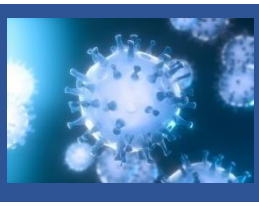

RESEARCH PUBLICATIONS

Publication Date: Oct 28, 2020

Multi-Omics resolves a sharp disease-state shift between mild and moderate COVID-19

Abstract

An integrated analysis was presented of the clinical measurements, immune cells, and plasma multi-omics of 139 COVID-19 patients representing all levels of disease severity, from serial blood draws collected during the first week of infection following diagnosis. A major shift between mild and moderate disease was identified, at which point elevated inflammatory signaling is accompanied by the loss of specific classes of metabolites and metabolic processes. Within this stressed plasma environment at moderate disease, multiple unusual immune cell phenotypes emerge and amplify with increasing disease severity. We condensed over 120,000 immune features into a single axis to capture how different immune cell classes coordinate in response to SARS-CoV-2. This immune-response axis independently aligns with the major plasma composition changes, with clinical metrics of blood clotting, and with the sharp transition between mild and moderate disease. This study suggests that moderate disease may provide the most effective setting for therapeutic intervention.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31444-6

The SARS-CoV-2 targets by the pscRNA profiling of ACE2, TMPRSS2 and furin proteases

Abstract

The cellular targets of SARS-CoV-2, the novel coronavirus causing the COVID-19 pandemic, is still rudimentary. Here, the protein information was incorporated to analyse the expression of ACE2, the SARS-CoV-2 receptor, together with co-factors, TMPRSS2 and Furin, at single cell level in situ, which we called protein-proofed single-cell RNA (pscRNA) profiling. Systemic analysis across 36 tissues revealed a rank list of candidate cells potentially vulnerable to SARS-CoV-2. The top targets are lung AT2 cells and macrophages, then cardiomyocytes and adrenal gland stromal cells, followed by stromal cells in testis, ovary and thyroid. Whereas, the kidney proximal tubule cells, cholangiocytes and enterocytes are less likely to be the primary SARS-CoV-2 targets. Actually, the stomach may constitute a physical barrier against SARS-CoV-2 as the acidic environment (pH < 2.0) could completely inactivate SARS-CoV-2 pseudo-viruses. Together, we provide a comprehensive view on the potential SARS-CoV-2 targets by pscRNA profiling.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(20)30941-X

Pharmacological inhibition of acid sphingomyelinase prevents uptake of SARS-CoV-2 by epithelial cells

Abstract

The acid sphingomyelinase/ceramide system plays an important role in bacterial and viral infections. Here, it was reported that either pharmacological inhibition of acid sphingomyelinase with amitriptyline, imipramine, fluoxetine, sertraline, escitalopram, or maprotiline, or genetic downregulation of the enzyme prevents infection of cultured cells or freshy isolated human nasal epithelial cells with SARS-CoV-2 or pseudoviral pp-VSV-SARS-CoV-2 particles expressing spike, a bona fide system mimicking SARS-CoV-2 infection. Infection activates acid sphingomyelinase and triggers a release of ceramide on the cell surface. Neutralization or consumption of surface ceramide reduces infection with pp-VSV-SARS-CoV-2 spike. Treating volunteers with a low dose of amitriptyline prevents infection of freshly isolated nasal epithelial cells with pp-VSV-SARS-CoV-2

spike. The data justify clinical studies investigating whether amitriptyline, a safe drug used clinically for almost 60 years, or other antidepressants that functionally block acid sphingomyelinase prevent SARS-CoV-2 infection.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30186-5

Publication Date: Oct 27, 2020

Residential context and COVID-19 mortality among adults aged 70 years and older in Stockholm: A population-based, observational study using individual-level data

Abstract

Background: Housing characteristics and neighbourhood context are considered risk factors for COVID-19 mortality among older adults. The aim of this study was to investigate how individual-level housing and neighbourhood characteristics are associated with COVID-19 mortality in older adults.

Methods: For this population-based, observational study, we used data from the cause-of-death register held by the Swedish National Board of Health and Welfare to identify recorded COVID-19 mortality and mortality from other causes among individuals (aged ≥70 years) in Stockholm county, Sweden, between March 12 and May 8, 2020. This information was linked to population-register data from December, 2019, including socioeconomic, demographic, and residential characteristics. We ran Cox proportional hazards regressions for the risk of dying from COVID-19 and from all other causes. The independent variables were area (m2) per individual in the household, the age structure of the household, type of housing, confirmed cases of COVID-19 in the borough, and neighbourhood population density. All models were adjusted for individual age, sex, country of birth, income, and education.

Findings: Of 279 961 individuals identified to be aged 70 years or older on March 12, 2020, and residing in Stockholm in December, 2019, 274 712 met the eligibility criteria and were included in the study population. Between March 12 and May 8, 2020, 3386 deaths occurred, of which 1301 were reported as COVID-19 deaths. In fully adjusted

models, household and neighbourhood characteristics were independently associated with COVID-19 mortality among older adults. Compared with living in a household with individuals aged 66 years or older, living with someone of working age (<66 years) was associated with increased COVID-19 mortality (hazard ratio 1·6; 95% CI 1·3–2·0). Living in a care home was associated with an increased risk of COVID-19 mortality (4·1; 3·5–4·9) compared with living in independent housing. Living in neighbourhoods with the highest population density (≥5000 individuals per km^2) was associated with higher COVID-19 mortality (1·7; 1·1–2·4) compared with living in the least densely populated neighbourhoods (0 to <150 individuals per km^2).

Interpretation: Close exposure to working-age household members and neighbours is associated with increased COVID-19 mortality among older adults. Similarly, living in a care home is associated with increased mortality, potentially through exposure to visitors and care workers, but also due to poor underlying health among care-home residents. These factors should be considered when developing strategies to protect this group.

Reference

https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(20)30016-7/fulltext

What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2

Abstract

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused more than 1 million deaths in the first 6 months of the pandemic and huge economic and social upheaval internationally. An efficacious vaccine is essential to prevent further morbidity and mortality. Although some countries might deploy COVID-19 vaccines on the strength of safety and immunogenicity data alone, the goal of vaccine development is to gain direct evidence of vaccine efficacy in protecting humans against SARS-CoV-2 infection and COVID-19 so that manufacture of efficacious vaccines can be selectively upscaled. A candidate vaccine against SARS-CoV-2 might act against infection, disease, or transmission, and a vaccine capable of reducing any of these elements could contribute to disease control. However, the most important efficacy endpoint, protection against severe disease and death, is difficult to

assess in phase 3 clinical trials. In this Review, it was explored the challenges in assessing the efficacy of candidate SARS-CoV-2 vaccines, discuss the caveats needed to interpret reported efficacy endpoints, and provide insight into answering the seemingly simple question, “Does this COVID-19 vaccine work?”

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30773-8/fulltext

Robust and specific secretory IgA against SARS-CoV-2 detected in human milk

Abstract

The SARS-CoV-2 immune response in human milk has not yet been examined, although protecting infants and young children from COVID-19 is critical for limiting community transmission and preventing serious illness and death. Here, milk samples from eight COVID-19-recovered and seven COVID-19-suspected donors were tested for antibody (Ab) binding to the SARS-CoV-2 Spike protein. All samples exhibited significant specific IgA reactivity to the full Spike, whereas 80% exhibited significant IgA and secretory (s)Ab binding to the Receptor-Binding Domain (RBD). Additionally, 67% samples exhibited IgG and/or IgM binding to RBD. IgA and sAb titers were highly correlated, indicating most IgA to be sIgA. Overall, these data indicate that a robust sIgA-dominant SARS-CoV-2 Ab response in human milk after infection should be expected in a significant majority of individuals. Further research is highly warranted to determine Ab functionality and the potential for exploiting extracted milk sIgA for therapeutic use.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(20)30932-9

β-Coronaviruses use lysosomes for egress instead of the biosynthetic secretory pathway

Abstract

β-Coronaviruses are a family of positive-strand enveloped RNA viruses that includes the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Much is known regarding their cellular entry and replication pathways, but their mode of egress remains uncertain. Using imaging methodologies and virus-specific reporters, we demonstrate that β-coronaviruses utilize lysosomal trafficking for egress rather than the biosynthetic secretory pathway more commonly used by other enveloped viruses. This unconventional egress is regulated by the Arf-like small GTPase Arl8b and can be blocked by the Rab7 GTPase competitive inhibitor CID1067700. Such non-lytic release of β-coronaviruses results in lysosome deacidification, inactivation of lysosomal degradation enzymes, and disruption of antigen presentation pathways. β-Coronavirus-induced exploitation of lysosomal organelles for egress provides insights into the cellular and immunological abnormalities observed in patients and suggests new therapeutic modalities.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31446-X

Publication Date: Oct 24, 2020

Diagnosis of COVID-19 by analysis of breath with gas chromatography-ion mobility spectrometry - A feasibility study

Abstract

Background: There is an urgent need to rapidly distinguish COVID-19 from other respiratory conditions, including influenza, at first-presentation. Point-of-care tests not requiring laboratory- support will speed diagnosis and protect health-care staff. We studied the feasibility of using breath-analysis to distinguish these conditions with near-patient gas chromatography-ion mobility spectrometry (GC-IMS).

Methods: Independent observational prevalence studies at Edinburgh, UK, and Dortmund, Germany, recruited adult patients with possible COVID-19 at hospital

presentation. Participants gave a single breath-sample for VOC analysis by GC-IMS. COVID-19 infection was identified by transcription polymerase chain reaction (RT-qPCR) of oral/nasal swabs together with clinical-review. Following correction for environmental contaminants, potential COVID-19 breath-biomarkers were identified by multi-variate analysis and comparison to GC-IMS databases. A COVID-19 breath-score based on the relative abundance of a panel of volatile organic compounds was proposed and tested against the cohort data.

Findings: Ninety-eight patients were recruited, of whom 21/33 (63.6%) and 10/65 (15.4%) had COVID-19 in Edinburgh and Dortmund, respectively. Other diagnoses included asthma, COPD, bacterial pneumonia, and cardiac conditions. Multivariate analysis identified aldehydes (ethanal, octanal), ketones (acetone, butanone), and methanol that discriminated COVID-19 from other conditions. An unidentified-feature with significant predictive power for severity/death was isolated in Edinburgh, while heptanal was identified in Dortmund. Differentiation of patients with definite diagnosis (25 and 65) of COVID-19 from non-COVID-19 was possible with 80% and 81.5% accuracy in Edinburgh and Dortmund respectively (sensitivity/specificity 82.4%/75%; area-under-the-receiver- operator-characteristic [AUROC] 0.87 95% CI 0.67 to 1) and Dortmund (sensitivity / specificity 90%/80%; AUROC 0.91 95% CI 0.87 to 1).

Interpretation: These two studies independently indicate that patients with COVID-19 can be rapidly distinguished from patients with other conditions at first healthcare contact. The identity of the marker compounds is consistent with COVID-19 derangement of breath-biochemistry by ketosis, gastrointestinal effects, and inflammatory processes. Development and validation of this approach may allow rapid diagnosis of COVID-19 in the coming endemic flu seasons.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30353-9/fulltext

Identification of required host factors for SARS-CoV-2 infection in human cells

Abstract

To better understand host-virus genetic dependencies and find potential therapeutic targets for COVID-19, a genome-scale CRISPR loss-of-function screen was performed to identify host factors required for SARS-CoV-2 viral infection of human alveolar epithelial cells. Top-ranked genes cluster into distinct pathways, including the vacuolar ATPase proton pump, Retromer, and Commander complexes. These gene targets were validated using several orthogonal methods such as CRISPR knockout, RNA interference knockdown, and small-molecule inhibitors. Using single-cell RNA-sequencing, we identify shared transcriptional changes in cholesterol biosynthesis upon loss of top-ranked genes. In addition, given the key role of the ACE2 receptor in the early stages of viral entry, we show that loss of RAB7A reduces viral entry by sequestering the ACE2 receptor inside cells. Overall, this work provides a genome-scale, quantitative resource of the impact of the loss of each host gene on fitness/response to viral infection.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31394-5

Publication Date: Oct 23, 2020

De novo design of picomolar SARS-CoV-2 miniprotein inhibitors

Abstract

Targeting the interaction between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein and the human angiotensin-converting enzyme 2 (ACE2) receptor is a promising therapeutic strategy. We designed inhibitors using two de novo design approaches. Computer-generated scaffolds were either built around an ACE2 helix that interacts with the spike receptor binding domain (RBD) or docked against the RBD to identify new binding modes, and their amino acid sequences were designed to optimize target binding, folding, and stability. Ten designs bound the RBD, with affinities ranging from 100 picomolar to 10 nanomolar, and blocked SARS-CoV-2 infection of Vero E6 cells with median inhibitory concentration (IC50) values between 24 picomolar and 35 nanomolar. The most potent, with new binding modes, are 56- and 64-residue

proteins (IC50 ~ 0.16 nanograms per milliliter). Cryo–electron microscopy structures of these minibinders in complex with the SARS-CoV-2 spike ectodomain trimer with all three RBDs bound are nearly identical to the computational models. These hyperstable minibinders provide starting points for SARS-CoV-2 therapeutics.

Reference

https://science.sciencemag.org/content/370/6515/426

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Abstract

Clinical outcome upon infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ranges from silent infection to lethal coronavirus disease 2019 (COVID-19). We have found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern Toll-like receptor 3 (TLR3)– and interferon regulatory factor 7 (IRF7)–dependent type I interferon (IFN) immunity to influenza virus in 659 patients with life-threatening COVID-19 pneumonia relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, we experimentally defined LOF variants underlying autosomal-recessive or autosomal-dominant deficiencies in 23 patients (3.5%) 17 to 77 years of age. We show that human fibroblasts with mutations affecting this circuit are vulnerable to SARS-CoV-2. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

Reference

https://science.sciencemag.org/content/370/6515/eabd4570

Autoantibodies against type I IFNs in patients with life-threatening COVID-19

Abstract

Interindividual clinical variability in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is vast. We report that at least 101 of 987 patients with life-threatening coronavirus disease 2019 (COVID-19) pneumonia had neutralizing immunoglobulin G (IgG) autoantibodies (auto-Abs) against interferon-ω (IFN-ω) (13 patients), against the 13 types of IFN-α (36), or against both (52) at the

onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 of the 101 were men. A B cell autoimmune phenocopy of inborn errors of type I IFN immunity accounts for life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.

Reference

https://science.sciencemag.org/content/370/6515/eabd4585

Impaired spermatogenesis in COVID-19 patients

Abstract

Background: The current study aimed to determine the impact of SARS-CoV-2 infection on male fertility.

Methods: This is a single-center, hospital-based observational study that included autopsied testicular and epididymal specimens of deceased COVID-19 male patients (n=6) and recruited recovering COVID-19 inpatients (n=23) with an equal number of age-matched controls, respectively. We performed histopathological examinations on testicular and epididymal specimens, and also performed TUNEL assay and immunohistochemistry. Whereas, we investigated the semen specimen for sperm parameters and immune factors.

Findings: Autopsied testicular and epididymal specimens of COVID-19 showed the presence of interstitial edema, congestion, red blood cell exudation in testes, and epididymides. Thinning of seminiferous tubules was observed. The number of apoptotic cells within seminiferous tubules was significantly higher in COVID-19 compared to control cases. It also showed an increased concentration of CD3+ and CD68+ in the interstitial cells of testicular tissue and the presence of IgG within seminiferous tubules. Semen from COVID-19 inpatients showed that 39.1% (n=9) of them have oligozoospermia, and 60.9% (n=14) showed a significant increase in leucocytes in semen. Decreased sperm concentration, and increased seminal levels of IL-6, TNF-α, and MCP-1 compared to control males were observed.

Interpretation: Impairment of spermatogenesis was observed in COVID-19 patients, which could be partially explained as a result of an elevated immune response in testis. Additionally, autoimmune orchitis occurred in some COVID-19 patients. Further research on the reversibility of impairment and developing treatment are warranted.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30348-5/fulltext

Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): A national, multicentre, observational cohort study

Abstract

Background: Little is known about the practice of ventilation management in patients with COVID-19. We aimed to describe the practice of ventilation management and to establish outcomes in invasively ventilated patients with COVID-19 in a single country during the first month of the outbreak.

Methods: PRoVENT-COVID is a national, multicentre, retrospective observational study done at 18 intensive care units (ICUs) in the Netherlands. Consecutive patients aged at least 18 years were eligible for participation if they had received invasive ventilation for COVID-19 at a participating ICU during the first month of the national outbreak in the Netherlands. The primary outcome was a combination of ventilator variables and parameters over the first 4 calendar days of ventilation: tidal volume, positive end-expiratory pressure (PEEP), respiratory system compliance, and driving pressure. Secondary outcomes included the use of adjunctive treatments for refractory hypoxaemia and ICU complications. Patient-centred outcomes were ventilator-free days at day 28, duration of ventilation, duration of ICU and hospital stay, and mortality. PRoVENT-COVID is registered at ClinicalTrials.gov (NCT04346342).

Findings: Between March 1 and April 1, 2020, 553 patients were included in the study. Median tidal volume was 6·3 mL/kg predicted bodyweight (IQR 5·7–7·1), PEEP was 14·0 cm H2O (IQR 11·0–15·0), and driving pressure was 14·0 cm H2O (11·2–16·0). Median respiratory system compliance was 31·9 mL/cm H2O (26·0–39·9). Of the adjunctive treatments for refractory hypoxaemia, prone positioning was most often used

in the first 4 days of ventilation (283 [53%] of 530 patients). The median number of ventilator-free days at day 28 was 0 (IQR 0–15); 186 (35%) of 530 patients had died by day 28. Predictors of 28-day mortality were gender, age, tidal volume, respiratory system compliance, arterial pH, and heart rate on the first day of invasive ventilation.

Interpretation: In patients with COVID-19 who were invasively ventilated during the first month of the outbreak in the Netherlands, lung-protective ventilation with low tidal volume and low driving pressure was broadly applied and prone positioning was often used. The applied PEEP varied widely, despite an invariably low respiratory system compliance. The findings of this national study provide a basis for new hypotheses and sample size calculations for future trials of invasive ventilation for COVID-19. These data could also help in the interpretation of findings from other studies of ventilation practice and outcomes in invasively ventilated patients with COVID-19.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30459-8/fulltext

Malleability of the SARS-CoV-2 3CL M^{pro} active-site cavity facilitates binding of clinical antivirals

Abstract

The COVID-19 pandemic caused by SARS-CoV-2 requires rapid development of specific therapeutics and vaccines. The main protease of SARS-CoV-2, 3CL Mpro, is an established drug target for the design of inhibitors to stop the virus replication. Repurposing existing clinical drugs can offer a faster route to treatments. Here, we report on the binding mode and inhibition properties of several inhibitors using room temperature X-ray crystallography and in vitro enzyme kinetics. The enzyme active-site cavity reveals a high degree of malleability, allowing aldehyde leupeptin and hepatitis C clinical protease inhibitors (telaprevir, narlaprevir, and boceprevir) to bind and inhibit SARS-CoV-2 3CL Mpro. Narlaprevir, boceprevir, and telaprevir are low-micromolar inhibitors, whereas the binding affinity of leupeptin is substantially weaker. Repurposing hepatitis C clinical drugs as COVID-19 treatments may be a useful option to pursue. The observed malleability of the enzyme active-site cavity should be considered for the successful design of specific protease inhibitors.

Reference

https://www.cell.com/structure/fulltext/S0969-2126(20)30379-8

Publication Date: Oct 22, 2020

The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (R) of SARS-CoV-2: A modelling study across 131 countries

Abstract

Background: Non-pharmaceutical interventions (NPIs) were implemented by many countries to reduce the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of COVID-19. A resurgence in COVID-19 cases has been reported in some countries that lifted some of these NPIs. It was aimed to understand the association of introducing and lifting NPIs with the level of transmission of SARS-CoV-2, as measured by the time-varying reproduction number (R), from a broad perspective across 131 countries.

Methods: In this modelling study, data was linked on daily country-level estimates of R from the London School of Hygiene & Tropical Medicine (London, UK) with data on country-specific policies on NPIs from the Oxford COVID-19 Government Response Tracker, available between Jan 1 and July 20, 2020. We defined a phase as a time period when all NPIs remained the same, and we divided the timeline of each country into individual phases based on the status of NPIs. The R ratio was calculated as the ratio between the daily R of each phase and the R from the last day of the previous phase (ie, before the NPI status changed) as a measure of the association between NPI status and transmission of SARS-CoV-2. Then the R ratio was modelled using a log-linear regression with introduction and relaxation of each NPI as independent variables for each day of the first 28 days after the change in the corresponding NPI. In an ad-hoc analysis, we estimated the effect of reintroducing multiple NPIs with the greatest effects, and in the observed sequence, to tackle the possible resurgence of SARS-CoV-2.

Findings: 790 Phases from 131 countries were included in the analysis. A decreasing trend over time in the R ratio was found following the introduction of school closure, workplace closure, public events ban, requirements to stay at home, and internal

movement limits; the reduction in R ranged from 3% to 24% on day 28 following the introduction compared with the last day before introduction, although the reduction was significant only for public events ban (R ratio 0·76, 95% CI 0·58–1·00); for all other NPIs, the upper bound of the 95% CI was above 1. An increasing trend over time in the R ratio was found following the relaxation of school closure, bans on public events, bans on public gatherings of more than ten people, requirements to stay at home, and internal movement limits; the increase in R ranged from 11% to 25% on day 28 following the relaxation compared with the last day before relaxation, although the increase was significant only for school reopening (R ratio 1·24, 95% CI 1·00–1·52) and lifting bans on public gatherings of more than ten people (1·25, 1·03–1·51); for all other NPIs, the lower bound of the 95% CI was below 1. It took a median of 8 days (IQR 6–9) following the introduction of an NPI to observe 60% of the maximum reduction in R and even longer (17 days [14–20]) following relaxation to observe 60% of the maximum increase in R. In response to a possible resurgence of COVID-19, a control strategy of banning public events and public gatherings of more than ten people was estimated to reduce R, with an R ratio of 0·71 (95% CI 0·55–0·93) on day 28, decreasing to 0·62 (0·47–0·82) on day 28 if measures to close workplaces were added, 0·58 (0·41–0·81) if measures to close workplaces and internal movement restrictions were added, and 0·48 (0·32–0·71) if measures to close workplaces, internal movement restrictions, and requirements to stay at home were added.

Interpretation: Individual NPIs, including school closure, workplace closure, public events ban, ban on gatherings of more than ten people, requirements to stay at home, and internal movement limits, are associated with reduced transmission of SARS-CoV-2, but the effect of introducing and lifting these NPIs is delayed by 1–3 weeks, with this delay being longer when lifting NPIs. These findings provide additional evidence that can inform policy-maker decisions on the timing of introducing and lifting different NPIs, although R should be interpreted in the context of its known limitations.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30785-4/fulltext

Publication Date: Oct 19, 2020

Dexamethasone and remdesivir: Finding method in the COVID-19 madness

A pandemic produces record advances—and painful missteps. The infectious-disease community is now leading multinational randomised clinical trials whose magnitude and logistical challenges resemble those of cardiovascular medicine. They achieve enviable statistical power and speed but must sacrifice complexity and nuance to do so. Data entry must be minimal and outcomes easily measurable, precluding virological and other laboratory-based assessments. Before peer review, their potentially blunted messages are broadcast to non-experts by press releases and preprint websites run by a confusing mix of commercial and non-profit organisations. The principles of evidence-based medicine are being increasingly set aside in favour of strong opinions and politically loaded statements.

Large-scale randomised controlled trials and the accessibility of their findings was grateful. But specific expertise is often needed to help parse results: Rigorous critical appraisals should accompany journalistic and lay-public summaries, as patients and other stakeholders might lack the time and background to examine new evidence in detail. More explanatory research assessing key microbiological outcomes is needed. And although new or repurposed therapies might draw the attention of an anxious, pandemic-weary public, we must adhere to fact: access to oxygen and well-staffed supportive care reduces mortality more than any medicinal product.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30173-7/fulltext

Publication Date: Oct 23, 2020

Susceptibility to severe COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has led to unprecedented changes in all aspects of our lives and has placed biomedical research at the forefront. One of the many pressing questions surrounding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is identifying the determinants of the clinical spectrum, from people with asymptomatic disease to patients with severe COVID-19. Up to 40% of infections may be asymptomatic, suggesting that a large proportion of people may be protected from disease. On the other end of the spectrum is severe disease, with an overall estimated fatality rate near 1%. On pages 422 and 424 of this issue, Zhang *et al.* and Bastard *et al.*, respectively, report analyses of >1600 patients infected with SARS-CoV-2 from >15 countries to identify endogenous factors that determine susceptibility to severe COVID-19.

Many studies have focused on characterizing the heterogeneity of COVID-19 in terms of demographics, with clear evidence of higher mortality in men and older individuals. The adaptive immune system, including both B and T cells, has recently been recognized to play a critical role in providing preexisting immunity to SARS-CoV-2. These studies have highlighted mechanisms that protect against severe symptoms but have not revealed factors that predispose to mortality. Consequently, acquired immune responses to prior infections may account for a large percentage of the variability in disease presentation, although questions remain about additional determinants of disease, such as preexisting comorbidities. Host genetic risk factors have also emerged as a potential explanation for clinical heterogeneity and additionally offer the potential for understanding molecular pathways for tailored therapeutic intervention.

Small-scale studies have implicated the type I interferon (IFN) pathway as protective against SARS-CoV-2. The type I IFN pathway plays a crucial role in mediating innate immune responses to viral infections. This family of cytokines is comprised of 13 IFN-α subtypes, IFN-β, IFN-ω, IFN-κ, and IFN-ϵ, which all signal through the heterodimeric IFN I receptor, composed of IFN-α/β receptor 1 (IFNAR1) and IFNAR2 (see the figure). In host cells, type I IFNs are expressed at low amounts, poised to combat infections.

Upon infection, they are rapidly produced by immune cells, such as macrophages and dendritic cells, to limit the spread of pathogens. In addition, type I IFNs induce the expression of several hundred interferon stimulated genes that can further limit pathogen replication through various mechanisms. However, this typically protective immune response can, when overactivated, lead to autoimmune diseases. Conversely, loss-of-function variants in genes encoding members of the type I IFN pathway lead to severe immunodeficiencies characterized by life-threatening viral infections. Recently, multiple studies demonstrated that impaired type 1 IFN responses may be a hallmark of severe COVID-19, but why this pathway was suppressed remained unclear.

Reference

https://science.sciencemag.org/content/370/6515/404

The engines of SARS-CoV-2 spread

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly across the globe, causing epidemics that range from quickly controlled local outbreaks (such as New Zealand) to large ongoing epidemics infecting millions (such as the United States). A tremendous volume of scientific literature has followed, as has vigorous debate about poorly understood facets of the disease, including the relative importance of various routes of transmission, the roles of asymptomatic and presymptomatic infections, and the susceptibility and transmissibility of specific age groups. This discussion may create the impression that our understanding of transmission is frequently overturned. Although our knowledge of SARS-CoV-2 transmission is constantly deepening in important ways, the fundamental engines that drive the pandemic are well established and provide a framework for interpreting this new information.

The majority of SARS-CoV-2 infections likely occur within households and other residential settings (such as nursing homes). This is because most individuals live with other people, and household contacts include many forms of close, high-intensity, and long-duration interaction. Both early contact tracing studies and a large study of more than 59,000 case contacts in South Korea found household contacts to be greater than six times more likely to be infected with SARS-CoV-2 than other close contacts. Household contacts accounted for 57% of identified secondary infections in the South Korean study, despite exhaustive tracking of community contacts. Globally, the

proportion of cases attributable to household transmission will vary because of multiple factors, including household size. Contact studies suggest that 17 to 38% of contacts occur in households, implying that 46 to 66% of transmission is household-based (using the standard formula for attributable fraction). This is consistent with household contact being a key driver of transmission for other respiratory viruses.

Even among close contacts within households, there are considerable heterogeneities in transmission risk. Spouses of index cases are more than twice as likely to be infected as other adult household members, and symptomatic index cases may be more likely to transmit the virus. Moreover, older age is associated with increased susceptibility to infection, increased transmissibility, and severe disease. Older members may face extra risk in multigenerational households if younger members have unavoidable work or school obligations, although young children may be less susceptible to infection and transmit the virus less readily.

Reference

https://science.sciencemag.org/content/370/6515/406

COVID-19 can affect the heart

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

The four “common cold” human coronaviruses—HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1—have not been associated with heart abnormalities. There were isolated reports of patients with Middle East respiratory syndrome (MERS; caused by MERS-CoV) with myocarditis and a limited number of case series of cardiac disease

in patients with SARS (caused by SARS-CoV). Therefore, a distinct feature of SARS-CoV-2 is its more extensive cardiac involvement, which may also be a consequence of the pandemic and the exposure of tens of millions of people to the virus.

What appears to structurally differentiate SARS-CoV-2 from SARS is a furin polybasic site that, when cleaved, broadens the types of cells (tropism) that the virus can infect. The virus targets the angiotensin-converting enzyme 2 (ACE2) receptor throughout the body, facilitating cell entry by way of its spike protein, along with the cooperation of the cellular serine protease transmembrane protease serine 2 (TMPRSS2), heparan sulfate, and other proteases. The heart is one of the many organs with high expression of ACE2. Moreover, the affinity of SARS-CoV-2 to ACE2 is significantly greater than that of SARS. The tropism to other organs beyond the lungs has been studied from autopsy specimens: SARS-CoV-2 genomic RNA was highest in the lungs, but the heart, kidney, and liver also showed substantial amounts, and copies of the virus were detected in the heart from 16 of 22 patients who died. In an autopsy series of 39 patients dying from COVID-19, the virus was not detectable in the myocardium in 38% of patients, whereas 31% had a high viral load above 1000 copies in the heart.

Reference

https://science.sciencemag.org/content/370/6515/408

Publication Date: Oct 22, 2020

CGRP Receptor antagonism in COVID-19: Potential cardiopulmonary adverse effects

Recently, the US FDA has authorized a drug repurposing trial with calcitonin gene-related peptide (CGRP) receptor antagonists to reduce lung inflammation in coronavirus 2019 (COVID-19). However, the well-established cardiopulmonary protective effects of CGRP raise concerns about the safety of antagonizing CGRP in COVID-19. Awareness regarding potential cardiopulmonary adverse effects may enable their early detection and prevent illness from worsening. For more details, read the link given below.

Reference

https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914(20)30267-7

Publication Date: Oct 28, 2020

Inflammatory biomarker trends predict respiratory decline in COVID-19 patients

In this single-center, retrospective cohort analysis of hospitalized coronavirus disease 2019 (COVID-19) patients, we investigate whether inflammatory biomarker levels predict respiratory decline in patients who initially present with stable disease. Examination of C-reactive protein (CRP) trends reveals that a rapid rise in CRP levels precedes respiratory deterioration and intubation, although CRP levels plateau in patients who remain stable. Increasing CRP during the first 48 h of hospitalization is a better predictor (with higher sensitivity) of respiratory decline than initial CRP levels or ROX indices (a physiological score of respiratory function). CRP, the proinflammatory cytokine interleukin-6 (IL-6), and physiological measures of hypoxemic respiratory failure are correlated, which suggests a mechanistic link. Our work shows that rising CRP predicts subsequent respiratory deterioration in COVID-19 and may suggest mechanistic insight and a potential role for targeted immunomodulation in a subset of patients early during hospitalization.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30188-9

Publication Date: Oct 27, 2020

Transparency assessment of COVID-19 models

The COVID-19 pandemic has strained societal structures and created a global crisis. Scientific models have a crucial role in mitigating harm from the pandemic, by estimating the spread of outbreaks of the virus and analysing the effects of public health policies. The context-sensitive and time-sensitive measures provided by COVID-19 models offer real population health impacts and are of great importance. However, these models must be completely transparent before policies and insights are enacted.

Transparency is a cornerstone of scientific methodology, and efforts to improve transparency and reproducibility of research have been increasing over the past

decade. Researchers have called for complete transparency of COVID-19 models. An absence of transparency in the design, development, and analysis of these models reduces the trust in their timely messages and limits their reproducibility, impeding scientists from verifying the findings and improving the model's performance. Many modellers have already shared the details of their models openly. However, the overall status of transparency of COVID-19 models remains unknown. We assessed whether COVID-19 modellers adhere to best practices in reporting and documentation; we did not evaluate whether a model's projections are correct.

Reference

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30447-2/fulltext

Publication Date: Oct 28, 2020

Public health antibody screening indicates a six-fold higher SARS-CoV-2 exposure rate than reported cases in children

Background: Antibody responses to virus reflect exposure and potential protection.

Methods: A highly specific and sensitive approach was developed to measuring antibodies against SARS-CoV-2 for population-scale immune surveillance. Antibody positivity was defined as a dual-positive response against both the receptor binding domain and nucleocapsid proteins of SARS-CoV-2. Antibodies were measured by immuno-precipitation assays in capillary blood from 15,771 children aged 1 to 18 years living in Bavaria, Germany, and participating in a public health type 1 diabetes screening program (Clinicaltrials.gov NCT04039945), in 1,916 dried blood spots from neonates in a Bavarian screening study (Clinicaltrials.gov NCT03316261), and in 75 SARS-CoV-2 positive individuals. Virus positive incidence was obtained from Bavarian health authority data.

Findings: Dual-antibody positivity was detected in none of 3887 children in 2019 (100% specificity) and 73 of 75 SARS-CoV-2 positive individuals (97.3% sensitivity). Antibody surveillance in children during 2020 resulted in frequencies of 0.08% in January to March, 0.61% in April, 0.74% in May, 1.13% in June and 0.91% in July. Antibody prevalence from April 2020 was six-fold higher than the incidence of authority-reported cases (156 per 100,000 children), showed marked variation between the seven Bavarian regions ($P<0.0001$), and was not associated with age or sex. Transmission in children with virus-positive family members was 35%; 47% of positive children were asymptomatic. No association with type 1 diabetes autoimmunity was observed. Antibody frequency in newborns was 0.47%.

Conclusion: It was demonstrated the value of population-based screening programs for pandemic monitoring.

Reference

https://www.cell.com/med/fulltext/S2666-6340(20)30020-9