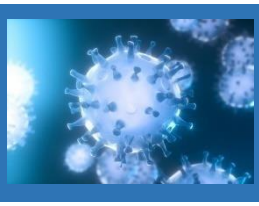
COVID-19

Jan 14 - 20, 2021



RESEARCH PUBLICATIONS

Publication Date: Jan 20, 2021

Identification of 3-chymotrypsin like protease (3CLPro) inhibitors as potential anti-SARS-CoV-2 agents

Abstract

Emerging outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a major threat to public health. The morbidity is increasing due to lack of SARS-CoV-2 specific drugs. Herein, we have identified potential drugs that target the 3-chymotrypsin like protease (3CLpro), the main protease that is pivotal for the replication of SARS-CoV-2. Computational molecular modeling was used to screen 3987 FDA approved drugs, and 47 drugs were selected to study their inhibitory effects on SARS-CoV-2 specific 3CLpro enzyme in vitro. Our results indicate that boceprevir, ombitasvir, paritaprevir, tipranavir, ivermectin, and micafungin exhibited inhibitory effect towards 3CLpro enzymatic activity. The 100 ns molecular dynamics simulation studies showed that ivermectin may require homodimeric form of 3CLpro enzyme for its inhibitory activity. In summary, these molecules could be useful to develop highly specific therapeutically viable drugs to inhibit the SARS-CoV-2 replication either alone or in combination with drugs specific for other SARS-CoV-2 viral targets.

Reference

https://www.nature.com/articles/s42003-020-01577-x

Elucidation of interactions regulating conformational stability and dynamics of SARS-CoV-2 S-protein

Abstract

Ongoing COVID-19 pandemic caused by new coronavirus, SARS-CoV-2, calls for urgent developments of vaccines and antiviral drugs. The spike protein of SARS-CoV-2 (S-protein), which consists of trimeric polypeptide chains with glycosylated residues on the surface, triggers the virus entry into a host cell. Extensive structural and functional studies on this protein have rapidly advanced our understanding of the S-protein structure at atomic resolutions, while most of structural studies overlook the effect of glycans attached to S-protein on the conformational stability and functional motions between the inactive Down and the active Up forms. Here, all-atom molecular dynamics (MD) simulations were performed of both Down and Up forms of a fully glycosylated S-protein in solution as well as targeted MD (TMD) simulations between them to elucidate key inter-domain interactions for stabilizing each form and inducing the large-scale conformational transitions. The residue-level interaction analysis of the simulation trajectories detects distinct amino-acid residues and N-glycans as determinants on conformational stability of each form. During the conformational transitions between them, inter-domain interactions mediated by glycosylated residues are switched to play key roles on the stabilization of another form. Electrostatic interactions as well as hydrogen bonds between the three receptor binding domains work as driving forces to initiate the conformational transitions toward the active form. This study sheds light on the mechanisms underlying conformational stability and functional motions of S-protein, which are relevant for vaccines and antiviral drugs developments.

Reference

https://www.cell.com/biophysj/fulltext/S0006-3495(21)00049-7

Maternal endothelial dysfunction in HIV-associated preeclampsia comorbid with COVID-19: A review

Abstract

This review assesses markers of endothelial dysfunction (ED) associated with the maternal syndrome of preeclampsia (PE). The role of antiretroviral therapy (ART) in

human immunodeficiency virus (HIV)-infected preeclamptic women was evaluated. Furthermore, it was briefly discussed the potential of lopinavir/ritonavir (LPV/r), dolutegravir (DTG) and remdesivir (RDV) in drug repurposing and their safety in pregnancy complicated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In HIV infection, the trans-activator of transcription protein, which has homology with vascular endothelial growth factor, impairs angiogenesis, leading to endothelial injury and possible PE development despite neutralization of their opposing immune states. Markers of ED show strong evidence supporting the adverse role of ART in PE development and mortality compared to treatment-naïve pregnancies. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 infection, exploits angiotensin-converting enzyme 2 (ACE 2) to induce ED and hypertension, thereby mimicking angiotensin II-mediated PE in severe cases of infection. Upregulated ACE 2 in pregnancy is a possible risk factor for SARS-CoV-2 infection and subsequent PE development. The potential effectiveness of LPV/r against COVID-19 is inconclusive; however, defective decidualization, along with elevated markers of ED, was observed. Therefore, the safety of these drugs in HIV-positive pregnancies complicated by COVID-19 requires attention. Despite the observed endothelial protective properties of DTG, there is a lack of evidence of its effects on pregnancy and COVID-19 therapeutics. Understanding RDV-ART interactions and the inclusion of pregnant women in antiviral drug repurposing trials is essential. This review provides a platform for further research on PE in the HIV-COVID-19 syndemic.

Reference

https://www.nature.com/articles/s41440-020-00604-y

The complex structure of GRL0617 and SARS-CoV-2 PLpro reveals a hot spot for antiviral drug discovery

Abstract

SARS-CoV-2 is the pathogen responsible for the COVID-19 pandemic. The SARS-CoV-2 papain-like cysteine protease (PLpro) has been implicated in playing important roles in virus maturation, dysregulation of host inflammation, and antiviral immune responses. The multiple functions of PLpro render it a promising drug target. Therefore, a library of approved drugs was screened and also examined available inhibitors against PLpro.

Inhibitor GRL0617 showed a promising in vitro IC50 of 2.1 μM and an effective antiviral inhibition in cell-based assays. The co-crystal structure of SARS-CoV-2 PLproC111S in complex with GRL0617 indicates that GRL0617 is a non-covalent inhibitor and it resides in the ubiquitin-specific proteases (USP) domain of PLpro. NMR data indicate that GRL0617 blocks the binding of ISG15 C-terminus to PLpro. Using truncated ISG15 mutants, we show that the C-terminus of ISG15 plays a dominant role in binding PLpro. Structural analysis reveals that the ISG15 C-terminus binding pocket in PLpro contributes a disproportionately large portion of binding energy, thus this pocket is a hot spot for antiviral drug discovery targeting PLpro.

Reference

https://www.nature.com/articles/s41467-020-20718-8

Molecular determinants and mechanism for antibody cocktail preventing SARS-CoV-2 escape

Abstract

Antibody cocktails represent a promising approach to prevent SARS-CoV-2 escape. The determinants for selecting antibody combinations and the mechanism that antibody cocktails prevent viral escape remain unclear. The critical residues were compared in the receptor-binding domain (RBD) used by multiple neutralizing antibodies and cocktails and identified a combination of two antibodies CoV2-06 and CoV2-14 for preventing viral escape. The two antibodies simultaneously bind to non-overlapping epitopes and independently compete for receptor binding. SARS-CoV-2 rapidly escapes from individual antibodies by generating resistant mutations *in vitro*, but it doesn't escape from the cocktail due to stronger mutational constraints on RBD-ACE2 interaction and RBD protein folding requirements. A conserved neutralizing epitope was also identified, which was shared between SARS-CoV-2 and SARS-CoV for antibody CoV2-12. Treatments with CoV2-06 and CoV2-14 individually and in combination confer protection in mice. These findings provide insights for rational selection and mechanistic understanding of antibody cocktails as candidates for treating COVID-19.

Reference

https://www.nature.com/articles/s41467-020-20789-7

Quarantine and testing strategies in contact tracing for SARS-CoV-2: A modelling study

Abstract

Background: In most countries, contacts of confirmed COVID-19 cases are asked to quarantine for 14 days after exposure to limit asymptomatic onward transmission. While theoretically effective, this policy places a substantial social and economic burden on both the individual and wider society, which might result in low adherence and reduced policy effectiveness. It was aimed to assess the merit of testing contacts to avert onward transmission and to replace or reduce the length of quarantine for uninfected contacts.

Methods: An agent-based model was used to simulate the viral load dynamics of exposed contacts, and their potential for onward transmission in different quarantine and testing strategies. The performance of quarantines of differing durations were compared, testing with either PCR or lateral flow antigen (LFA) tests at the end of quarantine, and daily LFA testing without quarantine, against the current 14-day quarantine strategy. We also investigated the effect of contact tracing delays and adherence to both quarantine and self-isolation on the effectiveness of each strategy.

Findings: Assuming moderate levels of adherence to quarantine and self-isolation, self-isolation on symptom onset alone can prevent 37% (95% uncertainty interval [UI] 12–56) of onward transmission potential from secondary cases. 14 days of post-exposure quarantine reduces transmission by 59% (95% UI 28–79). Quarantine with release after a negative PCR test 7 days after exposure might avert a similar proportion (54%, 95% UI 31–81; risk ratio [RR] 0·94, 95% UI 0·62–1·24) to that of the 14-day quarantine period, as would quarantine with a negative LFA test 7 days after exposure (50%, 95% UI 28–77; RR 0·88, 0·66–1·11) or daily testing without quarantine for 5 days after tracing (50%, 95% UI 23–81; RR 0·88, 0·60–1·43) if all tests are returned negative. A stronger effect might be possible if individuals isolate more strictly after a positive test and if contacts can be notified faster.

Interpretation: Testing might allow for a substantial reduction in the length of, or replacement of, quarantine with a small excess in transmission risk. Decreasing test and trace delays and increasing adherence will further increase the effectiveness of these strategies. Further research is required to empirically evaluate the potential costs

(increased transmission risk, false reassurance) and benefits (reduction in the burden of quarantine, increased adherence) of such strategies before adoption as policy.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30308-X/fulltext

Publication Date: Jan 19, 2021

Epitope-resolved profiling of the SARS-CoV-2 antibody response identifies cross-reactivity with endemic human coronaviruses

Abstract

The SARS-CoV-2 proteome shares regions of conservation with endemic human coronaviruses (CoVs), but it remains unknown to what extent these may be cross-recognized by the antibody response. Here, a cross-reactivity was studied using a highly multiplexed peptide assay (PepSeq) to generate an epitope-resolved view of IgG reactivity across all human CoVs in both COVID-19 convalescent and negative donors. PepSeq resolves epitopes across the SARS-CoV-2 Spike and Nucleocapsid proteins that are commonly targeted in convalescent donors, including several sites also recognized in some uninfected controls. By comparing patterns of homologous reactivity between CoVs and using targeted antibody-depletion experiments, we demonstrate that SARS-CoV-2 elicits antibodies that cross-recognize pandemic and endemic CoV antigens at two Spike S2 subunit epitopes. It was further shown that these cross-reactive antibodies preferentially bind endemic homologs. Our findings highlight sites at which the SARS-CoV-2 response appears to be shaped by previous CoV exposures and which have the potential to raise broadly neutralizing responses.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30244-5

Mask-wearing and control of SARS-CoV-2 transmission in the USA: A cross-sectional study

Abstract

Background: Face masks have become commonplace across the USA because of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic. Although

evidence suggests that masks help to curb the spread of the disease, there is little empirical research at the population level. It was investigated that the association between self-reported mask-wearing, physical distancing, and SARS-CoV-2 transmission in the USA, along with the effect of statewide mandates on mask uptake.

Methods: Serial cross-sectional surveys were administered *via* a web platform to randomly surveyed US individuals aged 13 years and older, to query self-reports of face mask-wearing. Survey responses were combined with instantaneous reproductive number (Rt) estimates from two publicly available sources, the outcome of interest. Measures of physical distancing, community demographics, and other potential sources of confounding (from publicly available sources) were also assessed. We fitted multivariate logistic regression models to estimate the association between mask-wearing and community transmission control (Rt<1). Additionally, mask-wearing in 12 states was evaluated 2 weeks before and after statewide mandates.

Findings: 378 207 individuals responded to the survey between June 3 and July 27, 2020, of which 4186 were excluded for missing data. We observed an increasing trend in reported mask usage across the USA, although uptake varied by geography. A logistic model controlling for physical distancing, population demographics, and other variables found that a 10% increase in self-reported mask-wearing was associated with an increased odds of transmission control (odds ratio 3·53, 95% CI 2·03–6·43). We found that communities with high reported mask-wearing and physical distancing had the highest predicted probability of transmission control. Segmented regression analysis of reported mask-wearing showed no statistically significant change in the slope after mandates were introduced; however, the upward trend in reported mask-wearing was preserved.

Interpretation: The widespread reported use of face masks combined with physical distancing increases the odds of SARS-CoV-2 transmission control. Self-reported mask-wearing increased separately from government mask mandates, suggesting that supplemental public health interventions are needed to maximise adoption and help to curb the ongoing epidemic.

Reference

https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30293-4/fulltext

Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: An observational cohort study

Abstract

Background: Haematopoietic stem-cell transplantation (HSCT) recipients are considered at high risk of poor outcomes after COVID-19 on the basis of their immunosuppressed status, but data from large studies in HSCT recipients are lacking. This study describes the characteristics and outcomes of HSCT recipients after developing COVID-19.

Methods: In response to the pandemic, the Center for International Blood and Marrow Transplant Research (CIBMTR) implemented a special form for COVID-19-related data capture on March 27, 2020. All patients—irrespective of age, diagnosis, donor type, graft source, or conditioning regimens—were included in the analysis with data cutoff of Aug 12, 2020. The main outcome was overall survival 30 days after a COVID-19 diagnosis. Overall survival probabilities were calculated using Kaplan-Meier estimator. Factors associated with mortality after COVID-19 diagnosis were examined using Cox proportional hazard models.

Findings: 318 HSCT recipients diagnosed with COVID-19 were reported to the CIBMTR. The median time from HSCT to COVID-19 diagnosis was 17 months (IQR 8–46) for allogeneic HSCT recipients and 23 months (8–51) for autologous HSCT recipients. The median follow-up of survivors was 21 days (IQR 8–41) for allogeneic HSCT recipients and 25 days (12–35) for autologous HSCT recipients. 34 (18%) of 184 allogeneic HSCT recipients were receiving immunosuppression within 6 months of COVID-19 diagnosis. Disease severity was mild in 155 (49%) of 318 patients, while severe disease requiring mechanical ventilation occurred in 45 (14%) of 318 patients—ie, 28 (15%) of 184 allogeneic HSCT recipients and 17 (13%) of 134 autologous HSCT recipients. At 30 days after the diagnosis of COVID-19, overall survival was 68% (95% CI 58–77) for recipients of allogeneic HSCT and 67% (55–78) for recipients of autologous HSCT. Age 50 years or older (hazard ratio 2·53, 95% CI 1·16–5·52; p=0·020); male sex (3·53; 1·44–8·67; p=0·006), and development of COVID-19 within 12 months of transplantation (2·67, 1·33–5·36; p=0·005) were associated with a higher risk of mortality among allogeneic HSCT recipients, and a disease indication of

lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma (2·41, [1·08–5·38]; p=0·033) in autologous HSCT recipients.

Interpretation: Recipients of autologous and allogeneic HSCT who develop COVID-19 have poor overall survival. These data emphasise the need for stringent surveillance and aggressive treatment measures in HSCT recipients who develop COVID-19.

Reference

https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30429-4/fulltext

Insight into the practical performance of RT-PCR testing for SARS-CoV-2 using serological data: A cohort study

Abstract

Background: Virological detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through RT-PCR has limitations for surveillance. Serological tests can be an important complementary approach. It was aimed to assess the practical performance of RT-PCR-based surveillance protocols and determine the extent of undetected SARS-CoV-2 infection in Shenzhen, China.

Methods: A cohort study was done in Shenzhen, China and attempted to recruit by telephone all RT-PCR-negative close contacts (defined as those who lived in the same residence as, or shared a meal, travelled, or socially interacted with, an index case within 2 days before symptom onset) of all RT-PCR-confirmed cases of SARS-CoV-2 detected since January, 2020, via contact tracing. Anti-SARS-CoV-2 antibodies was measured in serum samples from RT-PCR-negative close contacts 2–15 weeks after initial virological testing by RT-PCR, using total antibody, IgG, and IgM ELISAs. In addition, we did a serosurvey of volunteers from neighbourhoods with no reported cases, and from neighbourhoods with reported cases. We assessed rates of infection undetected by RT-PCR, performance of RT-PCR over the course of infection, and characteristics of individuals who were seropositive on total antibody ELISA but RT-PCR negative.

Findings: Between April 12 and May 4, 2020, we enrolled and collected serological samples from 2345 (53·0%) of 4422 RT-PCR-negative close contacts of cases of RT-PCR-confirmed SARS-CoV-2. 1175 (50·1%) of 2345 were close contacts of cases diagnosed in Shenzhen with contact tracing details, and of these, 880 (74·9%) had

serum samples collected more than 2 weeks after exposure to an index case and were included in our analysis. 40 (4·5%) of 880 RT-PCR-negative close contacts were positive on total antibody ELISA. The seropositivity rate with total antibody ELISA among RT-PCR-negative close contacts, adjusted for assay performance, was 4·1% (95% CI 2·9–5·7), which was significantly higher than among individuals residing in neighbourhoods with no reported cases (0·0% [95% CI 0·0–1·1]). RT-PCR-positive individuals were 8·0 times (95% CI 5·3–12·7) more likely to report symptoms than those who were RT-PCR-negative but seropositive, but both groups had a similar distribution of sex, age, contact frequency, and mode of contact. RT-PCR did not detect 48 (36% [95% CI 28–44]) of 134 infected close contacts, and false-negative rates appeared to be associated with stage of infection.

Interpretation: Even rigorous RT-PCR testing protocols might miss a substantial proportion of SARS-CoV-2 infections, perhaps in part due to difficulties in determining the timing of testing in asymptomatic individuals for optimal sensitivity. RT-PCR-based surveillance and control protocols that include rapid contact tracing, universal RT-PCR testing, and mandatory 2-week quarantine were, nevertheless, able to contain community spread in Shenzhen, China.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30200-7/fulltext

Clinical and laboratory features of hypercoagulability in COVID-19 and other respiratory viral infections amongst predominantly younger adults with few comorbidities

Abstract

COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and other respiratory viral (non-CoV-2-RV) infections are associated with thrombotic complications. The differences in prothrombotic potential between SARS-CoV-2 and non-CoV-2-RV have not been well characterised. It was compared that thrombotic rates between these two groups of patients directly and further delved into their coagulation profiles. In this single-center, retrospective cohort study, all consecutive COVID-19 and non-CoV-2-RV patients admitted between January 15th and April 10th 2020 were included. Coagulation parameters studied were prothrombin time and activated partial

thromboplastin time and its associated clot waveform analysis (CWA) parameter, min1, min2 and max2. In the COVID-19 (n = 181) group there were two (1.0 event/1000-hospital-days) myocardial infarction events while one (1.8 event/1000-hospital-day) was reported in the non-CoV-2-RV (n = 165) group. These events occurred in patients who were severely ill. There were no venous thrombotic events. Coagulation parameters did not differ throughout the course of mild COVID-19. However, CWA parameters were significantly higher in severe COVID-19 compared with mild disease, suggesting hypercoagulability (min1: 6.48%/s vs 5.05%/s, P < 0.001; min2: 0.92%/s2 vs 0.74%/s2, P = 0.033). In conclusion, the thrombotic rates were low and did not differ between COVID-19 and non-CoV-2-RV patients. The hypercoagulability in COVID-19 is a highly dynamic process with the highest risk occurring when patients were most severely ill. Such changes in haemostasis could be detected by CWA. In our population, a more individualized thromboprophylaxis approach, considering clinical and laboratory factors, is preferred over universal pharmacological thromboprophylaxis for all hospitalized COVID-19 patients and such personalized approach warrants further research.

Reference

https://www.nature.com/articles/s41598-021-81166-y

The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients

Abstract

To explore the value, and influencing factors, of D-dimer on the prognosis of patients with COVID-19. A total of 1,114 patients with confirmed COVID-19 who were admitted to three designated COVID-19 hospitals in Wuhan, China from January 18, 2020, to March 24, 2020, were included in this study. The relationship between peripheral blood levels of D-dimer was examined, and clinical classification and prognosis, as well as its related influencing factors. D-dimer levels were found to be related to the clinical classification and the prognosis of clinical outcome. D-dimer levels were more likely to be abnormal in severely and critically ill patients compared with mild and ordinary cases, while D-dimer levels of patients who had died were significantly higher than those of surviving patients according to the results of the first and last lab tests. The results from ROC analyses for mortality risk showed that the AUCs of D-dimer were

0.909, YI was 0.765 at the last lab test, and a D-dimer value of 2.025 mg/L was regarded to be the optimal probability cutoff for a prognosis of death. In addition, we found that patients with advanced age, male gender, dyspnea symptoms, and some underlying diseases have a higher D-dimer value ($p < 0.05$). In short, D-dimer is related to the clinical classification and can be used to evaluate the prognosis of COVID-19 patients. The D-dimer value of 2.025 mg/L was the optimal probability cutoff for judging an outcome of death. Advanced age, male gender, dyspnea symptoms, and some underlying diseases are influencing factors for D-dimer levels, which impacts the prognosis of patients.

Reference

https://www.nature.com/articles/s41598-021-81300-w

Genomic epidemiology of SARS-CoV-2 reveals multiple lineages and early spread of SARS-CoV-2 infections in Lombardy, Italy

Abstract

From February to April 2020, Lombardy (Italy) reported the highest numbers of SARS-CoV-2 cases worldwide. By analyzing 346 whole SARS-CoV-2 genomes, the presence of seven viral lineages in Lombardy was demonstrated, and frequently sustained by local transmission chains and at least two likely to have originated in Italy. Six single nucleotide polymorphisms (five of them non-synonymous) characterized the SARS-CoV-2 sequences, none of them affecting N-glycosylation sites. The seven lineages, and the presence of local transmission clusters within three of them, revealed that sustained community transmission was underway before the first COVID-19 case had been detected in Lombardy.

Reference

https://www.nature.com/articles/s41467-020-20688-x

Direct detection of SARS-CoV-2 using non-commercial RT-LAMP reagents on heat-inactivated samples

Abstract

RT-LAMP detection of SARS-CoV-2 has been shown to be a valuable approach to scale up COVID-19 diagnostics and thus contribute to limiting the spread of the disease. Here the optimization of highly cost-effective in-house produced enzymes were presented, and their performance was benchmarked against commercial alternatives. The compatibility was explored between multiple DNA polymerases with high strand-displacement activity and thermostable reverse transcriptases required for RT-LAMP. Reaction conditions were optimized and demonstrate their applicability using both synthetic RNA and clinical patient samples. Finally, it was validated that the optimized RT-LAMP assay for the detection of SARS-CoV-2 in unextracted heat-inactivated nasopharyngeal samples from 184 patients. It was anticipated that optimized and affordable reagents for RT-LAMP will facilitate the expansion of SARS-CoV-2 testing globally, especially in sites and settings where the need for large scale testing cannot be met by commercial alternatives.

Reference

https://www.nature.com/articles/s41598-020-80352-8

The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial

Abstract

Background: Ivermectin inhibits the replication of SARS-CoV-2 in vitro at concentrations not readily achievable with currently approved doses. There is limited evidence to support its clinical use in COVID-19 patients. A Pilot, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of a single dose of ivermectin reduce the transmission of SARS-CoV-2 when administered early after disease onset.

Methods: Consecutive patients with non-severe COVID-19 and no risk factors for complicated disease attending the emergency room of the Clínica Universidad de

Navarra between July 31, 2020 and September 11, 2020 were enrolled. All enrollments occurred within 72 h of onset of fever or cough. Patients were randomized 1:1 to receive ivermectin, 400 mcg/kg, single dose (n = 12) or placebo (n = 12). The primary outcome measure was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7 post-treatment. The primary outcome was supported by determination of the viral load and infectivity of each sample. The differences between ivermectin and placebo were calculated using Fisher's exact test and presented as a relative risk ratio. This study is registered at ClinicalTrials.gov: NCT04390022.

Findings: All patients recruited completed the trial (median age, 26 [IQR 19–36 in the ivermectin and 21–44 in the controls] years; 12 [50%] women; 100% had symptoms at recruitment, 70% reported headache, 62% reported fever, 50% reported general malaise and 25% reported cough). At day 7, there was no difference in the proportion of PCR positive patients (RR 0·92, 95% CI: 0·77–1·09, p = 1·0). The ivermectin group had non-statistically significant lower viral loads at day 4 (p = 0·24 for gene E; p = 0·18 for gene N) and day 7 (p = 0·16 for gene E; p = 0·18 for gene N) post treatment as well as lower IgG titers at day 21 post treatment (p = 0·24). Patients in the ivermectin group recovered earlier from hyposmia/anosmia (76 vs 158 patient-days; p < 0.001).

Interpretation: Among patients with non-severe COVID-19 and no risk factors for severe disease receiving a single 400 mcg/kg dose of ivermectin within 72 h of fever or cough onset there was no difference in the proportion of PCR positives. There was however a marked reduction of self-reported anosmia/hyposmia, a reduction of cough and a tendency to lower viral loads and lower IgG titers which warrants assessment in larger trials.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30464-8/fulltext

Publication Date: Jan 18, 2021

Mathematical model of COVID-19 intervention scenarios for São Paulo—Brazil

Abstract

With COVID-19 surging across the world, understanding the effectiveness of intervention strategies on transmission dynamics is of primary global health importance.

Here, an epidemiological compartmental model was developed and analyzed using multi-objective genetic algorithm design optimization to compare scenarios related to strategy type, the extent of social distancing, time window, and personal protection levels on the transmission dynamics of COVID-19 in São Paulo, Brazil. The results indicate that the optimal strategy for São Paulo is to reduce social distancing over time with a stepping-down reduction in the magnitude of social distancing every 80-days. The results also indicate that the ability to reduce social distancing depends on a 5–10% increase in the current percentage of people strictly following protective guidelines, highlighting the importance of protective behavior in controlling the pandemic. The framework can be extended to model transmission dynamics for other countries, regions, states, cities, and organizations.

Reference

https://www.nature.com/articles/s41467-020-20687-y

Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: A retrospective observational study

Abstract

Background: Wuhan was the first epicentre of COVID-19 in the world, accounting for 80% of cases in China during the first wave. It was aimed to assess household transmissibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and risk factors associated with infectivity and susceptibility to infection in Wuhan.

Methods: This retrospective cohort study included the households of all laboratory-confirmed or clinically confirmed COVID-19 cases and laboratory-confirmed asymptomatic SARS-CoV-2 infections identified by the Wuhan Center for Disease Control and Prevention between Dec 2, 2019, and April 18, 2020. We defined households as groups of family members and close relatives who did not necessarily live at the same address and considered households that shared common contacts as epidemiologically linked. A statistical transmission model was used to estimate household secondary attack rates and to quantify risk factors associated with infectivity and susceptibility to infection, accounting for individual-level exposure history. It was assessed how intervention policies affected the household reproductive number, defined as the mean number of household contacts a case can infect.

Findings: 27 101 households with 29 578 primary cases and 57 581 household contacts were identified. The secondary attack rate estimated with the transmission model was 15·6% (95% CI 15·2–16·0), assuming a mean incubation period of 5 days and a maximum infectious period of 22 days. Individuals aged 60 years or older were at a higher risk of infection with SARS-CoV-2 than all other age groups. Infants aged 0–1 years were significantly more likely to be infected than children aged 2–5 years (odds ratio [OR] 2·20, 95% CI 1·40–3·44) and children aged 6–12 years (1·53, 1·01–2·34). Given the same exposure time, children and adolescents younger than 20 years of age were more likely to infect others than were adults aged 60 years or older (1·58, 1·28–1·95). Asymptomatic individuals were much less likely to infect others than were symptomatic cases (0·21, 0·14–0·31). Symptomatic cases were more likely to infect others before symptom onset than after (1·42, 1·30–1·55). After mass isolation of cases, quarantine of household contacts, and restriction of movement policies were implemented, household reproductive numbers declined by 52% among primary cases (from 0·25 [95% CI 0·24–0·26] to 0·12 [0·10–0·13]) and by 63% among secondary cases (from 0·17 [0·16–0·18] to 0·063 [0·057–0·070]).

Interpretation: Within households, children and adolescents were less susceptible to SARS-CoV-2 infection but were more infectious than older individuals. Presymptomatic cases were more infectious and individuals with asymptomatic infection less infectious than symptomatic cases. These findings have implications for devising interventions for blocking household transmission of SARS-CoV-2, such as timely vaccination of eligible children once resources become available.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30981-6/fulltext

Effects of social distancing on the spreading of COVID-19 inferred from mobile phone data

Abstract

A better understanding of how the COVID-19 pandemic responds to social distancing efforts is required for the control of future outbreaks and to calibrate partial lock-downs. We present quantitative relationships between key parameters characterizing the COVID-19 epidemiology and social distancing efforts of nine selected European

countries. Epidemiological parameters were extracted from the number of daily deaths data, while mitigation efforts are estimated from mobile phone tracking data. The decrease of the basic reproductive number (R_0) as well as the duration of the initial exponential expansion phase of the epidemic strongly correlates with the magnitude of mobility reduction. Utilizing these relationships we decipher the relative impact of the timing and the extent of social distancing on the total death burden of the pandemic.

Reference

https://www.nature.com/articles/s41598-021-81308-2

Structural basis of SARS-CoV-2 polymerase inhibition by Favipiravir

Abstract

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has developed into an unprecedented global pandemic. Nucleoside analogues, such as Remdesivir and Favipiravir, can serve as the first-line broad-spectrum antiviral drugs by targeting the viral polymerases. However, the underlying mechanisms for the antiviral efficacies of these drugs are far from well understood. Here it was revealed that Favipiravir, as a pyrazine derivative, could be incorporated into the viral RNA products by mimicking both adenine and guanine nucleotides. This drug thus inhibits viral replication mainly by inducing mutations in progeny RNAs, different from Remdesivir or other RNA-terminating nucleoside analogues that impair the elongation of RNA products. It was further determined that the cryo-EM structure of Favipiravir bound to the replicating polymerase complex of SARS-CoV-2 in the pre-catalytic state. This structure provides a missing snapshot for visualizing the catalysis dynamics of coronavirus polymerase, and reveals an unexpected base-pairing pattern between Favipiravir and pyrimidine residues which may explain its capacity for mimicking both adenine and guanine nucleotides. These findings shed lights on the mechanism of coronavirus polymerase catalysis and provide a rational basis for developing antiviral drugs to combat the SARS-CoV-2 pandemic.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758(21)00005-9

Evolution of antibody immunity to SARS-CoV-2

Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected 78 million individuals and is responsible for over 1.7 million deaths to date. Infection is associated with development of variable levels of antibodies with neutralizing activity that can protect against infection in animal models. Antibody levels decrease with time, but the nature and quality of the memory B cells that would be called upon to produce antibodies upon re-infection has not been examined. Here it was reported on the humoral memory response in a cohort of 87 individuals assessed at 1.3 and 6.2 months after infection. It was found that IgM, and IgG anti-SARS-CoV-2 spike protein receptor binding domain (RBD) antibody titres decrease significantly with IgA being less affected. Concurrently, neutralizing activity in plasma decreases by fivefold in pseudotype virus assays. In contrast, the number of RBD-specific memory B cells is unchanged. Memory B cells display clonal turnover after 6.2 months, and the antibodies they express have greater somatic hypermutation, increased potency and resistance to RBD mutations, indicative of continued evolution of the humoral response. Analysis of intestinal biopsies obtained from asymptomatic individuals 4 months after the onset of coronavirus disease-2019 (COVID-19), using immunofluorescence, or polymerase chain reaction, revealed persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel of 7 out of 14 volunteers. It was concluded that the memory B cell response to SARS-CoV-2 evolves between 1.3 and 6.2 months after infection in a manner that is consistent with antigen persistence.

Reference

https://www.nature.com/articles/s41586-021-03207-w

Predicting mammalian species at risk of being infected by SARS-CoV-2 from an ACE2 perspective

Abstract

SARS-CoV-2 can transmit efficiently in humans, but it is less clear which other mammals are at risk of being infected. SARS-CoV-2 encodes a Spike (S) protein that binds to human ACE2 receptor to mediate cell entry. A species with a human-like ACE2

receptor could therefore be at risk of being infected by SARS-CoV-2. It was compared between 132 mammalian ACE2 genes and between 17 coronavirus S proteins. It was shown that while global similarities reflected by whole ACE2 gene alignments are poor predictors of high-risk mammals, local similarities at key S protein-binding sites highlight several high-risk mammals that share good ACE2 homology with human. Bats are likely reservoirs of SARS-CoV-2, but there are other high-risk mammals that share better ACE2 homologies with human. Both SARS-CoV-2 and SARS-CoV are closely related to bat coronavirus. Yet, among host-specific coronaviruses infecting high-risk mammals, key ACE2-binding sites on S proteins share highest similarities between SARS-CoV-2 and Pangolin-CoV and between SARS-CoV and Civet-CoV. These results suggest that direct coronavirus transmission from bat to human is unlikely, and that rapid adaptation of a bat SARS-like coronavirus in different high-risk intermediate hosts could have allowed it to acquire distinct high binding potential between S protein and human-like ACE2 receptors.

Reference

https://www.nature.com/articles/s41598-020-80573-x

Publication Date: Jan 17, 2021

Employing a systematic approach to biobanking and analyzing clinical and genetic data for advancing COVID-19 research

Abstract

Within the GEN-COVID Multicenter Study, biospecimens from more than 1000 SARS-CoV-2 positive individuals have thus far been collected in the GEN-COVID Biobank (GCB). Sample types include whole blood, plasma, serum, leukocytes, and DNA. The GCB links samples to detailed clinical data available in the GEN-COVID Patient Registry (GCPR). It includes hospitalized patients (74.25%), broken down into intubated, treated by CPAP-biPAP, treated with O2 supplementation, and without respiratory support (9.5%, 18.4%, 31.55% and 14.8, respectively); and non-hospitalized subjects (25.75%), either pauci- or asymptomatic. More than 150 clinical patient-level data fields have been collected and binarized for further statistics according to the organs/systems primarily affected by COVID-19: heart, liver, pancreas, kidney,

chemosensors, innate or adaptive immunity, and clotting system. Hierarchical clustering analysis identified five main clinical categories: (1) severe multisystemic failure with either thromboembolic or pancreatic variant; (2) cytokine storm type, either severe with liver involvement or moderate; (3) moderate heart type, either with or without liver damage; (4) moderate multisystemic involvement, either with or without liver damage; (5) mild, either with or without hyposmia. GCB and GCPR are further linked to the GCGDR, which includes data from whole-exome sequencing and high-density SNP genotyping. The data are available for sharing through the Network for Italian Genomes, found within the COVID-19 dedicated section. The study objective is to systematize this comprehensive data collection and begin identifying multi-organ involvement in COVID-19, defining genetic parameters for infection susceptibility within the population, and mapping genetically COVID-19 severity and clinical complexity among patients.

Reference

https://www.nature.com/articles/s41431-020-00793-7

Publication Date: Jan 16, 2021

Cell-free DNA tissues-of-origin by methylation profiling reveals significant cell, tissue and organ-specific injury related to COVID-19 severity

Abstract

Background: COVID-19 primarily affects the lungs, but evidence of systemic disease with multi-organ involvement is emerging. Here, we developed a blood test to broadly quantify cell, tissue, and organ specific injury due to COVID-19.

Methods: Our test leverages genome-wide methylation profiling of circulating cell-free DNA in plasma. We assessed the utility of this test to identify subjects with severe disease in two independent, longitudinal cohorts of hospitalized patients. Cell-free DNA profiling was performed on 104 plasma samples from 33 COVID-19 patients and compared to samples from patients with other viral infections and healthy controls.

Findings: We found evidence of injury to the lung and liver and involvement of red blood cell progenitors associated with severe COVID-19. The concentration of cell-free DNA correlated with the WHO ordinal scale for disease progression and was significantly increased in patients requiring intubation.

Conclusion: This study points to the utility of cell-free DNA as an analyte to monitor and study COVID-19.

Reference

https://www.cell.com/med/fulltext/S2666-6340(21)00031-3

Inflammatory leptomeningeal cytokines mediate COVID-19 neurologic symptoms in cancer patients

Abstract

SARS-CoV-2 infection induces a wide spectrum of neurologic dysfunction that emerges weeks following the acute respiratory infection. To better understand this pathology, we prospectively analyzed of a cohort of cancer patients with neurologic manifestations of COVID- 19, including a targeted proteomics analysis of the cerebrospinal fluid. We find that cancer patients with neurologic sequela of COVID-19 harbor leptomeningeal inflammatory cytokines in the absence of viral neuro-invasion. The majority of these inflammatory mediators are driven by type 2 interferon and are known to induce neuronal injury in other disease states. In these patients, levels of matrix metalloproteinase-10 within the spinal fluid correlate with the degree of neurologic dysfunction. Furthermore, this neuroinflammatory process persists weeks following convalescence from acute respiratory infection. These prolonged neurologic sequelae following systemic cytokine release syndrome lead to long-term neurocognitive dysfunction. Our findings suggest a role for anti-inflammatory treatment(s) in the management of neurologic complications of COVID-19 infection.

Reference

https://www.cell.com/cancer-cell/fulltext/S1535-6108(21)00051-9

Sensitive detection of total anti-Spike antibodies and isotype switching in asymptomatic and symptomatic COVID-19 patients

Abstract

Early detection of infections is crucial to limit the spread of coronavirus 2019 disease (COVID-19). Here, we develop a flow cytometry-based assay to detect SARS-CoV-2 Spike protein (S protein) antibodies in COVID-19 patients. The assay detects specific

IgM, IgA and IgG in COVID-19 patients and also the acquisition of all IgG subclasses, with IgG1 being the most dominant. The antibody response is significantly higher at a later stage of the infection. Furthermore, asymptomatic COVID-19 patients also develop specific IgM, IgA and IgG, with IgG1 as the most dominant subclass. Although the antibody levels are lower in asymptomatic infections, the assay is highly sensitive and detect 97% of asymptomatic infections. These findings demonstrate that the assay can be used for serological analysis of symptomatic infections, and also asymptomatic infections, which may, otherwise, go undetected.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00004-5

Publication Date: Jan 15, 2021

Characterisation of the first 250 000 hospital admissions for COVID-19 in Brazil: A retrospective analysis of nationwide data

Abstract

Background: Most low-income and middle-income countries (LMICs) have little or no data integrated into a national surveillance system to identify characteristics or outcomes of COVID-19 hospital admissions and the impact of the COVID-19 pandemic on their national health systems. It was aimed to analyse characteristics of patients admitted to hospital with COVID-19 in Brazil, and to examine the impact of COVID-19 on health-care resources and in-hospital mortality.

Methods: We did a retrospective analysis of all patients aged 20 years or older with quantitative RT-PCR (RT-qPCR)-confirmed COVID-19 who were admitted to hospital and registered in SIVEP-Gripe, a nationwide surveillance database in Brazil, between Feb 16 and Aug 15, 2020 (epidemiological weeks 8–33). It was also examined the progression of the COVID-19 pandemic across three 4-week periods within this timeframe (epidemiological weeks 8–12, 19–22, and 27–30). The primary outcome was in-hospital mortality. It was compared the regional burden of hospital admissions stratified by age, intensive care unit (ICU) admission, and respiratory support. We analysed data from the whole country and its five regions: North, Northeast, Central-West, Southeast, and South.

Findings: Between Feb 16 and Aug 15, 2020, 254 288 patients with RT-qPCR-confirmed COVID-19 were admitted to hospital and registered in SIVEP-Gripe. The mean age of patients was 60 (SD 17) years, 119 657 (47%) of 254 288 were aged younger than 60 years, 143 521 (56%) of 254 243 were male, and 14 979 (16%) of 90 829 had no comorbidities. Case numbers increased across the three 4-week periods studied: by epidemiological weeks 19–22, cases were concentrated in the North, Northeast, and Southeast; by weeks 27–30, cases had spread to the Central-West and South regions. 232 036 (91%) of 254 288 patients had a defined hospital outcome when the data were exported; in-hospital mortality was 38% (87 515 of 232 036 patients) overall, 59% (47 002 of 79 687) among patients admitted to the ICU, and 80% (36 046 of 45 205) among those who were mechanically ventilated. The overall burden of ICU admissions per ICU beds was more pronounced in the North, Southeast, and Northeast, than in the Central-West and South. In the Northeast, 1545 (16%) of 9960 patients received invasive mechanical ventilation outside the ICU compared with 431 (8%) of 5388 in the South. In-hospital mortality among patients younger than 60 years was 31% (4204 of 13 468) in the Northeast versus 15% (1694 of 11 196) in the South.

Interpretation: It was observed a widespread distribution of COVID-19 across all regions in Brazil, resulting in a high overall disease burden. In-hospital mortality was high, even in patients younger than 60 years, and worsened by existing regional disparities within the health system. The COVID-19 pandemic highlights the need to improve access to high-quality care for critically ill patients admitted to hospital with COVID-19, particularly in LMICs.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30560-9/fulltext

Plasma tissue plasminogen activator and plasminogen activator inhibitor-1 in hospitalized COVID-19 patients

Abstract

Patients with coronavirus disease-19 (COVID-19) are at high risk for thrombotic arterial and venous occlusions. However, bleeding complications have also been observed in some patients. Understanding the balance between coagulation and fibrinolysis will help inform optimal approaches to thrombosis prophylaxis and potential utility of fibrinolytic-

targeted therapies. 118 hospitalized COVID-19 patients and 30 healthy controls were included in the study. Plasma antigen levels were measured of tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) and performed spontaneous clot-lysis assays. It was found that markedly elevated tPA and PAI-1 levels in patients hospitalized with COVID-19. Both factors demonstrated strong correlations with neutrophil counts and markers of neutrophil activation. High levels of tPA and PAI-1 were associated with worse respiratory status. High levels of tPA, in particular, were strongly correlated with mortality and a significant enhancement in spontaneous ex vivo clot-lysis. While both tPA and PAI-1 are elevated among COVID-19 patients, extremely high levels of tPA enhance spontaneous fibrinolysis and are significantly associated with mortality in some patients. These data indicate that fibrinolytic homeostasis in COVID-19 is complex with a subset of patients expressing a balance of factors that may favor fibrinolysis. Further study of tPA as a biomarker is warranted.

Reference

https://www.nature.com/articles/s41598-020-80010-z

Increase in suicide following an initial decline during the COVID-19 pandemic in Japan

Abstract

There is increasing concern that the coronavirus disease 2019 (COVID-19) pandemic could harm psychological health and exacerbate suicide risk. Here, based on month-level records of suicides covering the entire Japanese population in 1,848 administrative units, we assessed whether suicide mortality changed during the pandemic. Using difference-in-difference estimation, we found that monthly suicide rates declined by 14% during the first 5 months of the pandemic (February to June 2020). This could be due to a number of complex reasons, including the government's generous subsidies, reduced working hours and school closure. By contrast, monthly suicide rates increased by 16% during the second wave (July to October 2020), with a larger increase among females (37%) and children and adolescents (49%). Although adverse impacts of the COVID-19 pandemic may remain in the long term, its modifiers (such as government subsidies) may not be sustained. Thus, effective suicide prevention—particularly among vulnerable populations—should be an important public health consideration.

Reference

https://www.nature.com/articles/s41562-020-01042-z

SARS-CoV-2 infection susceptibility influenced by ACE2 genetic polymorphisms: Insights from Tehran Cardio-Metabolic Genetic Study

Abstract

The genetic variations among individuals are one of the notable factors determining disease severity and drug response. Nowadays, COVID-19 pandemic has been adversely affecting many aspects of human life. We used the Tehran Cardio-Metabolic Genetic Study (TCGS) data that is an ongoing genetic study including the whole-genome sequencing of 1200 individuals and chip genotyping of more than 15,000 participants. Here, the effect of ACE2 variations by focusing on the receptor-binding site of SARS-CoV-2 and ACE2 cleavage by TMPRSS2 protease were investigated through simulations study. After analyzing TCGS data, 570 genetic variations on the ACE2 gene, including single nucleotide polymorphisms (SNP) and insertion/deletion (INDEL) were detected. Interestingly, two observed missense variants, K26R and S331F, which only the first one was previously reported, can reduce the receptor affinity for the viral Spike protein. Moreover, our bioinformatics simulation of 3D structures and docking of proteins explains important details of ACE2-Spike and ACE2-TMPRSS2 interactions, especially the critical role of Arg652 of ACE2 for protease function of TMPRSS2 was uncovered. As our results show that the genetic variation of ACE2 can at least influence the affinity of this receptor to its partners, we need to consider the genetic variations on ACE2 as well as other genes in the pathways that contribute to the pathogenesis of COVID-19 for designing efficient drugs and vaccines.

Reference

https://www.nature.com/articles/s41598-020-80325-x

Improving SARS-CoV-2 structures: Peer review by early coordinate release

Abstract

This work builds upon the record-breaking speed and generous immediate release of new experimental 3D structures of the SARS-CoV-2 proteins and complexes, which are crucial to downstream vaccine and drug development. We have surveyed those

structures to catch the occasional errors that could be significant for those important uses and for which we were able to provide demonstrably higher-accuracy corrections. This process relied on new validation and correction methods such as CaBLAM and ISOLDE, not yet in routine use. We found such important and correctable problems in seven early SARS-CoV-2 structures. Two of the structures were soon superseded by new higher-resolution data, confirming our proposed changes. For the other five, we emailed the depositors a documented and illustrated report, and encouraged them to make the model corrections themselves and use the new option at the worldwide Protein Data Base for depositors to re-version their coordinates without changing the PDB code. This quickly and easily makes the better-accuracy coordinates available to anyone who examines or downloads their structure, even before formal publication. The changes have involved sequence misalignments, incorrect RNA conformations near a bound inhibitor, incorrect metal ligands, and cis-trans or peptide flips that prevent good contact at interaction sites. These improvements have propagated into nearly all related structures done afterward. This process constitutes a new form of highly rigorous peer review, which is actually faster and more strict than standard publication review, because it has access to coordinates and maps; journal peer review would also be strengthened by such access.

Reference

https://www.cell.com/biophysj/fulltext/S0006-3495(21)00046-1

The challenges of containing SARS-CoV-2 *via* test-trace-and-isolate

Abstract

Without a cure, vaccine, or proven long-term immunity against SARS-CoV-2, test-trace-and-isolate (TTI) strategies present a promising tool to contain its spread. For any TTI strategy, however, mitigation is challenged by pre- and asymptomatic transmission, TTI-avoiders, and undetected spreaders, which strongly contribute to ”hidden" infection chains. Here, we study a semi-analytical model and identify two tipping points between controlled and uncontrolled spread: (1) the behavior-driven reproduction number R_t^H of the hidden chains becomes too large to be compensated by the TTI capabilities, and (2) the number of new infections exceeds the tracing capacity. Both trigger a self-accelerating spread. We investigate how these tipping points depend on challenges like

limited cooperation, missing contacts, and imperfect isolation. Our results suggest that TTI alone is insufficient to contain an otherwise unhindered spread of SARS-CoV-2, implying that complementary measures like social distancing and improved hygiene remain necessary.

Reference

https://www.nature.com/articles/s41467-020-20699-8

Publication Date: Jan 14, 2021

Lessons from the COVID-19 pandemic for advancing computational drug repurposing strategies

Abstract

Responding quickly to unknown pathogens is crucial to stop uncontrolled spread of diseases that lead to epidemics, such as the novel coronavirus, and to keep protective measures at a level that causes as little social and economic harm as possible. This can be achieved through computational approaches that significantly speed up drug discovery. A powerful approach is to restrict the search to existing drugs through drug repurposing, which can vastly accelerate the usually long approval process. In this Review, we examine a representative set of currently used computational approaches to identify repurposable drugs for COVID-19, as well as their underlying data resources. Furthermore, we compare drug candidates predicted by computational methods to drugs being assessed by clinical trials. Finally, we discuss lessons learned from the reviewed research efforts, including how to successfully connect computational approaches with experimental studies, and propose a unified drug repurposing strategy for better preparedness in the case of future outbreaks.

Reference

https://www.nature.com/articles/s43588-020-00007-6

SARS-CoV-2 antibody testing for estimating COVID-19 prevalence in the population

Abstract

Reliable antibody testing against SARS-CoV-2 has the potential to uncover the population wide spread of COVID-19, which is critical for making informed healthcare and economic decisions. Here, we review different types of antibody tests available for SARS-CoV-2 and their application for population scale testing. Biases due to varying test accuracy, results of ongoing large-scale serological studies, and the use of antibody testing for monitoring the development of herd immunity are summarized. While current SARS-CoV-2 antibody testing efforts have generated valuable insights, the accuracy of serological tests and the selection criteria of the tested cohorts need to be carefully evaluated.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00002-1

Cannabis compounds exhibit anti-inflammatory activity in vitro in COVID-19-related inflammation in lung epithelial cells and pro-inflammatory activity in macrophages

Abstract

Cannabis sativa is widely used for medical purposes and has anti-inflammatory activity. This study intended to examine the anti-inflammatory activity of cannabis on immune response markers associated with coronavirus disease 2019 (COVID-19) inflammation. An extract fraction from C. sativa Arbel strain (FCBD) substantially reduced (dose dependently) interleukin (IL)-6 and -8 levels in an alveolar epithelial (A549) cell line. FCBD contained cannabidiol (CBD), cannabigerol (CBG) and tetrahydrocannabivarin (THCV), and multiple terpenes. Treatments with FCBD and a FCBD formulation using phytocannabinoid standards (FCBD:std) reduced IL-6, IL-8, C–C Motif Chemokine Ligands (CCLs) 2 and 7, and angiotensin I converting enzyme 2 (ACE2) expression in the A549 cell line. Treatment with FCBD induced macrophage (differentiated KG1 cell line) polarization and phagocytosis in vitro, and increased CD36 and type II receptor for the Fc region of IgG (FcγRII) expression. FCBD treatment also substantially increased

IL-6 and IL-8 expression in macrophages. FCBD:std, while maintaining anti-inflammatory activity in alveolar epithelial cells, led to reduced phagocytosis and pro-inflammatory IL secretion in macrophages in comparison to FCBD. The phytocannabinoid formulation may show superior activity versus the cannabis-derived fraction for reduction of lung inflammation, yet there is a need of caution proposing cannabis as treatment for COVID-19.

Reference

https://www.nature.com/articles/s41598-021-81049-2

Simulating SARS-CoV-2 epidemics by region-specific variables and modeling contact tracing app containment

Abstract

Targeted contact-tracing through mobile phone apps has been proposed as an instrument to help contain the spread of COVID-19 and manage the lifting of nation-wide lock-downs currently in place in USA and Europe. However, there is an ongoing debate on its potential efficacy, especially in light of region-specific demographics. An expanded SIR model of COVID-19 epidemic was built that accounts for region-specific population densities, and we used it to test the impact of a contact-tracing app in a number of scenarios. Using demographic and mobility data from Italy and Spain, the model was used to simulate scenarios that vary in baseline contact rates, population densities, and fraction of app users in the population. Our results show that, in support of efficient isolation of symptomatic cases, app-mediated contact-tracing can successfully mitigate the epidemic even with a relatively small fraction of users, and even suppress altogether with a larger fraction of users. However, when regional differences in population density are taken into consideration, the epidemic can be significantly harder to contain in higher density areas, highlighting potential limitations of this intervention in specific contexts. This work corroborates previous results in favor of app-mediated contact-tracing as mitigation measure for COVID-19, and draws attention on the importance of region-specific demographic and mobility factors to achieve maximum efficacy in containment policies.

Reference

https://www.nature.com/articles/s41746-020-00374-4

SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice

Abstract

The COVID-19 pandemic continues to spread throughout the world with an urgent need for a safe and protective vaccine to effectuate herd protection and control the spread of SARS-CoV-2. Here, we report the development of a SARS-CoV-2 subunit vaccine (NVX-CoV2373) from the full-length spike (S) protein that is stable in the prefusion conformation. NVX-CoV2373 S form 27.2-nm nanoparticles that are thermostable and bind with high affinity to the human angiotensin-converting enzyme 2 (hACE2) receptor. In mice, low-dose NVX-CoV2373 with saponin-based Matrix-M adjuvant elicit high titer anti-S IgG that blocks hACE2 receptor binding, neutralize virus, and protects against SARS-CoV-2 challenge with no evidence of vaccine-associated enhanced respiratory disease. NVX-CoV2373 also elicits multifunctional CD4+ and CD8+ T cells, CD4+ follicular helper T cells (Tfh), and antigen-specific germinal center (GC) B cells in the spleen. In baboons, low-dose levels of NVX-CoV2373 with Matrix-M was also highly immunogenic and elicited high titer anti-S antibodies and functional antibodies that block S-protein binding to hACE2 and neutralize virus infection and antigen-specific T cells. These results support the ongoing phase 1/2 clinical evaluation of the safety and immunogenicity of NVX-CoV2373 with Matrix-M (NCT04368988).

Reference

https://www.nature.com/articles/s41467-020-20653-8

PERSPECTIVE

Publication Date: Jan 19, 2021

Looking beyond COVID-19 vaccine phase 3 trials

Recent After the recent announcement of COVID-19 vaccine efficacy in clinical trials by several manufacturers for protection against severe disease, a comprehensive post-efficacy strategy for the next steps to ensure vaccination of the global population is now required. These considerations should include how to manufacture billions of doses of high-quality vaccines, support for vaccine purchase, coordination of supply, the equitable distribution of vaccines and the logistics of global vaccine delivery, all of which are a prelude to a massive vaccination campaign targeting people of all ages. Furthermore, additional scientific questions about the vaccines remain that should be answered to improve vaccine efficacy, including questions regarding the optimization of vaccination regimens, booster doses, the correlates of protection, vaccine effectiveness, safety and enhanced surveillance. The timely and coordinated execution of these post-efficacy tasks will bring the pandemic to an effective, and efficient, close.

Reference

https://www.nature.com/articles/s41591-021-01230-y

Publication Date: Jan 15, 2021

Lessons from the host defences of bats, a unique viral reservoir

There have been several major outbreaks of emerging viral diseases, including Hendra, Nipah, Marburg and Ebola virus diseases, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)—as well as the current pandemic of coronavirus disease 2019 (COVID-19). Notably, all of these outbreaks have been linked to suspected zoonotic transmission of bat-borne viruses. Bats—the only flying mammal—display several additional features that are unique among mammals, such as a long lifespan relative to body size, a low rate of tumorigenesis and an exceptional ability to host viruses without presenting clinical disease. Here the mechanisms were discussed that underpin the host defence system and immune tolerance of bats, and

their ramifications for human health and disease. Recent studies suggest that 64 million years of adaptive evolution have shaped the host defence system of bats to balance defence and tolerance, which has resulted in a unique ability to act as an ideal reservoir host for viruses. Lessons from the effective host defence of bats would help us to better understand viral evolution and to better predict, prevent and control future viral spillovers. Studying the mechanisms of immune tolerance in bats could lead to new approaches to improving human health. We strongly believe that it is time to focus on bats in research for the benefit of both bats and humankind. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41586-020-03128-0

Herd immunity by infection is not an option

Herd immunity is expected to arise when a virus cannot spread readily, because it encounters a population that has a level of immunity that reduces the number of individuals susceptible to infection. In this issue, Buss et al. describe the extent of the largely uncontrolled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic in Manaus, the capital of Amazonas state in Brazil. Their data show the impact on mortality rates of a largely unmitigated outbreak where even with an estimated 76% of the population being infected, herd immunity was not achieved. Manaus provides a cautionary example of unmitigated spread across a population, showing that herd immunity is likely not achieved even at high levels of infection and that it comes with unacceptably high costs.

Buss et al. used data on the occurrence of SARS-CoV-2–specific antibodies (seroprevalence) in blood donors, adjusted for waning antibody responses over time, to calculate an estimated attack rate for COVID-19 of 66% in June, rising to 76% in October, in Manaus. The attack rate is the proportion of at-risk people who develop infection after exposure in a period of time. This attack rate resulted in a factor of 4.5 excess mortality in 2020 relative to previous years. The infection fatality rate was estimated to be between 0.17% and 0.28%, consistent with the population being predominantly young and at reduced risk of death from COVID-19. Manaus recorded 2642 [1193/million inhabitants (mil)] confirmed deaths from COVID-19 and 3789

(1710/mil) deaths from severe acute respiratory syndrome likely to have been caused by SARS-CoV-2 infection. These figures are starkly different from the fatality rates during the same period (until 1 October) in the United Kingdom (620/mil), France (490/mil), and the United States (625/mil), and orders of magnitude higher than in Australia (36/mil), Taiwan (0.3/mil), and New Zealand (5/mil). Despite such a high proportion of the population being infected, transmission in Manaus has continued, even in the presence of nonpharmaceutical interventions (NPIs), with the effective reproduction rate (R) near 1. These data have numerous implications. In particular, the herd immunity threshold (HIT), the proportion of the population that needs to be immune to reduce the number of susceptible individuals sufficiently to reverse epidemic growth, is likely to be high for SARS-CoV-2. If the basic reproduction number (R0)—that is, the average number of secondary infections resulting from an index case in a fully susceptible population—is 2.5 to 3, as estimated within Manaus, the expected attack rate would be 89 to 94% and the HIT is expected to be 60 to 70% for a homogeneous population. Although the epidemic was largely unmitigated in Manaus at the outset, the subsequent introduction of behavioral change (such as social distancing) and NPIs (such as masks), together with nonhomogeneous population mixing, may explain the lower than expected attack rate. However, even with an estimated 76% of the population being infected, it appears the HIT was not reached. It is unclear whether this is due to waning immunity after infection, to a higher HIT than previously anticipated, or possibly a lower attack rate than estimated. Accruing data on reinfection with SARS-CoV-2 suggests that primary infection may not consistently confer long-term immunity to all infected, although the frequency of reinfection and the correlates of an effective immune response remain poorly understood. If immunity wanes over time, exposed individuals may revert to becoming susceptible, providing a new susceptible population that may then contribute to transmission. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/371/6526/230

A comprehensive review on plasmonic-based biosensors used in viral diagnostics

The proliferation and transmission of viruses has become a threat to worldwide biosecurity, as exemplified by the current COVID-19 pandemic. Early diagnosis of viral infection and disease control have always been critical. Virus detection can be achieved based on various plasmonic phenomena, including propagating surface plasmon resonance (SPR), localized SPR, surface-enhanced Raman scattering, surface-enhanced fluorescence and surface-enhanced infrared absorption spectroscopy. The present review covers all available information on plasmonic-based virus detection, and collected data on these sensors based on several parameters. These data will assist the audience in advancing research and development of a new generation of versatile virus biosensors.

Reference

https://www.nature.com/articles/s42003-020-01615-8

Publication Date: Jan 19, 2021

Rogue antibodies could be driving severe COVID-19

More than a year after COVID-19 emerged, many mysteries persist about the disease: why do some people get so much sicker than others? Why does lung damage sometimes continue to worsen well after the body seems to have cleared the SARS-CoV-2 virus? And what is behind the extended, multi-organ illness that lasts for months in people with 'long COVID'? A growing number of studies suggest that some of these questions might be explained by the immune system mistakenly turning against the body — a phenomenon known as autoimmunity. "This is a rapidly evolving area, but all the evidence is converging," says Aaron Ring, an immunologist at the Yale School of Medicine in New Haven, Connecticut. Early in the pandemic, researchers suggested that some people have an overactive immune response to COVID infection. Immune-system signalling proteins called cytokines can ramp up to dangerous levels, leading to 'cytokine storms' and damage to the body's own cells. Clinical trials have now shown that some drugs that broadly dampen immune activity seem to reduce death rates in critically ill people, if administered at the right time. But scientists studying COVID are increasingly also highlighting the role of autoantibodies: rogue antibodies that attack either elements of the body's immune defences or specific proteins in organs such as the heart. In contrast to cytokine storms, which tend to cause systemic, short-duration problems, autoantibodies are thought to result in targeted, longer-term damage, says immunologist Akiko Iwasaki, a colleague of Ring's at Yale.

Even healthy people make autoantibodies, but not generally in large amounts, and the molecules don't usually seem to cause damage or attack the immune system. Yet researchers also have evidence that nefarious autoantibodies do have a role in many infectious diseases. There are several theories to explain how autoimmunity might emerge from COVID and other infections. Some people might be predisposed to producing autoantibodies that can then wreak havoc during an infection. Alternatively, infections could even trigger the production of autoantibodies. If researchers can establish the link, they might be able to come up with avenues for treatment, both for

the repercussions of COVID and for other diseases caused by viruses. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-021-00149-1

Publication Date: Jan 15, 2021

The game-changing COVID-19 antibody test

BioSURE COVID-19 Triple Antibody Rapid Test is quick and effective method for screening COVID-19 for your dental team. It is simple to perform and only requires 5 ul of capillary blood to deliver results in just ten minutes. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41407-021-0518-y

Alarming COVID variants show vital role of genomic surveillance

2021 is shaping up to be the year of COVID-19 variants. In the past two months, scientists have identified several fast-spreading variants that have prompted government restrictions in many countries — and new variants are being detected more frequently. The pandemic has ushered in an era of genomic surveillance in which scientists are tracking genomic changes to a virus at a speed and scale never seen before. But surveillance is patchy globally, particularly in the United States, which has the world's largest COVID-19 outbreak, and in many low- and middle-income countries. Scientists warn that worrying variants are probably spreading undetected in these regions. "Genomic epidemiology has come of age during this pandemic," says Oliver Pybus, who studies infectious disease evolution at the University of Oxford, UK. It has transformed from a "theoretical backwater" to a tool that helps drive public-health decisions quickly, he says. But to be as effective as possible, surveillance needs to be widespread, standardized and embedded in national pandemic-prevention programmes, scientists say. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-021-00065-4

COMMENT

Publication Date: Jan 19, 2021

Face masks help control transmission of COVID-19

In their paper on self-reported face mask wearing and control of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission in the US. Rader and colleagues showed an elegant ecological analysis of data from across the US, estimating the effect of face mask use on the transmission of COVID-19 infection. The authors made use of online survey responses of mask usage from thousands of individuals across the country over time to measure the relationship between mask wearing and community transmission control, as characterised by the instantaneous reproductive number. Based on 378 207 responses, an increase in community transmission control with increasing face mask usage was found, which remains after accounting for other differences across the country, such as mobility, and control is enhanced when mask wearing is combined with physical distancing. Rader and colleagues support an increasingly convincing body of evidence that speaks to the importance of mask wearing to mitigate ongoing waves of transmission as vaccines begin to be rolled out. Face mask mandates have been divisive in many countries. The face mask debate has been complicated by the two modes by which wearing a mask affects transmission: masks might protect the wearer from infection or masks might prevent the wearer transmitting the virus, if infected. For preventing transmission, non-targeted interventions, such as face masks, are especially important given the high proportion of asymptomatic and paucisymptomatic cases and the risk of transmission from these individuals, and from the presymptomatic period. An ecological analysis, such as that of Rader and colleagues, measures the overall effect of face mask wearing on transmission, and thus obviates the need to disentangle the two modes of effect. The findings support laboratory evidence and other ecological studies that have shown that face masks do indeed reduce the overall transmission of SARS-CoV-2. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/landig/article/PIIS2589-7500(21)00003-0/fulltext

COVID-19 vaccination in the UK: Addressing vaccine hesitancy

With the success of COVID-19 vaccine trials and its official rollout in the UK, the attention has turned towards vaccine distribution and its uptake. Vaccine hesitancy, one of the top ten public health threats according to the World Health Organization, has taken a toll on immunization programmes globally and is lurking as a major barrier to achieving optimal vaccination goals. In the recent issue of The Lancet Regional Health-Europe, Paul et al present their findings on the prevalence of negative vaccination attitudes and the lack of willingness to receive the COVID-19 vaccine among sociodemographic subgroups in the UK. The study utilized data from a large online survey that collected information on general vaccination attitudes [measured using the Vaccination Attitudes Examination (VAX) Scale] and the intention to receive the COVID-19 vaccine from 32,361 adult participants in the UK. About 16% of the participants expressed a high level of mistrust, with an extremely negative attitude [a score of 5–6 on a scale of 1 to 6] on at least one of the four dimensions of hesitancy, including vaccine safety concerns (16.3%), a preference for natural immunity (6.6%), concerns about commercial profiteering (5.8%), and a general distrust in the benefit of vaccines (5.3%). More than one-third of the participants reported unwillingness or uncertainty regarding the COVID-19 vaccination. Notably, females, participants living with children, and those with low-income appear to be at higher risk of COVID-19 vaccine refusal. Expectedly, acutely negative vaccination attitudes were associated with greater unwillingness or uncertainty to receive the COVID vaccine. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(20)30016-8/fulltext

HIGHLIGHTS

Publication Date: Jan 18, 2021

Not only ACE2—the quest for additional host cell mediators of SARS-CoV-2 infection: Neuropilin-1 (NRP1) as a novel SARS-CoV-2 host cell entry mediator implicated in COVID-19

Two recently published studies published in Science by Daly et al. and Cantuti-Castelvetri et al.2 identified neuropilin-1 (NRP1) as an additional cellular mediator which may facilitate the entry of the new severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 (SARS-CoV-2) into host cells. The findings of these elegant studies collectively indicate that, in addition to the role of angiotensin-converting enzyme 2 (ACE2) in mediating the cellular entry of SARS-CoV-2, NRP1 may act as a host cell mediator that can increase the infectivity and may thus contribute to the tissue/organ tropism of this coronavirus. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41392-020-00460-9

Publication Date: Jan 14, 2021

SARS-CoV-2 infection in K18-ACE2 transgenic mice replicates human pulmonary disease in COVID-19

Over the last several months, a global pandemic has developed due to the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is capable of infecting humans. The lack of preexisting immunity to SARS-CoV-2 in humans has prompted the scientific community to strive to understand the mechanisms underlying SARS-CoV-2 pathogenesis and to test new therapeutic agents and vaccines for the clinical management of coronavirus disease 2019 (COVID-19). In these efforts, the development of appropriate animal models of the disease is one of the most valuable strategies. Winkler et al. recently reported the use of transgenic mice expressing hACE2 driven by the cytokeratin-18 (K18) gene promoter (K18-hACE2), a

model that was originally developed for the severe acute respiratory syndrome (SARS), to investigate the effects of SARS-CoV-2 infection.

In summary, the animal model proposed for COVID-19 mimics many of the clinical features of the disease, making it one of the best models available. A future comprehensive model will include additional aspects, such as the vasculopathy and coagulopathy associated with SARS-CoV-2 infection in humans or the effects of different chronic diseases, advanced age, or male sex, which put patients at greater risk of adverse outcomes after viral infection. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41423-020-00616-1

CORRESPONDANCE

Publication Date: Jan 15, 2021

Assessing the importance of interleukin-6 in COVID-19

The systematic review and meta-analysis of interleukin (IL)-6 in COVID-19, by Daniel Leisman and colleagues, provides a crucial comparison with other inflammatory syndromes, showing that IL-6 is more markedly elevated in conditions such as sepsis and acute respiratory distress syndrome (ARDS). We credit the authors for this key undertaking. However, we would like to raise two relevant considerations regarding aspects of the study design and the conceptualisation of hyperinflammatory syndromes in which IL-6 is elevated.

First, in performing meta-analyses on retrospective studies, counting the same cohort of patients multiple times introduces replication. The authors include data on what they believe to be 1245 patients with COVID-19. However, of the 25 reports included, 17 contain patients treated at the same hospital during overlapping time periods. These patients were counted in the pooled analysis as many as four times. Taking the approach recommended by the Cochrane Handbook for Systematic Reviews of Interventions and counting only one report from each centre, the number of patients would be 852. Furthermore, only studies available before April 14, 2020, were included in the analysis, and thus 23 of 25 studies were early reports from China. Subsequent studies from Europe and North America that show markedly elevated IL-6 concentrations in COVID-19 were excluded. Second, we believe that the manuscript misconstrues the significance of elevated IL-6 in COVID-19. Although IL-6 is often higher in other inflammatory conditions, this finding has limited bearing on the pathophysiology of immune misfiring in COVID-19. The association between initial IL-6 concentrations greater than 80 pg/mL and outcomes such as respiratory failure and death has been confirmed in numerous studies. The authors omit any discussion of prognostic models, such as the ISARIC-4C, or COVID-19-associated hyperinflammatory syndrome, which highlight C-reactive protein and IL-6 as prognostic markers. Markedly elevated serum IL-6 concentrations are not a prerequisite for clinical response to IL-6 blockade. In approved disease indications such as multicentric Castleman disease and

giant cell arteritis, median pretreatment IL-6 concentrations are only moderately elevated. Although preliminary results from randomised controlled trials of IL-6 blockade have been largely negative, other studies of immunomodulatory therapies examining both short-term and long-term outcomes are ongoing.6 COVID-19 is a heterogeneous disease, with diverse manifestations of immune dysregulation ranging from cytokine storm, through so-called long-hauler syndrome, to multisystem inflammatory disorder in children. Serum IL-6 remains the best available biomarker for severity of COVID-19 and still holds great potential for guiding treatment of this disease.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30600-7/fulltext

REPORT

Publication Date: Jan 16, 2021

Use of machine learning to identify a T cell response to SARS-CoV-2

The identification of SARS-CoV-2-specific T cell receptor (TCR) sequences is critical for understanding T cell responses to SARS-CoV-2. Accordingly, it was reanalysed publicly available data from SARS-CoV-2-recovered patients who had low severity disease (n=17) and SARS-CoV-2 infection-naïve (control) individuals (n=39). Applying a machine learning approach to TCR beta (TRB) repertoire data, we can classify patient/ control samples with a training sensitivity, specificity and accuracy of 88.2%, 100%, and 96.4%, and a testing sensitivity, specificity and accuracy of 82.4%, 97.4%, and 92.9%, respectively.

Interestingly, the same machine learning approach cannot separate SARS-CoV-2 recovered from SARS-CoV-2 infection-naive individual samples on the basis of B cell receptor (IGH) repertoire data, suggesting that the T cell response to SARS-CoV-2 may be more stereotyped and longer-lived. Following validation in larger cohorts, our method may be useful in detecting protective immunity acquired through natural infection or in determining the longevity of vaccine-induced immunity.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00003-3