic compared with those expected from historical trends have been unequally distributed, both geographically and socioeconomically. Not all excess deaths have been directly related to COVID-19 infection. Geographical and socioeconomic patterns were investigated in excess deaths for major groups of underlying causes during the pandemic.

Methods: Weekly mortality data from 27/12/2014 to 2/10/2020 for England and Wales were obtained from the Office of National Statistics. Negative binomial regressions were used to model death counts based on pre-pandemic trends for deaths caused directly by COVID-19 (and other respiratory causes) and those caused indirectly by it (cardiovascular disease or diabetes, cancers, and all other indirect causes) over the first 30 weeks of the pandemic (7/3/2020–2/10/2020).

Findings: There were 62,321 (95% CI: 58,849 to 65,793) excess deaths in England and Wales in the first 30 weeks of the pandemic. Of these, 46,221 (95% CI: 45,439 to 47,003) were attributable to respiratory causes, including COVID-19, and 16,100 (95% CI: 13,410 to 18,790) to other causes. Rates of all-cause excess mortality ranged from 78 per 100,000 in the South West of England and in Wales to 130 per 100,000 in the West Midlands; and from 93 per 100,000 in the most affluent fifth of areas to 124 per 100,000 in the most deprived. The most deprived areas had the highest rates of death attributable to COVID-19 and other indirect deaths, but there was no socioeconomic gradient for excess deaths from cardiovascular disease/diabetes and cancer.

Interpretation: During the first 30 weeks of the COVID-19 pandemic there was significant geographic and socioeconomic variation in excess deaths for respiratory causes, but not for cardiovascular disease, diabetes and cancer. Pandemic recovery plans, including vaccination programmes, should take account of individual characteristics including health, socioeconomic status and place of residence.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00121-6/fulltext

Exposures associated with SARS-CoV-2 infection in France: A nationwide online case-control study

Abstract

Background: It was aimed to assess the role of different setting and activities in acquiring SARS-CoV-2 infection.

Methods: In this nationwide case-control study, cases were SARS-CoV-2 infected adults recruited between 27 October and 30 November 2020. Controls were individuals from the Ipsos market research database matched to cases by age, sex, region, population density and time period. Participants completed an online questionnaire on recent activity-related exposures.

Findings: Among 3426 cases and 1713 controls, in multivariable analysis, an increased risk of infection was found, which was associated with any additional person living in the household (adjusted-OR: 1•16; 95%CI: 1•11-1•21); having children attending day-care (aOR: 1•31; 95%CI: 1•02-1•62), kindergarten (aOR: 1•27; 95%CI: 1•09-1•45), middle school (aOR: 1•30; 95%CI: 1•15-1•47), or high school (aOR: 1•18; 95%CI: 1•05-1•34); with attending professional (aOR: 1•15; 95%CI: 1•04-1•26) or private gatherings (aOR: 1•57; 95%CI: 1•45-1•71); and with having frequented bars and restaurants (aOR: 1•95; 95%CI: 1•76-2•15), or having practiced indoor sports activities (aOR: 1•36; 95%CI: 1•15-1•62). No increase in risk was found, associated with frequenting shops, cultural or religious gatherings, or with transportation, except for carpooling (aOR: 1•47; 95%CI: 1•28-1•69). Teleworking was associated with decreased risk of infection (aOR: 0•65; 95%CI: 0•56-0•75).

Interpretation: Places and activities during which infection prevention and control measures may be difficult to fully enforce were those with increased risk of infection. Children attending day-care, kindergarten, middle and high schools, but not primary schools, were potential sources of infection for the household.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00125-3/fulltext

Publication Date: June 05, 2021

The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies

Abstract

Monoclonal antibodies against SARS-CoV-2 are a clinically validated therapeutic option against COVID-19. Because rapidly emerging virus mutants are becoming the next major concern in the fight against the global pandemic, it is imperative that these therapeutic treatments provide coverage against circulating variants and do not contribute to development of treatment-induced emergent resistance. To this end, it was investigated the sequence diversity of the spike protein and monitored emergence of virus variants in SARS-COV-2 isolates found in COVID-19 patients treated with the two-antibody combination REGEN-COV, as well as in preclinical in vitro studies using single, dual, or triple antibody combinations, and in hamster in vivo studies using REGEN-COV or single monoclonal antibody treatments. The study demonstrates that the combination of non-competing antibodies in REGEN-COV provides protection against all current SARS-CoV-2 variants of concern/interest and also protects against emergence of new variants and their potential seeding into the population in a clinical setting.

Reference

https://www.cell.com/cell/fulltext/S0092-8674%2821%2900703-0

Seroconversion rates following COVID-19 vaccination among patients with cancer

Abstract

As COVID-19 adversely affects patients with cancer, prophylactic strategies are critically needed. Using a validated antibody assay against SARS-CoV-2 spike protein, we determined a high seroconversion rate (94%) in 200 patients with cancer in New York City that had received full dosing with one of the FDA-approved COVID-19 vaccines. On comparison with solid tumors (98%), a significantly lower rate of seroconversion was observed in patients with hematologic malignancies (85%), particularly recipients following highly immunosuppressive therapies such as anti-CD20 therapies (70%) and stem cell transplantation (73%). Patients receiving immune checkpoint inhibitor therapy (97%) or hormonal therapies (100%) demonstrated high seroconversion post vaccination. Patients with prior COVID-19 infection demonstrated higher anti-spike IgG titers post vaccination. Relatively lower IgG titers were observed following vaccination with the adenoviral than with mRNA-based vaccines. These data demonstrate generally high immunogenicity of COVID-19 vaccination in oncology patients and identify immunosuppressed cohorts that need novel vaccination or passive immunization strategies.

Reference

https://www.cell.com/cancer-cell/fulltext/S1535-6108%2821%2900285-3

Uncovering transmission patterns of COVID-19 outbreaks: A region-wide comprehensive retrospective study in Hong Kong

Abstract

Background: Given the dynamism and heterogeneity of COVID-19 transmission patterns, determining the most effective yet timely strategies for specific regions remains a severe challenge for public health decision-makers.

Methods: In this work, a spatiotemporal connectivity analysis method was proposed for discovering transmission patterns across geographic locations and age-groups throughout different COVID-19 outbreak phases. First, the transmission networks of the confirmed cases were constructed during different phases by considering the

spatiotemporal connectivity of any two cases. Then, for each case and those cases immediately pointed from it, we characterized the corresponding cross-district/population transmission pattern by counting their district-to-district and age-to-age occurrences. By summating the cross-district/population transmission patterns of all cases during a given period, we obtained the aggregated cross-district and cross-population transmission patterns.

Findings: A region-wide comprehensive retrospective study was conducted in Hong Kong based on the complete data report of COVID-19 cases, covering all 18 districts between January 23, 2020, and January 8, 2021 (https://data.gov.hk/en-data/dataset/hk-dh-chpsebcddr-novel-infectious-agent). The spatiotemporal connectivity analysis clearly unveiled the quantitative differences among various outbreak waves in their transmission scales, durations, and patterns. Moreover, for the statistically similar waves, their cross-district/population transmission patterns could be quite different (e.g., the cross-district transmission of the fourth wave was more diverse than that of the third wave, while the transmission over age-groups of the fourth wave was more concentrated than that of the third wave). At an overall level, super-spreader individuals (highly connected cases in the transmission networks) were usually concentrated in only a few districts (2 out of 18 in our study) or age-groups (3 out of 11 in our study).

Interpretation: With the discovered cross-district or cross-population transmission patterns, all of the waves of COVID-19 outbreaks in Hong Kong can be systematically scrutinized. Among all districts, quite a few (e.g., the Yau Tsim Mong district) were instrumental in spreading the virus throughout the pandemic. Aside from being exceptionally densely populated, these districts were also social-economic centers. With a variety of situated public venues, such as restaurants and singing/dancing clubs, these districts played host to all kinds of social gathering events, thereby providing opportunities for widespread and rapid transmission of the virus. Thus, these districts should be given the highest priority when deploying district-specific social distancing or intervention strategies, such as lockdown and stringent mandatory coronavirus testing for identifying and obstructing the chain of transmission. It was also observed that most of the reported cases and the highly connected cases were middle-aged and elderly people (40- to 69-year-olds). People in these age-groups were active in various public

places and social activities, and thus had high chances of being infected by or infecting others.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00209-1/fulltext

Publication Date: June 04, 2021

Regulation of the acetylcholine/α7nAChR anti-inflammatory pathway in COVID-19 patients

Abstract

The cholinergic system has been proposed as a potential regulator of COVID-19-induced hypercytokinemia. Whole-blood expression of cholinergic system members was investigated and correlated it with COVID-19 severity. Patients with confirmed SARS-CoV-2 infection and healthy aged-matched controls were included in this non-interventional study. A whole blood sample was drawn between 9–11 days after symptoms onset, and peripheral leukocyte phenotyping, cytokines measurement, RNA expression and plasma viral load were determined. Additionally, whole-blood expression of native alpha-7 nicotinic subunit and its negative dominant duplicate (CHRFAM7A), choline acetyltransferase and acetylcholine esterase (AchE) were determined. Thirty-seven patients with COVID-19 (10 moderate, 11 severe and 16 with critical disease) and 14 controls were included. Expression of CHRFAM7A was significantly lower in critical COVID-19 patients compared to controls. COVID-19 patients not expressing CHRFAM7A had higher levels of CRP, more extended pulmonary lesions and displayed more pronounced lymphopenia. COVID-19 patients without CHRFAM7A expression also showed increased TNF pathway expression in whole blood. AchE was also expressed in 30 COVID-19 patients and in all controls. COVID-19-induced hypercytokinemia is associated with decreased expression of the pro-inflammatory dominant negative duplicate CHRFAM7A. Expression of this duplicate might be considered before targeting the cholinergic system in COVID-19 with nicotine.

Reference

https://www.nature.com/articles/s41598-021-91417-7

A single dose of the SARS-CoV-2 vaccine BNT162b2 elicits Fc-mediated antibody effector functions and T cell responses

Abstract

While the standard regimen of the BNT162b2 mRNA vaccine for SARS-CoV-2 includes two doses administered 3 weeks apart, some public health authorities are spacing these doses, raising concerns about efficacy. However, data indicate that a single dose can be up to 90% effective starting 14 days post-administration. To assess the mechanisms contributing to protection, humoral and T cell responses was analyzed for three weeks after a single BNT162b2 dose. Weak neutralizing activity elicited in SARS-CoV-2 naive individuals was observed but strong anti-receptor binding domain and spike antibodies with Fc-mediated effector functions and cellular CD4+ T cell responses. In previously infected individuals, a single dose boosted all humoral and T cell responses, with strong correlations between T helper and antibody immunity. The results highlight the potential role of Fc-mediated effector functions and T cell responses in vaccine efficacy. They also provide support for spacing doses to vaccinate more individuals in conditions of vaccine scarcity.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128%2821%2900279-1

SARS-CoV-2 elicits robust adaptive immune responses regardless of disease severity

Abstract

Background: The SARS-CoV-2 pandemic currently prevails worldwide. To understand the immunological signature of SARS-CoV-2 infections and aid the search and evaluation of new treatment modalities and vaccines, comprehensive characterization of adaptive immune responses towards SARS-CoV-2 is needed.

Methods: 203 Recovered SARS-CoV-2 infected patients were included in Denmark between April 3rd and July 9th 2020, at least 14 days after COVID-19 symptom recovery. The participants had experienced a range of disease severities from asymptomatic to severe. Plasma, serum and PBMC's were collected for analysis of SARS-CoV-2 specific antibody response by Meso Scale analysis including other

coronavirus strains, ACE2 competition, IgA ELISA, pseudovirus neutralization capacity, and dextramer flow cytometry analysis of CD8+ T cells. The immunological outcomes were compared amongst severity groups within the cohort, and 10 pre-pandemic SARS-CoV-2 negative controls.

Findings: Broad serological profiles were reported within the cohort, detecting antibody binding to other human coronaviruses. 202(>99%) participants had SARS-CoV-2 specific antibodies, with SARS-CoV-2 neutralization and spike-ACE2 receptor interaction blocking observed in 193(95%) individuals. A significant positive correlation (r=0.7804) between spike-ACE2 blocking antibody titers and neutralization potency was observed. Further, SARS-CoV-2 specific CD8+ T-cell responses were clear and quantifiable in 95 of 106(90%) HLA-A2+ individuals.

Interpretation: The viral surface spike protein was identified as the dominant target for both neutralizing antibodies and CD8+ T-cell responses. Overall, the majority of patients had robust adaptive immune responses, regardless of their disease severity.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00203-6/fulltext

Accuracy of four lateral flow immunoassays for anti SARS-CoV-2 antibodies: A head-to-head comparative study

Abstract

Background: SARS-CoV-2 antibody tests are used for population surveillance and might have a future role in individual risk assessment. Lateral flow immunoassays (LFIAs) can deliver results rapidly and at scale, but have widely varying accuracy.

Methods: In a laboratory setting, head-to-head comparisons of four LFIAs were performed: the Rapid Test Consortium's AbC-19TM Rapid Test, OrientGene COVID IgG/IgM Rapid Test Cassette, SureScreen COVID-19 Rapid Test Cassette, and Biomerica COVID-19 IgG/IgM Rapid Test. Blood samples were analysed from 2,847 key workers and 1,995 pre-pandemic blood donors with all four devices.

Findings: A clear trade-off between sensitivity and specificity were observed: the IgG band of the SureScreen device and the AbC-19TM device had higher specificities but OrientGene and Biomerica higher sensitivities. Based on analysis of pre-pandemic

samples, SureScreen IgG band had the highest specificity (98.9%, 95% confidence interval 98.3 to 99.3%), which translated to the highest positive predictive value across any pre-test probability: for example, 95.1% (95% uncertainty interval 92.6, 96.8%) at 20% pre-test probability. All four devices showed higher sensitivity at higher antibody concentrations ("spectrum effects"), but the extent of this varied by device.

Interpretation: The estimates of sensitivity and specificity can be used to adjust for test error rates when using these devices to estimate the prevalence of antibody. If tests were used to determine whether an individual has SARS-CoV-2 antibodies, in an example scenario in which 20% of individuals have antibodies we estimate around 5% of positive results on the most specific device would be false positives.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00207-3/fulltext

SARS-CoV-2 antibody seroprevalence follow-up in Malagasy blood donors during the 2020 COVID-19 Epidemic

Abstract

Background: The incidence of the 2020 COVID-19 epidemic in Africa seems to be different from that of the rest of the world, however its true extent is probably underestimated. Conducting population based sero-surveys during the epidemic has moreover been extremely challenging, driving the group and others to study blood donor samples.

Methods: Regional epidemiological COVID-19 surveillance data was collected, and simultaneously monitored anti-SARS-CoV-2 antibody seroprevalences monthly throughout the epidemic in 5 major Region-associated Blood Transfusion Centres of Madagascar over a period of 9 months.

Findings: Soon after attaining the first epidemic peaks between May and August 2020, both crude and population-weighted test-performance-adjusted seroprevalences of anti-SARS-CoV-2 antibodies was in Malagasy blood donors rapidly increased up to over 40% positivity.

Interpretation: These findings suggest a high cumulative incidence of infection and seroconversion, which may have contributed to the observed deceleration of infection

rates, but was not sufficient to prevent the second epidemic wave that struck Madagascar in Spring 2021.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00212-7/fulltext

Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): An open-label, multicentre, randomised, controlled trial

Abstract

Background: COVID-19 is associated with a prothrombotic state leading to adverse clinical outcomes. Whether therapeutic anticoagulation improves outcomes in patients hospitalised with COVID-19 is unknown. It was aimed to compare the efficacy and safety of therapeutic versus prophylactic anticoagulation in this population.

Methods: A pragmatic, open-label (with blinded adjudication), multicentre, randomised, controlled trial was done, at 31 sites in Brazil. Patients (aged ≥18 years) hospitalised with COVID-19 and elevated D-dimer concentration, and who had COVID-19 symptoms for up to 14 days before randomisation, were randomly assigned (1:1) to receive either therapeutic or prophylactic anticoagulation. Therapeutic anticoagulation was in-hospital oral rivaroxaban (20 mg or 15 mg daily) for stable patients, or initial subcutaneous enoxaparin (1 mg/kg twice per day) or intravenous unfractionated heparin (to achieve a 0·3–0·7 IU/mL anti-Xa concentration) for clinically unstable patients, followed by rivaroxaban to day 30. Prophylactic anticoagulation was standard in-hospital enoxaparin or unfractionated heparin. The primary efficacy outcome was a hierarchical analysis of time to death, duration of hospitalisation, or duration of supplemental oxygen to day 30, analysed with the win ratio method (a ratio >1 reflects a better outcome in the therapeutic anticoagulation group) in the intention-to-treat population. The primary safety outcome was major or clinically relevant non-major bleeding through 30 days. This study is registered with ClinicalTrials.gov (NCT04394377) and is completed.

Findings: From June 24, 2020, to Feb 26, 2021, 3331 patients were screened and 615 were randomly allocated (311 [50%] to the therapeutic anticoagulation group and 304 [50%] to the prophylactic anticoagulation group). 576 (94%) were clinically stable and

39 (6%) clinically unstable. One patient, in the therapeutic group, was lost to follow-up because of withdrawal of consent and was not included in the primary analysis. The primary efficacy outcome was not different between patients assigned therapeutic or prophylactic anticoagulation, with 28 899 (34·8%) wins in the therapeutic group and 34 288 (41·3%) in the prophylactic group (win ratio 0·86 [95% CI 0·59–1·22], p=0·40). Consistent results were seen in clinically stable and clinically unstable patients. The primary safety outcome of major or clinically relevant non-major bleeding occurred in 26 (8%) patients assigned therapeutic anticoagulation and seven (2%) assigned prophylactic anticoagulation (relative risk 3·64 [95% CI 1·61–8·27], p=0·0010). Allergic reaction to the study medication occurred in two (1%) patients in the therapeutic anticoagulation group and three (1%) in the prophylactic anticoagulation group.

Interpretation: In patients hospitalised with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation. Therefore, use of therapeutic-dose rivaroxaban, and other direct oral anticoagulants, should be avoided in these patients in the absence of an evidence-based indication for oral anticoagulation.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01203-4/fulltext

Initial observations on age, gender, BMI and hypertension in antibody responses to SARS-CoV-2 BNT162b2 vaccine

Abstract

Background: Literature data suggests that age, gender and body mass index (BMI) could be associated with difference in immune responses to vaccines. The first goal of the study was to analyze the antibody titre seven days after the second dose of BNT162b2 vaccine in a group of 248 healthcare workers (HCWs). The second goal was to analyze how antibody titre changes in correlation with age, gender, BMI and hypertension.

Methods: An immunogenicity evaluation was carried out among HCWs vaccinated at the Istituti Fisioterapici Ospitalieri (IFO), Rome, Italy. All HCWs were asked to be

vaccinated by the Italian national vaccine campaign at the beginning of 2021. 260 vaccinated HCWs were enrolled in the study. All eligible participants were assigned to receive the priming dose in two weeks' time and the booster dose exactly 21 days thereafter. Blood and nasopharyngeal swabs were collected at baseline and 7 days after second dose of vaccine. Quantitative measurements of IgG antibodies against S1/S2 antigens of SARS-CoV-2 were performed with a commercial chemiluminescent immunoassay. Presence of SARS-Cov-2 in nasopharyngeal swab was determined by commercial RT-PCR testing.

Findings: 248 HWCs were analyzed, 158 women (63.7%) and 90 men (36.3%). After the second dose of BNT162b2 vaccine, 99.5% of participants developed a humoral immune response. The geometric mean concentration of antibodies among the vaccinated subjects after booster dose (285.9 AU/mL 95% CI: 249.5–327.7) was higher than that of human convalescent sera (39.4 AU/mL, 95% CI: 33.1–46.9), with $p<0.0001$. Multivariate linear regression analysis of AU/mL by age, gender and BMI multivariate was performed by the inclusion of covariates. This analysis demonstrated that age ($p<0.0001$) and gender ($p = 0.038$) are statistically associated with differences in antibody response after vaccination, whereas BMI and hypertension have no statistically significant association ($p = 0.078$ and $p = 0.52$ respectively)

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00208-X/fulltext

Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial

Abstract

Background: Hyperimmune anti-COVID-19 Intravenous Immunoglobulin (C-IVIG) is an unexplored therapy amidst the rapidly evolving spectrum of medical therapies for COVID-19 and is expected to counter the three most life-threatening consequences of COVID-19 including lung injury by the virus, cytokine storm and sepsis.

Methods: A single center, phase I/II, randomized controlled, single-blinded trial was conducted at Dow University of Health Sciences, Karachi, Pakistan. Participants were COVID-19 infected individuals, classified as either severely or critically ill with Acute

Respiratory Distress Syndrome (ARDS). Participants were randomized through parallel-group design with sequential assignment in a 4:1 allocation to either intervention group with four C-IVIG dosage arms (0.15, 0.20, 0.25, 0.30 g/kg), or control group receiving standard of care only (n = 10). Primary outcomes were 28-day mortality, patient's clinical status on ordinal scale and Horowitz index (HI), and were analysed in all randomized participants that completed the follow-up period (intention-to-treat population). The trial was registered at clinicaltrials.gov (NCT04521309).

Findings: Fifty participants were enrolled in the study from June 19, 2020 to February 3, 2021 with a mean age of 56.54±13.2 years of which 22 patients (44%) had severe and 28 patients (56%) had critical COVID-19. Mortality occurred in ten of 40 participants (25%) in intervention group compared to six of ten (60%) in control group, with relative risk reduction in intervention arm I (RR, 0.333; 95% CI, 0.087–1.272), arm II (RR, 0.5; 95% CI, 0.171–1.463), arm III (RR, 0.167; 95% CI, 0.024–1.145), and arm IV (RR, 0.667; 95% CI, 0.268–1.660). In intervention group, median HI significantly improved to 359 mmHg [interquartile range (IQR) 127–400, P = 0.009)] by outcome day, while the clinical status of intervention group also improved as compared to control group, with around 15 patients (37.5%) being discharged by 7th day with complete recovery. Additionally, resolution of chest X-rays and restoration of biomarkers to normal levels were also seen in intervention groups. No drug-related adverse events were reported during the study.

Interpretation: Administration of C-IVIG in severe and critical COVID-19 patients was safe, increased the chance of survival and reduced the risk of disease progression.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00206-6/fulltext

Opioid use disorder and health service utilization among COVID-19 patients in the US: A nationwide cohort from the Cerner Real-World Data

Abstract

Background: Both opioid use and COVID-19 affect respiratory and pulmonary health, potentially putting individuals with opioid use disorders (OUD) at risk for complications from COVID-19. The relationship was examined between OUD and subsequent

hospitalization, length of stay, risk for invasive ventilator dependence (IVD), and COVID-19 mortality.

Methods: Multivariable logistic and exponential regression models using electronic health records data from the Cerner COVID-19 De-Identified Data Cohort from January through June 2020.

Findings: Out of 52,312 patients with COVID-19, 1.9% (n=1,013) had an OUD. COVID-19 patients with an OUD had higher odds of hospitalization (aOR=3.44, 95% CI=2.81–4.21), maximum length of stay (eβˆ=1.16, 95% CI=1.09–1.22), and odds of IVD (aOR=1.26, 95% CI=1.06–1.49) than patients without an OUD, but did not differ with respect to COVID-19 mortality. However, OUD patients under age 45 exhibited greater COVID-19 mortality (aOR=3.23, 95% CI=1.59–6.56) compared to patients under age 45 without an OUD. OUD patients using opioid agonist treatment (OAT) exhibited higher odds of hospitalization (aOR=5.14, 95% CI=2.75–10.60) and higher maximum length of stay (eβˆ=1.22, 95% CI=1.01–1.48) than patients without OUDs; however, risk for IVD and COVID-19 mortality did not differ. OUD patients using naltrexone had higher odds of hospitalization (aOR=32.19, 95% CI=4.29–4,119.83), higher maximum length of stay (eβˆ=1.59, 95% CI=1.06–2.38), and higher odds of IVD (aOR=3.15, 95% CI=1.04–9.51) than patients without OUDs, but mortality did not differ. OUD patients who did not use treatment medication had higher odds of hospitalization (aOR=4.05, 95% CI=3.32–4.98), higher maximum length of stay (eβˆ=1.14, 95% CI=1.08–1.21), and higher odds of IVD (aOR=1.25, 95% CI=1.04–1.50) and COVID-19 mortality (aOR=1.31, 95% CI=1.07–1.61) than patients without OUDs.

Interpretation: This study suggests people with OUD and COVID-19 often require higher levels of care, and OUD patients who are younger or not using medication treatment for OUDs are particularly vulnerable to death due to COVID-19.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01203-4/fulltext

Drug repurposing screens identify chemical entities for the development of COVID-19 interventions

Abstract

The ongoing pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), necessitates strategies to identify prophylactic and therapeutic drug candidates for rapid clinical deployment. Here, a screening pipeline was described for the discovery of efficacious SARS-CoV-2 inhibitors. A best-in-class drug repurposing library was screened, ReFRAME, against two high-throughput, high-content imaging infection assays: one using HeLa cells expressing SARS-CoV-2 receptor ACE2 and the other using lung epithelial Calu-3 cells. From nearly 12,000 compounds, we identify 49 (in HeLa-ACE2) and 41 (in Calu-3) compounds capable of selectively inhibiting SARS-CoV-2 replication. Notably, most screen hits are cell-line specific, likely due to different virus entry mechanisms or host cell-specific sensitivities to modulators. Among these promising hits, the antivirals nelfinavir and the parent of prodrug MK-4482 possess desirable in vitro activity, pharmacokinetic and human safety profiles, and both reduce SARS-CoV-2 replication in an orthogonal human differentiated primary cell model. Furthermore, MK-4482 effectively blocks SARS-CoV-2 infection in a hamster model. Overall, direct-acting antivirals were identified as the most promising compounds for drug repurposing, additional compounds that may have value in combination therapies, and tool compounds for identification of viral host cell targets.

Reference

https://www.nature.com/articles/s41467-021-23328-0

Depressive symptoms, mental wellbeing, and substance use among adolescents before and during the COVID-19 pandemic in Iceland: A longitudinal, population-based study

Abstract

Background: Adolescence represents a crucial developmental period in shaping mental health trajectories. In this study, the effect of the COVID-19 pandemic was investigated on mental health and substance use during this sensitive developmental stage.

Methods: In this longitudinal, population-based study, surveys were administered to a nationwide sample of 13–18-year-olds in Iceland in October or February in 2016 and 2018, and in October, 2020 (during the COVID-19 pandemic). The surveys assessed depressive symptoms with the Symptom Checklist-90, mental wellbeing with the Short Warwick Edinburgh Mental Wellbeing Scale, and the frequency of cigarette smoking, e-cigarette use, and alcohol intoxication. Demographic data were collected, which included language spoken at home although not ethnicity data. Mixed effects models were used to study the effect of gender, age, and survey year on trends in mental health outcomes.

Findings: 59 701 survey responses were included; response rates ranged from 63% to 86%. An increase in depressive symptoms (β 0·57, 95% CI 0·53 to 0·60) and worsened mental wellbeing (β −0·46, 95% CI −0·49 to −0·42) were observed across all age groups during the pandemic compared with same-aged peers before COVID-19. These outcomes were significantly worse in adolescent girls compared with boys (β 4·16, 95% CI 4·05 to 4·28, and β −1·13, 95% CI −1·23 to −1·03, respectively). Cigarette smoking (OR 2·61, 95% CI 2·59 to 2·66), e-cigarette use (OR 2·61, 95% CI 2·59 to 2·64), and alcohol intoxication (OR 2·59, 95% CI 2·56 to 2·64) declined among 15–18-year-olds during COVID-19, with no similar gender differences.

Interpretation: The results suggest that COVID-19 has significantly impaired adolescent mental health. However, the decrease observed in substance use during the pandemic might be an unintended benefit of isolation, and might serve as a protective factor against future substance use disorders and dependence. Population-level prevention efforts, especially for girls, are warranted.

Reference

https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(21)00156-5/fulltext

Highly efficient CD4+ T cell targeting and genetic recombination using engineered CD4+ cell-homing mRNA-LNP

Abstract

Nucleoside-modified messenger RNA (mRNA)-lipid nanoparticles (LNPs) are the basis for the first two EUA (Emergency Use Authorization) COVID-19 vaccines. The use of

nucleoside-modified mRNA as a pharmacological agent opens immense opportunities for therapeutic, prophylactic, and diagnostic molecular interventions. In particular, mRNA-based drugs may specifically modulate immune cells, such as T lymphocytes, for immunotherapy of oncologic, infectious and other conditions. The key challenge, however, is that T cells are notoriously resistant to transfection by exogenous mRNA. Here, we report that conjugating CD4 antibody to LNPs enables specific targeting and mRNA interventions to CD4+ cells, including T cells. After systemic injection in mice, CD4-targeted radiolabeled mRNA-LNPs accumulated in spleen, providing ~30-fold higher signal of reporter mRNA in T cells isolated from spleen as compared with non-targeted mRNA-LNP. Intravenous injection of CD4-targeted LNP loaded by Cre recombinase-encoding mRNA provided specific dose-dependent loxP-mediated genetic recombination, resulting in reporter gene expression in about 60% and 40% of CD4+ T cells in spleen and lymph nodes, respectively. T cell phenotyping showed uniform transfection of T cell subpopulations, with no variability in uptake of CD4-targeted mRNA-LNP in naive, central memory, and effector cells. The specific and efficient targeting and transfection of mRNA to T cells established in this study provides a platform technology for immunotherapy of devastating conditions and HIV cure.

Reference

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016%2821%2900310-5

Estimating epidemiologic dynamics from cross-sectional viral load distributions

Abstract

Estimating an epidemic's trajectory is crucial for developing public health responses to infectious diseases, but case data used for such estimation are confounded by variable testing practices. It was shown that the population distribution of viral loads observed under random or symptom-based surveillance, in the form of cycle threshold (Ct) values obtained from reverse-transcription quantitative polymerase chain reaction testing, changes during an epidemic. Thus, Ct values from even limited numbers of random samples can provide improved estimates of an epidemic's trajectory. Combining data from multiple such samples improves the precision and robustness of such estimation. Our methods were applied to Ct values from surveillance conducted during the SARS-

CoV-2 pandemic in a variety of settings and offer alternative approaches for real-time estimates of epidemic trajectories for outbreak management and response.

Reference

https://science.sciencemag.org/content/early/2021/06/02/science.abh0635

The influence of selection bias on identifying an association between allergy medication use and SARS-CoV-2 infection

Abstract

Background: Medications to prevent and treat SARS-CoV-2 infection are needed to complement emerging vaccinations. Recent in vitro and electronic health record (EHR) studies suggested that certain allergy medications could prevent SARS-CoV-2 infection. The potential selection bias was examined, associated with utilizing EHRs in these settings.

Methods: Associations of three allergy medications (cetirizine, diphenhydramine or hydroxyzine) were analyzed with testing negative for SARS-CoV-2, measuring the potential effect of selection bias on these associations. A retrospective cohort of EHR data was used from 230,376 patients (18 years+) who visited outpatient clinicians in a single, large academic center at least once but were never hospitalized (10/1/2019–6/1/2020). Main exposures included EHR documentation of three allergy medications and allergy, with an intermediate outcome of receipt of a SARS-CoV-2 test, and the primary outcome as testing negative.

Findings: SARS-CoV-2 testing rates varied by sex, age, race/ethnicity and insurance. Increasing age and public insurance were associated with a higher adjusted odds of test negativity, while being Black or Hispanic was significantly associated with test positivity. Allergy diagnosis and use of any of three allergy medications were each associated with a higher likelihood of receiving a test (e.g. diphenhydramine - Odds Ratio (OR) 2.99, 95% Confidence Interval (CI) 2.73, 3.28; cetirizine 1.75 (95% CI 1.60, 1.92)). Among those tested, only use of diphenhydramine was associated with a negative SARS-CoV-2 test (adjusted OR = 2.23, 95% CI 1.10, 4.55). However, analyses revealed that selection bias may be responsible for the apparent protective effect of diphenhydramine.

Interpretation: Diphenhydramine use was associated with more SARS-CoV-2 testing and subsequent higher odds for negative tests. While EHR-based observational studies can inform a need for interventional trials, this study revealed limitations of EHR data. The finding that diphenhydramine documentation conferred a higher odds of testing negative for SARS-CoV-2 must be interpreted with caution due to probable selection bias.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00216-9/fulltext

Convalescent plasma therapy in patients with moderate-to-severe COVID-19: A study from Indonesia for clinical research in low- and middle-income countries

Abstract

Background: The outcome of convalescent plasma (CP) treatment in patients were explored with moderate and severe coronavirus disease 2019 (COVID-19) and investigated variables for the design of further trials in Indonesia.

Methods: Hospitalised patients with moderate (n = 5) and severe (n = 5) COVID-19 were recruited and transfused with CP from donors who recovered from mild (n = 5), moderate (n = 5), or severe (n = 1) COVID-19. Neutralising antibodies (NAbs) to the virus were measured at the end of the study using a surrogate virus neutralisation test as an alternative to the plaque reduction assay. Clinical improvement was assessed based on the modified World Health Organization Research and Development Blueprint six-point scale, Brixia Chest-X-Ray scoring, and laboratory parameters. The study was registered at ClinicalTrials.gov (NCT04407208).

Findings: CP transfusion in three doses of 3 mL/kg of recipient body weight at 2-day intervals was well tolerated. Good clinical improvement was achieved in all patients with moderate disease and in two patients with severe disease. Most patients at baseline had detectable NAbs with median inhibition rates comparable to those of the donors (90·91% vs. 86·31%; p = 0·379). This could be due to the unavailability of pre-donation NAb testing and postponed CP administration that required communal consent.

Interpretation: This study highlights the safety of CP therapy. Although improvements were observed, we could not conclude that the outcomes were solely due to CP

treatment. Further randomised controlled trials that cover different disease stages with pre-donation NAb measurements using locally applicable strategies are warranted.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00211-X/fulltext

The early impact of COVID-19 on primary care psychological therapy services: A descriptive time series of electronic healthcare records

Abstract

Background: There are growing concerns about the impact of the COVID-19 pandemic on mental health. With government-imposed restrictions as well as a general burden on healthcare systems, the pandemic has the potential to disrupt the access to, and delivery of, mental healthcare.

Methods: Electronic healthcare records from primary care psychological therapy services (Improving Access to Psychological Therapy) in England were used to examine changes in access to mental health services and service delivery during early stages of the COVID-19 pandemic. A descriptive time series was conducted using data from five NHS trusts to examine patterns in referrals to services (1st January 2019 to 24th May 2020) and appointments (1st January 2020 to 24th May 2020) taking place.

Findings: The number of patients accessing mental health services dropped by an average of 55% in the early weeks after the March 2020 lockdown was announced, reaching a maximum reduction of 74% in the initial 3 weeks after lockdown in the UK, which gradually recovered to a 28% reduction by May. Some evidence suggesting changes were found in the sociodemographic and clinical characteristics of referrals. Despite a reduction in access, the impact on appointments appeared limited with service providers shifting to remote delivery of care.

Interpretation: Services appeared to adapt to provide continuity of care in mental healthcare. However, patients accessing services reduced, potentially placing a future burden on service. Despite the observational nature of the data, the present study can inform the planning of service provision and policy.

Reference

https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(21)00156-5/fulltext

CORRESPONDANCE

Publication Date: Jun 09, 2021

Persistence of SARS-CoV-2 RNA in lung tissue after mild COVID-19

On Dec 1, 2020, a successful case of double-lung transplantation was reported from a SARS-CoV-2 seropositive donor 105 days after the onset of mild COVID-19. Although repeated quantitative (q)RT-PCR analyses of donor nasopharyngeal swabs were negative, this technique detected RNA of the SARS-CoV-2 N gene (delta Ct 35) from a biopsy of the right lung taken during organ procurement. Viral culture of this biopsy was negative and donor-to-recipient transmission did not occur. Complementary orthogonal methods were needed to corroborate and interpret the qRT-PCR results.

Therefore, ultrasensitive single-molecule fluorescence RNA in-situ hybridisation was done with RNAscope technology on formalin-fixed paraffin-embedded sections of the same lung biopsy (appendix p 1), and compared the results with those of a lung biopsy from a deceased patient with acute COVID-19 (figure A and B; appendix p 2). 14 Slides of the donor lung biopsy were stained, each containing one 5 μm section, as follows: five slides with a probe for the N gene; five slides with a probe for the S gene; and four slides with probes for N and S. A probe for the basigin gene, which has been proposed to encode an alternative host recipient for SARS-CoV-2, served as a positive control on the ten slides stained for N or S only. Characteristic RNA scope puncta were identified in three out of nine slides for the N probe, and in six out of nine slides for the S probe (figure C and D). These puncta appeared to be located in clumps of sloughed-off material, and no cells or cell nuclei could be discerned in this debris-like tissue.

To our knowledge, this is the first report of long-term (>100 days) persistence of SARS-CoV-2 RNA in lung tissue of an immunocompetent patient after convalescing from COVID-19. The debris-like tissue that contained SARS-CoV-2 RNA might be composed of degenerated endothelial cells that had detached from vessel walls, dysmorphic syncytial elements of pneumocytes, or dead neutrophilic plugs in the interstitium. It was speculated that this debris-like tissue might shield SARS-CoV-2 RNA from degradation.

Data on sputum, nasopharyngeal swabs, and bronchoalveolar lavage fluid indicate that prolonged detection of SARS-CoV-2 RNA is rare and limited to a few weeks. By

contrast, SARS-CoV-2 RNA persisted in the lung parenchyma for 105 days after the onset of a mild course of COVID-19. Nonetheless, at the time of writing, 11 months after transplantation, the recipient is in good health. The data show that the persistence of SARS-CoV-2 RNA in this donor lung tissue has been inconsequential.

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Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00240-X/fulltext

Publication Date: Jun 05, 2021

The CEPI centralised laboratory network: Supporting COVID-19 vaccine development

With a wide range of COVID-19 vaccine development platforms and extensive variability between laboratory assays, comparison of results for vaccine trials can be challenging. The Coalition for Epidemic Preparedness Innovations (CEPI) has established a global network of laboratories to centralise testing and enable comparison of immunological responses generated by COVID-19 vaccines. The CEPI centralised laboratory network aims to enable key immunogenicity and efficacy endpoint evaluation, support COVID-19 vaccine developers in the pathway towards licensure, and help the identification of immune correlates of protection.

The selection of participating laboratories was carried out through two public requests for proposals. Applicants were evaluated on their technological expertise, successful track record of supporting clinical trials, appropriate quality system, and ability to work internationally to harmonise assay protocols. The laboratories currently included in the CEPI centralised laboratory network are Nexelis, Public Health England, VisMederi,

Viroclinics–DDL, International Centre for Diarrhoeal Disease Research Bangladesh, Translational Health Sciences and Technological Institute, UK National Institute for Biological Standards and Control, Q2 Solutions, and Universidad Nacional Autónoma de México (for geographical locations see appendix).

Six qualified assays were included to evaluate humoral and cellular immune responses after vaccination. The humoral response analysis includes the evaluation of binding and neutralising antibodies. The prefusion spike protein and receptor-binding domain ELISA were used to quantify anti-SARS-CoV-2 IgG antibodies in sera to the most common targets used in vaccine formulations. The nucleocapsid ELISA can be used to measure responses to immunisation with both whole virus vaccines and SARS-CoV-2 infection. The wild-type virus neutralisation assay (VNA) and the pseudovirus neutralising assay (PNA) measure virus-specific neutralising antibodies in serum samples. VNA targets the original SARS-CoV-2 Victoria/1/2020 (subsequently renamed BetaCoV/Australia/VIC01/2020) strain and requires biosafety level 3 facilities, whereas PNA allows determination of neutralisation activity in a standard biosafety level 2 laboratory. The ELISAs and the neutralisation assays are standardised to the WHO International Standard for anti-SARS-CoV-2 immunoglobulin developed by the National Institute for Biological Standards and Control, which will allow harmonisation of data produced in laboratories around the globe. Cell-mediated immunity is measured by the enzyme-linked immunospot (ELISpot) assay, which detects production of interferon-γ and interleukin-5 to SARS-CoV-2 spike protein peptides. CEPI is currently focusing on expanding to analysis of samples against the most relevant variants of concern.

The mentioned assays were developed and qualified by Public Health England (VNA) and Nexelis (ELISA, PNA, and ELISpot); validation is in progress. All assays are in the process of technology transfer to the other participating laboratories using common standardised operating procedures, the same key reagents, and standardised controls and acceptance criteria to ensure that all laboratories are generating concordant results.

The CEPI centralised laboratory network is a global resource, committed to provide testing support to all COVID-19 vaccine developers to facilitate standardised measurement of immune responses to vaccines. A global footprint reduces sample shipment challenges. Sample analysis requests from 60 vaccine developers were

received and, with the endorsement from regulators, we encourage all others to use this harmonised approach.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00982-X/fulltext

Publication Date: Jun 03, 2021

Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination

The SARS-CoV-2 B.1.617.2 Variant of Concern (VOC), first detected in India, is now dominant in the UK, having rapidly displaced the B.1.1.7 strain that emerged in the UK with the second COVID-19 wave in late 2020. The efficacy of currently licensed COVID-19 vaccines against B.1.617.2 is unknown; although it possesses 12 mutations in its spike protein relative to the wildtype SARS-CoV-2 first detected in Wuhan, China, in December, 2019, B.1.617.2 lacks mutations at amino acid positions 501 or 484 in its ACE2 receptor-binding domain, commonly associated with VOCs (appendix p 2) or escape from neutralising antibodies (NAbs).

To determine vaccine-induced NAb escape by B.1.617.2 and compare activity to previous strains with existing estimates for population-based vaccine efficacy, we carried out an initial analysis of the Legacy study, established in January, 2021, by University College London Hospital and the Francis Crick Institute in London, UK, to track serological responses to vaccination in prospectively recruited staff volunteers (appendix p 6). A detailed description of the methods, including the clinical cohort, virus culture conditions, genetic sequencing, and neutralisation assays, and the statistical analysis are available in the appendix (p 8). The Legacy study was approved by London Camden and Kings Cross Health Research Authority Research and Ethics committee (IRAS number 286469) and sponsored by University College London. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/langas/article/PIIS2468-1253(21)00184-9/fulltext

COMMENT

Anti-SARS-CoV-2 mRNA vaccine in patients with rheumatoid arthritis

Long-term vaccine-induced immunity is crucial for controlling the COVID-19 pandemic. Vaccination against COVID-19 is recommended for patients with rheumatic diseases, but a paucity of data are available regarding COVID-19 vaccines in patients with rheumatoid arthritis. Because patients receiving immunosuppressive treatment were excluded from the phase 3 clinical trials, it is not clear whether disease-modifying anti-rheumatic drug (DMARD) treatment should be continued before and after vaccination. In addition, some published reports are limited to follow-up after a single vaccine dose.

Here 53 consecutive patients were reported with rheumatoid arthritis on DMARDs and 20 healthy controls (appendix p 1), who were eligible for vaccination according to the Swiss federal regulations and were enrolled in the RECOVER study, a non-randomised, prospective, observational trial. The RECOVER study was approved by the Ethical Committee of St Gallen, Switzerland, and written consent was obtained from all patients before inclusion. The vaccination itself was not part of the study. Nine patients received two doses of the mRNA-1273 vaccine (Moderna), all others received two doses of the BNT162b2 vaccine (Pfizer–BioNTech). Serum samples were collected at baseline, 3 weeks after the first vaccination, and 2 weeks after the second vaccination. Quantitative antibody testing was done using the Roche Elecsys Anti-SARS-CoV-2 spike subunit 1 (S1) assay that measures antibodies to SARS-CoV-2 spike protein 1 (range 0·4–2500 U/mL) and to SARS-CoV-2 nucleoprotein. This assay was used because it can distinguish between people who develop an anti-S1 response after vaccination or after natural infection, when typically antibodies to both S1 and nucleoprotein are generated. The threshold for this anti-SARS-CoV-2 S1 assay that might correspond to neutralisation of viral infectivity is still being discussed, but a cutoff level of 133 U/mL has been proposed. A lower cutoff level of >15 U/mL has been suggested, emphasising the need to establish formal cutoff levels of anti-SARS-CoV-2 antibody titres associated with protection against SARS-CoV-2 infection and severe disease. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00186-7/fulltext

Procoagulant activity of extracellular vesicles in plasma of patients with SARS-CoV-2 infection

Extracellular vesicles (EVs) have been of special interest in recent years. Emerging evidence suggests that EVs play a key role in health and disease. Released by all cell types, EVs circulate freely, are present in all body fluids and mediate intercellular communication locally and systemically. Further, EVs reprogram functions of circulating and tissue-bound recipient cells in physiological and pathological conditions. EVs represent a heterogenous population of differently sized nanovesicles with distinct biogenesis that carry diverse molecular and genetic cargo and deliver it to recipient cells. Numbers of circulating EVs increase in inflammatory or infectious diseases, and their molecular/genetic content changes with disease progression. Therefore, EVs are being intensively evaluated as non-invasive liquid biomarkers of disease onset, progression and/or outcome. EVs are prominently involved in SARS-Cov-2 infection. A proteomic analysis of EVs isolated from plasma of COVID-19 patients identified several molecules involved in the immune response, inflammation, and activation of the coagulation and complement pathways, which are the main mechanisms of COVID-19-associated tissue damage and multiple organ dysfunctions. SARS-CoV-2, unlike other related viruses, shows tropism for alveolar epithelial cells and endothelial cells, which express the human counter-receptor, angiotensin converting enzyme 2 (ACE2). The virus replicates within infected cells causing a severe respiratory syndrome accompanied by systemic inflammation, which may result in multi-organ damage and death. The vascular and endothelial cell dysfunction associated with increased mortality appears to involve the coagulation pathway. Although procoagulant activity of circulating EVs has been known since 1967, the role these EV play in the COVID-19-induced pathology has not been defined.

A report by Balbi and colleagues shows that tissue factor (TF, CD142), a key initiator of the coagulation pathway, is present on the surface of circulating EVs in patients with SARS-CoV-2 infection. While surface TF expression in circulating EVs accumulating in high procoagulant pathological states was previously described, the Balbi et al. study, identifies TF as a prominent component of the antigenic signature characteristic for circulating EVs in COVID-19 patients and a potentially significant contributor to

thrombotic episodes commonly seen in SARS-CoV-2 infections. EVs in sera of 33 COVID(-) and 34 COVID(+) patients were immunocaptured using a cocktail of 37 colored beads, each coated with an antibody specific for one of the 37 target antigens. Fluorescein-labeled antibodies specific for CD9/CD63/CD81 (i.e., tetraspanins) were used for detection of the EV-associated antigens by flow cytometry. A panel of 7/37 EV-associated antigens (CD142, CD133/1, CD209, CD86, CD69, CD49e and CD20) with the highest scores in EVs of COVID(+) patients was identified. This antigen profile discriminated COVID(+) from COVID(-) patients. Among the 7 antigens in the profile, TF (CD142) had the highest discriminating score. Importantly, expression levels of CD142 on the EV surface correlated with increased serum levels of TNF-alpha in COVID(+) patients. Further, EV-associated TF was biologically active in an assay measuring amidolytic activity of the TF/FVIIa complex, and antibodies neutralizing TF activity significantly reduced procoagulant activity of these EVs. The identification of the EV associated protein signature that reliably discriminates COVID(+) from COVID(-) patients is a significant achievement: TF in EVs emerges as a potential noninvasive biomarker of COVID-19 infection. Even more significant is the finding that TF in EVs from sera of COVID(+) patients was bioactive in ex vivo assays.

Another observation, linking the TF scores and activity of EVs in COVID(+) patients with serum levels of an inflammatory cytokine, TNF alpha, adds special significance to this study. It is known that TF expressed on cell surfaces is “cryptic” and has a low procoagulant activity. To acquire the full-fledged procoagulant activity, membrane-associated TF is “decripted” by an oxidoreductase, protein disulfide isomerase (PDI). In COVID (+) patients with elevated serum levels of IL-6, IL-8 and TNF-alpha, a “cytokine storm” results in vascular injury and endothelial cell (EC) damage. Activated platelets adhering to damaged ECs release PDI, which enhances the TF decription, inducing a massive release from ECs of TF(+) EVs with high procoagulant activity. Balbi et al. demonstrated significant elevations in soluble TNF-alpha levels and in the concentration of circulating TF(+) EVs with strong procoagulant activity in COVID (+) relative to COVID(-) patients. The authors hypothesized that TNF-alpha in sera of COVID(+) patients binds to TNF receptors on the EC surface and induces activated ECs to release TF(+)EVs with strong pro-thrombotic activity. These TF-enriched EVs derived from virus-infected ECs might play a major role in vascular injury that characterizes COVID-19 infection.

In this study, Balbi et al. did not show that TF(+)EV derived from ECs directly contribute to vascular thrombosis in COVID-19 infection. Neither do the authors convincingly show that ECs rather than e.g., platelets, which are known to carry TF, are the source of TF(+) EVs. To do so, selective immune capture of EVs derived from ECs or from platelets would be necessary. The multiplex flow cytometry analysis of EVs from COVID(+) patients indicated that immune as well as non-immune cell types contributed to the total immunocaptured EV population. This emphasizes tremendous heterogeneity of the examined EVs. Based on expression of cell type-associated antigens, the majority of captured EVs originated from ECs or platelets. However, it remains unclear how many EV originating from ECs were TF(+)EVs. Nevertheless, multiplex flow cytometry on beads discriminated COVID(+) from COVID(-) patients by the EV protein profile that was significantly enriched in biologically-active TF only in COVID+ patients. Further, circulating EVs in COVID(+) patients with poor outcome carried significantly higher levels of CD142. The results suggest that TF(+)EVs not only have a diagnostic potential, but might also qualify as a non-invasive prognostic biomarker in SARS-CoV-2 infections. Future studies are necessary to confirm these promising results. Also, Balbi et al. provide a rationale for a future strategy of therapeutically targeting EVs in body fluids of COVID-19 patients. A depletion of pro-thrombotic TF(+)EVs and a pharmacologic blockade of TF activity in these EVs represent a potentially promising future therapeutic strategies.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00204-8/fulltext

REPORT

Publication Date: Jun 09, 2021

Young infants exhibit robust functional antibody responses and restrained IFN-γ production to SARS-CoV-2

Severe COVID-19 appears rare in children. This is unexpected, especially in young infants, who are vulnerable to severe disease caused by other respiratory viruses. We evaluate convalescent immune responses in 4 infants under 3 months old with confirmed COVID-19 who presented with mild febrile illness, alongside their parents, and adult controls recovered from confirmed COVID-19. Although not statistically significant, compared to seropositive adults, infants have high serum levels of IgG and IgA to SARS-CoV-2 spike protein, with a corresponding functional ability to block SARS-CoV-2 cellular entry. Infants also exhibit robust saliva anti-spike IgG and IgA responses. Spike-specific IFN-γ production by infant peripheral blood mononuclear cells appears restrained, but the frequency of spike-specific IFN-γ- and/or TNF-α-producing T cells is comparable between infants and adults. On principal-component analysis, infant immune responses appear distinct from their parents. Robust functional antibody responses alongside restrained IFN-γ production may help protect infants from severe COVID-19.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791%2821%2900170-1

Publication Date: Jun 07, 2021

Assessing the extent of community spread caused by mink-derived SARS-CoV-2 variants

SARS-CoV-2 has recently been found to have spread from humans to minks and then to have transmitted back to humans. However, it is unknown to what extent the human-to-human transmission caused by the variant has reached. Here, we used publicly available SARS-CoV-2 genomic sequences from both humans and minks collected in Denmark and the Netherlands, and combined phylogenetic analysis with Bayesian

inference under an epidemiological model, to trace the possibility of person-to-person transmission. The results showed that at least 12.5% of all people being infected with dominated mink-derived SARS-CoV-2 variants in Denmark and the Netherlands were caused by human-to-human transmission, indicating that this “back-to-human” SARS-CoV-2 variant has already caused human-to-human transmission. Our study also indicated the need for monitoring this mink-derived and other animal source “back-to-human” SARS-CoV-2 in future and that prevention and control measures should be tailored to avoid large-scale community transmission caused by the virus jumping between animals and humans.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758%2821%2900053-9

Publication Date: Jun 03, 2021

Fe-S cofactors in the SARS-CoV-2 RNA-dependent RNA polymerase are potential antiviral targets

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), uses an RNA-dependent RNA polymerase (RdRp) for the replication of its genome and the transcription of its genes. We found that the catalytic subunit of the RdRp, nsp12, ligates two iron-sulfur metal cofactors in sites that were modeled as zinc centers in the available cryo-electron microscopy structures of the RdRp complex. These metal binding sites are essential for replication and for interaction with the viral helicase. Oxidation of the clusters by the stable nitroxide TEMPOL caused their disassembly, potently inhibited the RdRp, and blocked SARS-CoV-2 replication in cell culture. These iron-sulfur clusters thus serve as cofactors for the SARS-CoV-2 RdRp and are targets for therapy of COVID-19.

Reference

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Repurposing drugs for treatment of COVID-19

Although the COVID-19 vaccine programme continues to be rolled out globally, there is still a need to identify effective treatments, particularly in countries where vaccine uptake is slow, and with the insidious threat of mutations resulting in vaccine escape. With the urgency of the pandemic making the timely discovery of new drugs almost impossible, the idea of repurposing existing drugs to treat COVID-19 is an attractive strategy, especially if they are already approved (for other indications) and have well established safety profiles.

Hundreds of medications have been trialled in mainly hospitalised patients with COVID-19, creating a huge amount of data of differing qualities. A central data repository called the CORONA Project was launched by the Castleman Disease Collaborative Network (Paso Robles, CA, USA) and the Center for Cytokine Storm Treatment & Laboratory (CSTL; Philadelphia, PA, USA) in early 2020 to track all treatments that have been used for COVID-19. The project, discussed by CSTL director David Fajgenbaum in a recent podcast with the ASCO Daily News, contains data for 443 medications that have been given to more than 340 000 patients. A panel of physicians and researchers assigns grades to all the drugs based on their effectiveness in randomised trials and whether they met their pre-specified primary endpoint. The grades range from A (established effectiveness; endorsement by professional societies) to F (unlikely to be effective; all or nearly all randomised trials are negative).

Reference

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