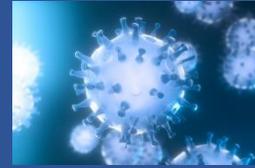


COVID-19

Sep 03 - 09, 2020



RESEARCH PUBLICATIONS

Publication Date: Sep 09, 2020

Chloroquine to fight COVID-19: A consideration of mechanisms and adverse effects?

Abstract

The COVID-19 outbreak emerged in December 2019 and has rapidly become a global pandemic. A great deal of effort has been made to find effective drugs against this disease. Chloroquine (CQ) and hydroxychloroquine (HCQ) were widely adopted in treating COVID-19, but the results were contradictory. CQ/HCQ have been used to prevent and treat malaria and are efficacious anti-inflammatory agents in rheumatoid arthritis and systemic lupus erythematosus. These drugs have potential broad-spectrum antiviral properties, but the underlying mechanisms are speculative. In this review, we re-evaluated the treatment outcomes and current hypothesis for the working mechanisms of CQ/HCQ as COVID-19 therapy with a special focus on disruption of Ca^{2+} signaling. In so doing, we attempt to show how the different hypotheses for CQ/HCQ action on coronavirus may interact and reinforce each other. The potential toxicity is also noted due to its action on Ca^{2+} and hyperpolarization-activated cyclic nucleotide-gated channels in cardiac myocytes and neuronal cells. We propose that intracellular calcium homeostasis is an alternative mechanism for CQ/HCQ pharmacology, which should be considered when evaluating the risks and benefits of therapy in these patients and other perspective applications.

Reference

[https://www.cell.com/heliyon/fulltext/S2405-8440\(20\)31743-6](https://www.cell.com/heliyon/fulltext/S2405-8440(20)31743-6)

The coding capacity of SARS-CoV-2

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the ongoing Coronavirus disease 19 (COVID-19) pandemic. In order to understand SARS-CoV-2 pathogenicity and antigenic potential, and to develop therapeutic tools, it is essential to portray the full repertoire of its expressed proteins. The SARS-CoV-2 coding capacity map is currently based on computational predictions and relies on homology to other coronaviruses. Since coronaviruses differ in their protein array, especially in the variety of accessory proteins, it is crucial to characterize the specific collection of SARS-CoV-2 proteins in an unbiased and open-ended manner. Using a suite of ribosome profiling techniques, we present a high-resolution map of the SARS-CoV-2 coding regions, allowing us to accurately quantify the expression of canonical viral open reading frames (ORFs) and to identify 23 unannotated viral ORFs. These ORFs include upstream ORFs (uORFs) that are likely playing a regulatory role, several in-frame internal ORFs lying within existing ORFs, resulting in N-terminally truncated products, as well as internal out-of-frame ORFs, which generate novel polypeptides. We further show that viral mRNAs are not translated more efficiently than host mRNAs; rather, virus translation dominates host translation due to high levels of viral transcripts. Our work provides a rich resource, which will form the basis of future functional studies.

Reference

<https://www.nature.com/articles/s41586-020-2739-1>

Projected health-care resource needs for an effective response to COVID-19 in 73 low-income and middle-income countries: A modelling study

Abstract

Background: Since WHO declared the COVID-19 pandemic a Public Health Emergency of International Concern, more than 20 million cases have been reported, as of Aug 24, 2020. This study aimed to identify what the additional health-care costs of a strategic preparedness and response plan (SPRP) would be if current transmission levels are

maintained in a status quo scenario, or under scenarios where transmission is increased or decreased by 50%.

Methods: The number of COVID-19 cases was projected for 73 low-income and middle-income countries for each of the three scenarios for both 4-week and 12-week timeframes, starting from June 26, 2020. An input-based approach was used to estimate the additional health-care costs associated with human resources, commodities, and capital inputs that would be accrued in implementing the SPRP.

Findings: The total cost estimate for the COVID-19 response in the status quo scenario was US\$52.45 billion over 4 weeks, at \$8.60 per capita. For the decreased or increased transmission scenarios, the totals were \$33.08 billion and \$61.92 billion, respectively. Costs would triple under the status quo and increased transmission scenarios at 12 weeks. The costs of the decreased transmission scenario over 12 weeks was equivalent to the cost of the status quo scenario at 4 weeks. By percentage of the overall cost, case management (54%), maintaining essential services (21%), rapid response and case investigation (14%), and infection prevention and control (9%) were the main cost drivers.

Interpretation: The sizeable costs of a COVID-19 response in the health sector will escalate, particularly if transmission increases. Instituting early and comprehensive measures to limit the further spread of the virus will conserve resources and sustain the response.

Reference

[https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30383-1/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30383-1/fulltext)

Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma

Abstract

Background: Outcome of patients with moderate and severe COVID-19 following treatment with convalescent plasma (CP) and the association with IgG levels in transfused CP was assessed.

Methods: A prospective cohort study. Primary outcome was improvement at day 14 defined as alive, not on mechanical ventilation, and moderate, mild, or recovered from COVID-19. Antibody levels in CP units were unknown at the time of treatment. IgG against the spike protein S1 was subsequently measured by ELISA. Neutralizing antibodies titers were determined in a subset. Outcome was assessed in relation to the mean antibody level transfused to the patients (≤ 4.0 versus > 4.0).

Findings: Of 49 patients, 11 (22.4%) had moderate, 38 (77.6%) had severe disease, 28 were ventilated. At day 14, 24 (49.0%) patients improved, 9 (18.4%) died, and 13 (26.5%) were ventilated. In 14/98 (14.3%) CP units IgG was < 1.1 (cutoff calibration) and in 60 (61.2%) ≤ 4.0 . IgG level and neutralizing antibody titer were correlated ($0.85 p < 0.001$). In patients receiving ≤ 4.0 antibody levels, 11/30 improved (36.7%) versus 13/19 (68.4%) in patients receiving > 4.0 odds ratio (OR) 0.267 [95% confidence interval (CI) 0.079–0.905], $P = 0.030$. In patients diagnosed > 10 days prior to treatment, 4/14 (22.4%) improved in the ≤ 4.0 antibody group, versus 6/7 (85.7%) in the > 4.0 antibody group, OR 0.048 (95% CI, 0.004–0.520), $P = 0.007$. No serious adverse events were reported.

Interpretation: Treatment with CP with higher levels of IgG against S1 may benefit patients with moderate and severe COVID-19. IgG against S1 level in CP predicts neutralization antibodies titers.

Reference

[https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370\(20\)30269-8/fulltext](https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30269-8/fulltext)

Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): A double-blind, randomised, phase 3A trial

Abstract

Background: Despite inhaled corticosteroid plus long-acting β 2-agonist (ICS/LABA) therapy, 30–50% of patients with moderate or severe asthma remain inadequately controlled. We investigated the safety and efficacy of single-inhaler fluticasone furoate plus umeclidinium plus vilanterol (FF/UMEC/VI) compared with FF/VI.

Methods: In this double-blind, randomised, parallel-group, phase 3A study (Clinical Study in Asthma Patients Receiving Triple Therapy in a Single Inhaler [CAPTAIN]), participants were recruited from 416 hospitals and primary care centres across 15 countries. Participants were eligible if they were aged 18 years or older, with inadequately controlled asthma (Asthma Control Questionnaire [ACQ]-6 score of ≥ 1.5) despite ICS/LABA, a documented health-care contact or a documented temporary change in asthma therapy for treatment of acute asthma symptoms in the year before screening, pre-bronchodilator FEV₁ between 30% and less than 85% of predicted normal value, and reversibility (defined as an increase in FEV₁ of $\geq 12\%$ and ≥ 200 mL in the 20–60 min after four inhalations of albuterol or salbutamol) at screening. Participants were randomly assigned (1:1:1:1:1), via central based randomisation stratified by pre-study ICS dose at study entry, to once-daily FF/VI (100/25 μ g or 200/25 μ g) or FF/UMEC/VI (100/31.25/25 μ g, 100/62.5/25 μ g, 200/31.25/25 μ g, or 200/62.5/25 μ g) administered via Ellipta dry powder inhaler (Glaxo Operations UK, Hertfordshire, UK). Patients, investigators, and the funder were masked to treatment allocation. Endpoints assessed in the intention-to-treat population were change from baseline in clinic trough FEV₁ at week 24 (primary) and annualised moderate and/or severe asthma exacerbation rate (key secondary). Other secondary endpoints were change from baseline in clinic FEV₁ at 3 h post-dose, St George's Respiratory Questionnaire (SGRQ) total score, and ACQ-7 total score, all at week 24. Change from baseline in Evaluating Respiratory Symptoms in Asthma total score at weeks 21–24 was also a secondary endpoint but is not reported here. Exploratory analyses of biomarkers of type 2 airway inflammation on treatment response were also done. This study is registered with ClinicalTrials.gov, NCT02924688, and is now complete.

Findings: Between Dec 16, 2016, and Aug 31, 2018, 5185 patients were screened and 2439 were recruited and randomly assigned to FF/VI (100/25 μ g n=407; 200/25 μ g n=406) or FF/UMEC/VI (100/31.25/25 μ g n=405; 100/62.5/25 μ g n=406; 200/31.25/25 μ g n=404; 200/62.5/25 μ g n=408), with three patients randomly assigned in error and not included in analyses. In the intention-to-treat population, 922 (38%) patients were men, the mean age was 53.2 years (SD 13.1) and body-mass index was 29.4 (6.6). Baseline demographics were generally similar across all treatment groups. The least squares mean improvement in FEV₁ change from baseline for FF/UMEC/VI 100/62.5/25 μ g versus FF/VI 100/25 μ g was 110 mL (95% CI 66–153; $p < 0.0001$) and

for 200/62.5/25 µg versus 200/25 µg was 92 mL (49–135; $p < 0.0001$). Adding UMEC 31.25 µg to FF/VI produced similar improvements (FF/UMEC/VI 100/31.25/25 µg vs FF/VI 100/25 µg: 96 mL [52–139; $p < 0.0001$]; and 200/31.25/25 µg vs 200/25 µg: 82 mL [39–125; $p = 0.0002$]). These results were supported by the analysis of clinic FEV₁ at 3 h post-dose. Non-significant reductions in moderate and/or severe exacerbation rates were observed for FF/UMEC 62.5 µg/VI versus FF/VI (pooled analysis), with rates lower in FF 200 µg-containing versus FF 100 µg-containing treatment groups. All pooled treatment groups demonstrated mean improvements (decreases) in SGRQ total score at week 24 compared with baseline in excess of the minimal clinically important difference of 4 points; however, there were no differences between treatment groups. For mean change from baseline to week 24 in asthma control questionnaire-7 score, improvements (decreases) exceeding the minimal clinically important difference of 0.5 points were observed in all pooled treatment groups. Adding UMEC to FF/VI resulted in small, dose-related improvements compared with FF/VI (pooled analysis: FF/UMEC 31.25 µg/VI versus FF/VI, -0.06 (95% CI -0.12 to 0.01 ; $p = 0.094$) FF/UMEC 62.5 µg/VI versus FF/VI, -0.09 (-0.16 to -0.02 , $p = 0.0084$). By contrast with adding UMEC, the effects of higher dose FF on clinic trough FEV₁ and annualised moderate and/or severe exacerbation rate were increased in patients with higher baseline blood eosinophil count and exhaled nitric oxide. Occurrence of adverse events was similar across treatment groups (patients with at least one event ranged from 210 [52%] to 258 [63%]), with the most commonly reported adverse events being nasopharyngitis (51 [13%]–63 [15%]), headache (19 [5%]–36 [9%]), and upper respiratory tract infection (13 [3%]–24 [6%]). The incidence of serious adverse events was similar across all groups (range 18 [4%]–25 [6%]). Three deaths occurred, of which one was considered to be related to study drug (pulmonary embolism in a patient in the FF/UMEC/VI 100/31.25/25 µg group).

Interpretation: In patients with uncontrolled moderate or severe asthma on ICS/LABA, adding UMEC improved lung function but did not lead to a significant reduction in moderate and/or severe exacerbations. For such patients, single-inhaler FF/UMEC/VI is an effective treatment option with a favourable risk–benefit profile. Higher dose FF primarily reduced the rate of exacerbations, particularly in patients with raised biomarkers of type 2 airway inflammation. Further confirmatory studies into the differentiating effect of type 2 inflammatory biomarkers on treatment outcomes in

asthma are required to build on these exploratory findings and further guide clinical practice.

Reference

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30389-1/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30389-1/fulltext)

Publication Date: Sep 08, 2020

Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant *in-vitro* susceptibilities: A retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals

Background: The prevalence and effects of inappropriate empirical antibiotic therapy for bloodstream infections are unclear. We aimed to establish the population-level burden, predictors, and mortality risk of in-vitro susceptibility-discordant empirical antibiotic therapy among patients with bloodstream infections.

Methods: Our retrospective cohort analysis of electronic health record data from 131 hospitals in the USA included patients with suspected—and subsequently confirmed—bloodstream infections who were treated empirically with systemic antibiotics between Jan 1, 2005, and Dec 31, 2014. We included all patients with monomicrobial bacteraemia caused by common bloodstream pathogens who received at least one systemic antibiotic either on the day blood cultures were drawn or the day after, and for whom susceptibility data were available. We calculated the prevalence of discordant empirical antibiotic therapy—which was defined as receiving antibiotics on the day blood culture samples were drawn to which the cultured isolate was not susceptible in vitro—overall and by hospital type by using regression tree analysis. We used generalised estimating equations to identify predictors of receiving discordant empirical antibiotic therapy, and used logistic regression to calculate adjusted odds ratios for the relationship between in-hospital mortality and discordant empirical antibiotic therapy.

Findings: 21 608 patients with bloodstream infections received empirical antibiotic therapy on the day of first blood culture collection. Of these patients, 4165 (19%) received discordant empirical antibiotic therapy. Discordant empirical antibiotic therapy was independently associated with increased risk of mortality (adjusted odds ratio 1.46

[95% CI, 1.28–1.66]; $p < 0.0001$), a relationship that was unaffected by the presence or absence of resistance or sepsis or septic shock. Infection with antibiotic-resistant species strongly predicted receiving discordant empirical therapy (adjusted odds ratio 9.09 [95% CI 7.68–10.76]; $p < 0.0001$). Most incidences of discordant empirical antibiotic therapy and associated deaths occurred among patients with bloodstream infections caused by *Staphylococcus aureus* or *Enterobacterales*.

Interpretation: Approximately one in five patients with bloodstream infections in US hospitals received discordant empirical antibiotic therapy, receipt of which was closely associated with infection with antibiotic-resistant pathogens. Receiving discordant empirical antibiotic therapy was associated with increased odds of mortality overall, even in patients without sepsis. Early identification of bloodstream pathogens and resistance will probably improve population-level outcomes.

Reference

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30477-1/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30477-1/fulltext)

Understanding clinical decision-making during the COVID-19 pandemic: A cross-sectional worldwide survey

Abstract

Background: The lack of evidence-based recommendations for therapeutic decisions during the early weeks of the COVID-19 pandemic creates a unique scenario of clinical decision making which is worth to analyze. We aim to identify the drivers of therapeutic aggressiveness during the first weeks of the COVID-19 pandemic.

Methods: This cross-sectional worldwide survey (conducted April 12 to 19, 2020) was aimed at physicians who managed patients diagnosed with COVID-19. Treatment preferences were collected in five different clinical scenarios. We used multilevel mixed-effects ordered logistic regression to identify variables that were associated with the use of more aggressive therapies.

Findings: The survey was completed by 852 physicians from 44 different specialties and 29 countries. The heterogeneity of therapeutic decisions increased as the clinical

scenario worsened. Factors associated with aggressive therapeutic decisions were higher self-perceived expertise (high vs. null, OR 1.95, 95%CI 1.31–2.89), perceived quality of COVID-19 publications (high vs. null, OR 1.92, 95%CI 1.17–3.16), and female sex (OR 1.17, 95%CI 1.02–1.33). Conversely, Infectious Diseases specialty, Latin American and North American origin, lower confidence in the treatments chosen, and having published articles indexed in PubMed as the first-author were associated with the use of less aggressive therapies.

Interpretation: Our study provides insight into the drivers of the decision-making process during a new and extreme health emergency. Different factors including the perceived expertise and quality of publications, gender, geographic origin, medical specialty and implication in medical research influenced this process. The clinical severity attenuated the physician's tolerance for uncertainty.

Reference

[https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370\(20\)30283-2/fulltext](https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30283-2/fulltext)

Publication Date: Sep 04, 2020

An immunoinformatics study on the spike protein of SARS-CoV-2 revealing potential epitopes as vaccine candidates

Abstract

Background: The pandemic situation of SARS-CoV-2 infection has sparked global concern due to the disease COVID-19 caused by it. Since the first cluster of confirmed cases in China in December 2019, the infection has been reported across the continents and inflicted upon a substantial number of populations.

Method: This study is focused on immunoinformatics analyses of the SARS-CoV-2 spike glycoprotein (S protein) which is key for the viral attachment to human host cells. Computational analyses were carried out for the prediction of B-cell and T-cell (MHC class I and II) epitopes of S protein and the analyses were extended further for the prediction of their immunogenic properties. The interaction and binding affinity of T-cell epitopes with HLA-B7 were also investigated by molecular docking.

Result: Three distinct epitopes for vaccine design were predicted from the sequence of S protein. The potential B-cell epitope was KNHTSPDVDLG possessing the highest antigenicity score of 1.4039 among other B-cell epitopes. T-cell epitope for human MHC class I was VVLSFELL with an antigenicity score of 1.0909 and binding ability to 29 MHC-I alleles. The predicted T-cell epitope for human MHC class II molecule was VVIGIVNNT with a corresponding 1.3063 antigenicity score, less digesting enzymes, and 7 MHC-II alleles binding ability. All these three peptides were predicted to be highly antigenic, non-allergenic, and non-toxic. Analyses of the physiochemical properties of these predicted epitopes indicate their stable nature for plausible vaccine design. Furthermore, molecular docking investigation between the MHC class-I epitopes and human HLA-B7 reflects the stable interaction with high affinity among them.

Conclusion: The present study posits three potential epitopes of S protein of SARS-CoV-2 predicted by immunoinformatic methods based on their immunogenic properties and interactions with the host counterpart that can facilitate the development of vaccine against SARS-CoV-2. This study can act as the springboard for the future development of the COVID-19 vaccine.

Reference

[https://www.cell.com/heliyon/fulltext/S2405-8440\(20\)31708-4](https://www.cell.com/heliyon/fulltext/S2405-8440(20)31708-4)

Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications

Abstract

Coronavirus disease 2019 (COVID-19) is currently a global pandemic, but human immune responses to the virus remain poorly understood. We used high-dimensional cytometry to analyze 125 COVID-19 patients and compare them with recovered and healthy individuals. Integrated analysis of ~200 immune and ~50 clinical features revealed activation of T cell and B cell subsets in a proportion of patients. A subgroup of patients had T cell activation characteristic of acute viral infection and plasmablast responses reaching >30% of circulating B cells. However, another subgroup had lymphocyte activation comparable with that in uninfected individuals. Stable versus dynamic immunological signatures were identified and linked to trajectories of disease

severity change. Our analyses identified three immunotypes associated with poor clinical trajectories versus improving health. These immunotypes may have implications for the design of therapeutics and vaccines for COVID-19.

Reference

Mathew, Divij, Josephine R. Giles, Amy E. Baxter, Derek A. Oldridge, Allison R. Greenplate, Jennifer E. Wu, Cécile Alanio et al. "Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications." *Science* 369, no. 6508 (2020) (I.F.: 41.845).

Multisystem inflammatory syndrome in children: A systematic review

Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multisystem syndrome, is a new dangerous childhood disease that is temporally associated with coronavirus disease 2019 (COVID-19). The aim was to describe the typical presentation and outcomes of children diagnosed with this hyperinflammatory condition.

Methods: A systematic review was conducted to communicate the clinical signs and symptoms, laboratory findings, imaging results, and outcomes of individuals with MIS-C. We searched four medical databases to encompass studies characterizing MIS-C from January 1st, 2020 to July 25th, 2020. Two independent authors screened articles, extracted data, and assessed risk of bias. This review was registered with PROSPERO CRD42020191515.

Findings: The search yielded 39 observational studies (n = 662 patients). While 71.0% of children (n = 470) were admitted to the intensive care unit, only 11 deaths (1.7%) were reported. Average length of hospital stay was 7.9 ± 0.6 days. Fever (100%, n = 662), abdominal pain or diarrhea (73.7%, n = 488), and vomiting (68.3%, n = 452) were the most common clinical presentation. Serum inflammatory, coagulative, and cardiac markers were considerably abnormal. Mechanical ventilation and extracorporeal membrane oxygenation were necessary in 22.2% (n = 147) and 4.4% (n = 29) of patients, respectively. An abnormal echocardiograph was observed in 314 of 581

individuals (54.0%) with depressed ejection fraction (45.1%, n = 262 of 581) comprising the most common aberrancy.

Interpretation: Multisystem inflammatory syndrome is a new pediatric disease associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is dangerous and potentially lethal. With prompt recognition and medical attention, most children will survive but the long-term outcomes from this condition are presently unknown.

Reference

Ahmed, M., Advani, S., Moreira, A., Zoretic, S., Martinez, J., Chorath, K., Acosta, S., Naqvi, R., Burmeister-Morton, F., Burmeister, F. and Tarriela, A., 2020. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine*, p.100527 (I.F.: 5.736).

Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans

Abstract

Coronavirus disease 2019 (COVID-19) represents a global crisis, yet major knowledge gaps remain about human immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We analyzed immune responses in 76 COVID-19 patients and 69 healthy individuals from Hong Kong and Atlanta, Georgia, United States. In the peripheral blood mononuclear cells (PBMCs) of COVID-19 patients, we observed reduced expression of human leukocyte antigen class DR (HLA-DR) and proinflammatory cytokines by myeloid cells as well as impaired mammalian target of rapamycin (mTOR) signaling and interferon- α (IFN- α) production by plasmacytoid dendritic cells. By contrast, we detected enhanced plasma levels of inflammatory mediators—including EN-RAGE, TNFSF14, and oncostatin M—which correlated with disease severity and increased bacterial products in plasma. Single-cell transcriptomics revealed a lack of type I IFNs, reduced HLA-DR in the myeloid cells of patients with severe COVID-19, and transient expression of IFN-stimulated genes. This was consistent with bulk PBMC transcriptomics and transient, low IFN- α levels in plasma

during infection. These results reveal mechanisms and potential therapeutic targets for COVID-19.

Reference

Arunachalam, Prabhu S., Florian Wimmers, Chris Ka Pun Mok, Ranawaka APM Perera, Madeleine Scott, Thomas Hagan, Natalia Sigal et al. "Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans." *Science* 369, no. 6508 (2020): 1210-1220 (I.F.: 41.845).

NEWS LETTER

Publication Date: Sep 09, 2020

Coronavirus research updates: The immune-cell traits that could predict severe COVID-19

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

The immune-cell traits that could predict severe COVID-19 (9 September 09, 2020):

Immune cells called neutrophils are more likely to be primed for action in people, who will eventually develop severe COVID-19 than in those who are will go on to become only mildly ill, according to a machine-learning analysis of data from 3,300 people. If the results can be reproduced, they could aid early identification of the people most likely to become critically ill. Neutrophils comprise an important part of the body's rapid response to infection, but can also damage uninfected tissue. Hyung Chun of Yale University in New Haven, Connecticut, and his colleagues used machine learning to analyse proteins in blood plasma taken from people hospitalized with COVID-19 (M. L. Meizlish *et al.* Preprint at medRxiv <https://doi.org/d8hm>; 2020). Several immune proteins that are associated with neutrophils were found at higher levels in the plasma of people who later became critically ill than in those whose illness did not become severe. A subsequent analysis of health records from about 3,300 people showed that high neutrophil counts were associated with increased COVID-19 mortality. The findings have not yet been peer reviewed.

Kids ravaged by COVID-19 show unique immune profile (September 08, 2020):

Most children infected with the new coronavirus show few signs of illness, if any. But a few children are struck by a severe form of COVID-19 that can cause multiple organ failure and even death. Now, scientists have begun to tease out the biology of this rare and devastating condition, called multisystem inflammatory syndrome in children, or MIS-C. Doctors have diagnosed hundreds of cases of MIS-C, which shares some similarities with the childhood illness Kawasaki's disease. To understand MIS-C's

biological profile, Petter Brodin at the Karolinska Institute in Stockholm and his colleagues looked at 13 children with MIS-C, 28 children with Kawasaki's disease and 41 with mild COVID-19 (C. R. Consiglio et al. Cell <https://doi.org/d8fh>; 2020). The researchers found that compared with children with Kawasaki's disease, those with MIS-C have lower levels of an immune chemical called IL-17A, which has been implicated in inflammation and autoimmune disorders. Unlike all the other children studied, children with MIS-C had no antibodies to two coronaviruses that cause the common cold. This deficit might be implicated in the origins of their condition, the authors say.

Powerful new evidence links steroid treatment to lower deaths (September 04, 2020):

People severely ill with COVID-19 are less likely to die if they are given drugs called corticosteroids than people who are not, according to an analysis of hospital patients on five continents. Earlier findings showed that the steroid dexamethasone cut deaths in people with COVID-19 on ventilators. To examine the effects of steroids in general, Jonathan Sterne at the University of Bristol, UK, and his colleagues did a meta-analysis that pooled data from seven clinical trials; each of the seven studied the use of steroids in people who were critically ill with COVID-19 (REACT Working Group *J. Am. Med. Assoc.* <https://doi.org/d7z8>; 2020). The trials included more than 1,700 people across 12 countries. The team analysed participants' status 28 days after they were randomly assigned to take either a steroid or a placebo. The risk of death was 32% for those who took a steroid and 40% for those who took a placebo. The authors say that steroids should be part of the standard treatment for people with severe COVID-19.

In a first, genomics shows that mink can pass SARS-CoV-2 to humans (September 03, 2020):

An investigation of Dutch mink farms has found the first documented cases of animal-to-human transmission of SARS-CoV-2. After SARS-CoV-2 outbreaks among farmed mink were first detected in late April, Marion Koopmans at Erasmus Medical Centre in Rotterdam, the Netherlands, and her colleagues used genome sequencing to track outbreaks among animals and workers at 16 mink farms (B. B. O. Munnink et al. Preprint at bioRxiv <https://doi.org/d7xn>; 2020). The team tested 97 farmworkers and their contacts, and found evidence for SARS-CoV-2 infection in 66 of them. Genetic analysis suggested that workers had introduced SARS-CoV-2 to mink, which spread the

virus back to workers, who might then have passed it on to other people. Outbreaks at mink farms have been detected in Denmark, Spain and the United States, and the researchers say unchecked spread could lead to the animals becoming a reservoir for human infections. The findings have not yet been peer reviewed.

Reference

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

COVACTA trial raises questions about tocilizumab's benefit in COVID-19

Hoffmann-La Roche has announced disappointing results from its much-anticipated phase 3 COVACTA trial of tocilizumab, raising questions about the efficacy of interleukin (IL)-6 blockade in patients with severe COVID-19 pneumonia.

SARS-CoV-2 induces production of inflammatory cytokines, including IL-6, which can contribute to cytokine storm syndromes that damage the lungs and other organs, ultimately killing many patients. Early observational studies have hinted at beneficial effects of drugs that block inflammatory cytokines, including IL-6 and IL-1.

But the randomised controlled COVACTA trial failed to meet its primary endpoint of improved clinical status, the company announced on July 29. Nor did tocilizumab improve patient mortality, although tocilizumab-treated patients spent roughly a week less in hospital compared with those given placebo, which could have a meaningful clinical impact in the face of surging capacity during a pandemic. Full results of the trial have not yet been published.

Reference

[https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30313-1/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30313-1/fulltext)

Publication Date: Sep 04, 2020

The Russian vaccine for COVID-19

On Aug 11, 2020, Russia became the first country in the world to approve a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine,

which is based on two adenovirus vectors, was developed by the Gamaleya National Center of Epidemiology and Microbiology (Moscow, Russia). Its approval was announced by President Vladimir Putin. “*I know [the vaccine] works quite effectively, helps to develop strong immunity, and has gone through all the necessary tests*”, declared Putin at a cabinet meeting. Nonetheless, there are widespread concerns that the approval is premature. At the time of approval, the vaccine had not even started phase 3 trials, nor had any results on the earlier stage trials been published. Since then, the phase 1/2 results have been published in *The Lancet*. The vaccine induced a strong immune response in all 76 participants. Presumably these results were available to the Russian Ministry of Health. For regulators, such as the US Food and Drug Administration (FDA) and the European Medicines Agency, however, data on immune response alone would not generally be an adequate basis for approving a vaccine. “Immune response might not be directly proportional to the degree of protection—you can only find this out in large-scale trials”, explains Peter Openshaw, professor of experimental medicine at Imperial College London (London, UK).

The Russian vaccine is named Sputnik V, after the Soviet-era space programme. The vaccine is financed by the Russian Direct Investment Fund (RDIF), the country's sovereign wealth fund. Mass production is expected to begin in September, 2020. Russia, which has seen almost 1 million cases of COVID-19, said that it would be able to provide 500 million doses of Sputnik V per year. The FDA has stipulated that a vaccine against COVID-19 should be at least 50% effective. Sputnik V might well meet this criterion. But until the phase 3 trial is completed and the results are made available, it will not be possible to make any judgement For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30402-1/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30402-1/fulltext)

PERSPECTIVE

Publication Date: Sep 04, 2020

A molecular trap against COVID-19

Abstract

The cell surface peptidase angiotensin-converting enzyme 2 (ACE2) is the primary receptor for the spike (S) fusion protein that facilitates cell entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Numerous studies are evaluating therapeutic and preventive treatments that block S protein interactions with ACE2 molecules that are expressed on host cells. For example, the ACE2 binding site can be occluded by monoclonal antibodies, several of which are rapidly advancing in clinical trials. Several vaccines undergoing clinical development also induce antibody responses that block ACE2–S protein interactions. On page 1261 of this issue, Chan et al. perform high-throughput mutagenesis and screening to reveal ACE2 mutations that enhance affinity for S protein, providing new insights into the ACE2–S protein interaction on which infection critically depends. The authors propose a strategy to apply engineered recombinant ACE2 variants as decoy receptors for coronavirus disease 2019 (COVID-19).

The dimeric ACE2 enzyme is a vasopeptidase expressed on the surface of epithelial cells in many tissues, including the lung, heart, blood vessels, kidneys, and gastrointestinal tract. It has a primary role in reducing blood pressure and inflammation as part of the renin-angiotensin-aldosterone system. ACE2 expression is closely associated with the tissue tropism of SARS-CoV-2 infection. The trimeric S protein comprises two subunits, S1 and S2. The S1 subunit contains a receptor binding domain (RBD), which binds to ACE2.

In addition to ACE2 binding, a protease cleavage of S protein is required for cell entry to allow S1 to release and reveal the hydrophobic cell fusion peptide of the S2 subunit. The cleavage between S1 and S2 can be accomplished by several different proteases, including transmembrane protease serine 2 (TMPRSS2), which is expressed in select tissues, and cathepsin L, which becomes activated in the low-pH endosomal

environment. The role of ACE2 in facilitating S1 shedding remains to be determined. Recent data show that S protein undergoes a conformational rearrangement at endosomal pH that modifies S trimer interactions and rotates the RBD from the “up” to the “down” conformation, which also influences ACE2 binding affinity. The predominant reliance of SARS-CoV-2 on ACE2 for cell entry has led to a focus on the development of new methods to disrupt ACE2 binding to S protein as potential COVID-19 medical interventions.

Reference

<https://science.sciencemag.org/content/369/6508/1167>

REPORT

Publication Date: Sep 06, 2020

Activation of the SARS-CoV-2 receptor ACE2 through JAK/STAT-dependent enhancers during pregnancy

ACE2 binds the coronavirus SARS-CoV-2 and facilitates its cellular entry. Interferons activate ACE2 expression in pneumocytes, suggesting a critical role of cytokines in SARS-CoV-2 target cells. Viral RNA was detected in breast milk in at least seven studies, raising the possibility that ACE2 is expressed in mammary tissue during lactation. Here we show that Ace2 expression in mouse mammary tissue is induced during pregnancy and lactation, which coincides with the activation of intronic enhancers. These enhancers are occupied by the prolactin-activated transcription factor STAT5 and additional regulatory factors, including Polymerase II. Deletion of Stat5a results in decommissioning of the enhancers and an 83% reduction of Ace2 mRNA. We also demonstrate that Ace2 expression increases during lactation in lung, but not in kidney and intestine. JAK/STAT components are present in a range of SARS-CoV-2 target cells opening the possibility that cytokines contribute to the viral load and extrapulmonary pathophysiology.

Reference

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(20\)31188-8](https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31188-8)

Publication Date: Sep 04, 2020

SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is increased by a naturally occurring elongation variant

One of the features distinguishing SARS-CoV-2 from its more pathogenic counterpart SARS-CoV is the presence of premature stop codons in its ORF3b gene. Here, we show that SARS-CoV-2 ORF3b is a potent interferon antagonist, suppressing the induction of type I interferon more efficiently than its SARS-CoV ortholog. Phylogenetic analyses and functional assays reveal that SARS-CoV-2-related viruses from bats and pangolins also encode truncated ORF3b gene products with strong anti-interferon

activity. Furthermore, analyses of approximately 17,000 SARS-CoV-2 sequences identify a natural variant, in which a longer ORF3b reading frame was reconstituted. This variant was isolated from two patients with severe disease and further increased the ability of ORF3b to suppress interferon induction. Thus, our findings not only help to explain the poor interferon response in COVID-19 patients, but also describe the emergence of natural SARS-CoV-2 quasispecies with an extended ORF3b gene that may potentially affect COVID-19 pathogenesis.

Reference

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(20\)31174-8](https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31174-8)

Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the current coronavirus disease 2019 (COVID-19) pandemic. A major virulence factor of SARS-CoVs is the nonstructural protein 1 (Nsp1), which suppresses host gene expression by ribosome association. Here, we show that Nsp1 from SARS-CoV-2 binds to the 40S ribosomal subunit, resulting in shutdown of messenger RNA (mRNA) translation both *in vitro* and in cells. Structural analysis by cryo-electron microscopy of *in vitro*-reconstituted Nsp1-40S and various native Nsp1-40S and -80S complexes revealed that the Nsp1 C terminus binds to and obstructs the mRNA entry tunnel. Thereby, Nsp1 effectively blocks retinoic acid-inducible gene I-dependent innate immune responses that would otherwise facilitate clearance of the infection. Thus, the structural characterization of the inhibitory mechanism of Nsp1 may aid structure-based drug design against SARS-CoV-2.

Reference

<https://science.sciencemag.org/content/369/6508/1249>

Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2

The spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds angiotensin-converting enzyme 2 (ACE2) on host cells to initiate entry, and soluble ACE2 is a therapeutic candidate that neutralizes infection by acting as a decoy. By using deep mutagenesis, mutations in ACE2 that increase S binding are found

across the interaction surface, in the asparagine 90–glycosylation motif and at buried sites. The mutational landscape provides a blueprint for understanding the specificity of the interaction between ACE2 and S and for engineering high-affinity decoy receptors. Combining mutations gives ACE2 variants with affinities that rival those of monoclonal antibodies. A stable dimeric variant shows potent SARS-CoV-2 and -1 neutralization in vitro. The engineered receptor is catalytically active, and its close similarity with the native receptor may limit the potential for viral escape.

Reference

<https://science.sciencemag.org/content/369/6508/1261>

Evolution and epidemic spread of SARS-CoV-2 in Brazil

Brazil currently has one of the fastest-growing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemics in the world. Because of limited available data, assessments of the impact of nonpharmaceutical interventions (NPIs) on this virus spread remain challenging. Using a mobility-driven transmission model, we show that NPIs reduced the reproduction number from >3 to 1 to 1.6 in São Paulo and Rio de Janeiro. Sequencing of 427 new genomes and analysis of a geographically representative genomic dataset identified >100 international virus introductions in Brazil. We estimate that most (76%) of the Brazilian strains fell in three clades that were introduced from Europe between 22 February and 11 March 2020. During the early epidemic phase, we found that SARS-CoV-2 spread mostly locally and within state borders. After this period, despite sharp decreases in air travel, we estimated multiple exportations from large urban centers that coincided with a 25% increase in average traveled distances in national flights. This study sheds new light on the epidemic transmission and evolutionary trajectories of SARS-CoV-2 lineages in Brazil and provides evidence that current interventions remain insufficient to keep virus transmission under control in this country.

Reference

<https://science.sciencemag.org/content/369/6508/1255>

EDITORIAL

Publication Date: Sep 09, 2020

Interfering too soon: Type I interferons can dampen antiviral immunity

During viral infection, type I interferons (IFN-I) are secreted to provide immediate antiviral innate immunity in part by promoting antigen presentation and activating the adaptive immune system. Immunology dogma states that a strong innate immune response begets a strong adaptive immune response. Still, is it possible that efficient control of viral replication by IFN-I signaling results in less antigen and is actually counterproductive for building immunological memory?

Palacio and colleagues investigated this question by inoculating mice with a variety of different viruses and simultaneously co-administering a one-time dose of an antibody that blocks the IFN-I receptor. This transient IFN-I blockade resulted in a brief spike in viral antigen, although amounts of circulating virus remained low and all mice cleared infection within a week. However, the abundance of viral antigen during this early phase of the adaptive immune response resulted in a more vigorous antiviral response, as demonstrated by higher numbers of circulating virus-specific effector memory cytotoxic T cells and more virus-specific antibody production. This correlated with enhanced host protection upon rechallenge with the same virus and cross-protection against different viral strains. The adjuvant effects of transient IFN-I blockade were observed only for viruses capable of infecting additional cells during the brief blockade. Once the blockade remitted, the consequent increase in viral load caused a surge in IFN-I levels, triggering dendritic cells to provide more effective stimulation of the adaptive immune system. Excitingly, Palacio and colleagues demonstrated that this immunostimulatory phenomenon extends to viral vaccines: transient IFN-I blockade in mice also improved vaccine immunogenicity and, in the case of an experimental Human Immunodeficiency Virus (HIV)-1 vaccine, enabled better recognition of a different strain of HIV.

The work of Palacio and colleagues is timely. Rational vaccine design is more pressing now during the COVID-19 pandemic than ever before. Additionally, IFN-I signaling has come under scrutiny for its role in aggravating disease in patients with COVID-19, with

dozens of studies examining a role for IFN-I signaling blockade in progress. Perhaps beyond attenuating excessive damage caused by the immune response, early blockade of IFN-I could promote durable immunity against many types of viral infections.

Reference

<https://stm.sciencemag.org/content/12/560/eabe1706>

COMMENT

Publication Date: Sep 08, 2020

Cancer, COVID-19, and antiviral immunity: the CAPTURE study

The SARS-CoV-2 pandemic has posed a significant challenge for risk evaluation and mitigation amongst cancer patients. Susceptibility to and severity of COVID-19 in cancer patients has not been studied in a prospective and broadly applicable manner. CAPTURE is a pan-cancer, longitudinal immune profiling study designed to address this knowledge gap.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(20\)31146-6](https://www.cell.com/cell/fulltext/S0092-8674(20)31146-6)

Why COVID-19 is more deadly in people with obesity—even if they're young

Since the pandemic began, dozens of studies have reported that many of the sickest COVID-19 patients have been people with obesity. In recent weeks, that link has come into sharper focus as large new population studies have cemented the association and demonstrated that even people who are merely overweight are at higher risk. For example, in the first metaanalysis of its kind, published on 26 August in *Obesity Reviews*, an international team of researchers pooled data from scores of peer-reviewed papers capturing 399,000 patients. They found that people with obesity who contracted SARS-CoV-2 were 113% more likely than people of healthy weight to land in the hospital, 74% more likely to be admitted to an ICU, and 48% more likely to die.

A constellation of physiological and social factors drives those grim numbers. The biology of obesity includes impaired immunity, chronic inflammation, and blood that's prone to clot, all of which can worsen COVID-19. And because obesity is so stigmatized, people with obesity may avoid medical care.

People with obesity are more likely than normal-weight people to have other diseases that are independent risk factors for severe COVID-19, including heart disease, lung disease, and diabetes. They are also prone to metabolic syndrome, in which blood

sugar levels, fat levels, or both are unhealthy and blood pressure may be high. A recent study from Tulane University of 287 hospitalized COVID-19 patients found that metabolic syndrome itself substantially increased the risks of ICU admission, ventilation, and death.

Reference

<https://www.sciencemag.org/news/2020/09/why-covid-19-more-deadly-people-obesity-even-if-theyre-young>

Publication Date: Sep 04, 2020

Azithromycin for severe COVID-19

Hydroxychloroquine with or without azithromycin was identified, outside of randomised controlled trials, as an early candidate for treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A number of trials evaluating hydroxychloroquine as pre-exposure prophylaxis, as early treatment, and in patients admitted to hospital with COVID-19 were subsequently initiated. To date, randomised trials have found no evidence of a benefit of hydroxychloroquine compared with placebo at any disease stage for COVID-19, and a number of trials were discontinued early because of difficulties with enrolment and emerging evidence that hydroxychloroquine was not effective.

Although the preponderance of evidence indicates that there is no benefit of hydroxychloroquine in the treatment of COVID-19, fewer studies have evaluated azithromycin, a broad-spectrum antibiotic that has anti-inflammatory properties. Azithromycin is commonly used for bacterial respiratory infections, and could potentially treat or prevent co-infection with SARS-CoV-2. Azithromycin might also have antiviral activity against some RNA viruses. Azithromycin has been shown to be effective in vitro against viruses such as Zika and rhinovirus, in addition to SARS-CoV-2, and to have antiviral effects in bronchial epithelial cells. Azithromycin has also been shown to be immunomodulatory, and can reduce exacerbations in chronic airway diseases. Azithromycin is widely available and has an excellent safety profile; thus, if shown to be effective, could be easily scaled up as a first-line treatment for patients with COVID-19. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31863-8/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31863-8/fulltext)

Immune profiling of COVID-19 patients

Abstract

Coronavirus disease 2019 (COVID-19) has affected millions of people globally, yet how the human immune system responds to and influences COVID-19 severity remains unclear. Mathew et al. present a comprehensive atlas of immune modulation associated with COVID-19. They performed high-dimensional flow cytometry of hospitalized COVID-19 patients and found three prominent and distinct immunotypes that are related to disease severity and clinical parameters. Arunachalam et al. report a systems biology approach to assess the immune system of COVID-19 patients with mild-to-severe disease. These studies provide a compendium of immune cell information and roadmaps for potential therapeutic interventions.

Reference

<https://science.sciencemag.org/content/369/6508/1203.12>