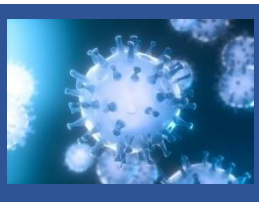
COVID-19

Nov 19 - 25, 2020



RESEARCH PUBLICATIONS

Publication Date: Nov 25, 2020

Nanoparticle vaccines based on the receptor binding domain (RBD) and heptad repeat (HR) of SARS-CoV-2 elicit robust protective immune responses

Abstract

Various vaccine strategies have been proposed in response to the global COVID-19 pandemic, each with unique strategies for eliciting immune responses. Here, nanoparticle vaccines were developed by covalently conjugating the self-assembled 24-mer ferritin to the receptor binding domain (RBD) and/or heptad repeat (HR) subunits of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) spike (S) protein. Compared to monomer vaccines, nanoparticle vaccines elicited more robust neutralizing antibodies and cellular immune responses. RBD and RBD-HR nanoparticle vaccinated hACE2 transgenic mice vaccinated with RBD and/or RBD-HR nanoparticles exhibited reduced viral load in the lungs after SARS-CoV-2 challenge. RBD-HR nanoparticle vaccines also promoted neutralizing antibodies and cellular immune responses against other coronaviruses. The nanoparticle vaccination of rhesus macaques induced neutralizing antibodies, and T and B cell responses prior to boost immunization; these responses persisted for more than three months. RBD- and HR-based nanoparticles thus present a promising vaccination approach against SARS-CoV-2 and other coronaviruses.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(20)30502-1

Cross-neutralization of a SARS-CoV-2 antibody to a functionally conserved site is mediated by avidity

Abstract

Most antibodies isolated from individuals with coronavirus disease 2019 (COVID-19) are specific to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, COVA1-16 is a relatively rare antibody that also cross-neutralizes SARS-CoV. Here, a crystal structure of the COVA1-16 antibody fragment (Fab) was determined with the SARS-CoV-2 receptor-binding domain (RBD) and negative-stain electron microscopy reconstructions with the spike glycoprotein trimer to elucidate the structural basis of its cross-reactivity. COVA1-16 binds a highly conserved epitope on the SARS-CoV-2 RBD, mainly through a long complementarity-determining region (CDR) H3, and competes with the angiotensin-converting enzyme 2 (ACE2) receptor because of steric hindrance rather than epitope overlap. COVA1-16 binds to a flexible up conformation of the RBD on the spike and relies on antibody avidity for neutralization. These findings, along with the structural and functional rationale for epitope conservation, provide insights for development of more universal SARS-like coronavirus vaccines and therapies.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(20)30464-7

Tracking COVID-19 using taste and smell loss Google searches is not a reliable strategy

Abstract

Web search tools are widely used by the general public to obtain health-related information, and analysis of search data is often suggested for public health monitoring. Popularity of searches related to smell loss and taste loss were analyzed, recently listed as symptoms of COVID-19. Searches on sight loss and hearing loss, which are not considered as COVID-19 symptoms, were used as control. Google Trends results per region in Italy or state in the US were compared to COVID-19 incidence in the corresponding geographical areas. The COVID-19 incidence did not correlate with searches for non-symptoms, but in some weeks had high correlation with

taste and smell loss searches, which also correlated with each other. Correlation of the sensory symptoms with new COVID-19 cases for each country as a whole was high at some time points, but decreased (Italy) or dramatically fluctuated over time (US). Smell loss searches correlated with the incidence of media reports in the US. Our results show that popularity of symptom searches is not reliable for pandemic monitoring. Awareness of this limitation is important during the COVID-19 pandemic, which continues to spread and to exhibit new clinical manifestations, and for potential future health threats.

Reference

https://www.nature.com/articles/s41598-020-77316-3

COVID-19 alters thinking and management in metabolic diseases

Abstract

Metabolic diseases emerged as important risk factors for severe COVID-19, but the mechanisms responsible remained unclear for some time. The severity of metabolic diseases was also associated with worse outcomes in patients with COVID-19, forcing clinicians to adjust their thinking on which patients with metabolic disease, but without COVID-19, to prioritize for treatment during and immediately after the pandemic. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41574-020-00449-y

Longitudinal proteomic profiling reveals increased early inflammation and sustained apoptosis proteins in severe COVID-19

Abstract

SARS-CoV-2 infection has a risk to develop into life-threatening COVID-19 disease. Whereas age, hypertension, and chronic inflammatory conditions are risk factors, underlying host factors and markers for disease severity, *e.g*. requiring intensive care unit (ICU) treatment, remain poorly defined. To this end, we longitudinally profiled blood

inflammation markers, antibodies, and 101 plasma proteins of hospitalized COVID-19 patients who did or did not require ICU admission. While essentially all patients displayed SARS-CoV-2-specific antibodies and virus-neutralization capacity within 12–15 days, a rapid, mostly transient upregulation of selective inflammatory markers including IL-6, CXCL10, CXCL11, IFNγ, IL-10, and monocyte-attracting CCL2, CCL7 and CCL8, was particularly evident in ICU patients. In addition, there was consistent and sustained upregulation of apoptosis-associated proteins CASP8, TNFSF14, HGF, and TGFB1, with HGF discriminating between ICU and non-ICU cohorts. Thus, COVID-19 is associated with a selective inflammatory milieu within which the apoptotic pathway is a cardinal feature with potential to aid risk-based patient stratification.

Reference

https://www.nature.com/articles/s41598-020-77525-w

In silico studies evidenced the role of structurally diverse plant secondary metabolites in reducing SARS-CoV-2 pathogenesis

Abstract

Plants are endowed with a large pool of structurally diverse small molecules known as secondary metabolites. The present study aims to virtually screen these plant secondary metabolites (PSM) for their possible anti-SARS-CoV-2 properties targeting four proteins/ enzymes which govern viral pathogenesis. Results of molecular docking with 4,704 ligands against four target proteins, and data analysis revealed a unique pattern of structurally similar PSM interacting with the target proteins. Among the top-ranked PSM which recorded lower binding energy (BE), > 50% were triterpenoids which interacted strongly with viral spike protein—receptor binding domain, > 32% molecules which showed better interaction with the active site of human transmembrane serine protease were belongs to flavonoids and their glycosides, > 16% of flavonol glycosides and > 16% anthocyanidins recorded lower BE against active site of viral main protease and > 13% flavonol glycoside strongly interacted with active site of viral RNA-dependent RNA polymerase. The primary concern about these PSM is their bioavailability. However, several PSM recorded higher bioavailability score and found fulfilling most of the drug-likeness characters as per Lipinski's rule (Coagulin K, Kamalachalcone C,

Ginkgetin, Isoginkgetin, 3,3′-Biplumbagin, Chrysophanein, Aromoline, etc.). Natural occurrence, bio-transformation, bioavailability of selected PSM and their interaction with the target site of selected proteins were discussed in detail. Present study provides a platform for researchers to explore the possible use of selected PSM to prevent/ cure the COVID-19 by subjecting them for thorough in vitro and in vivo evaluation for the capabilities to interfering with the process of viral host cell recognition, entry and replication.

Reference

https://www.nature.com/articles/s41598-020-77602-0

No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2

Abstract

COVID-19 is caused by the coronavirus SARS-CoV-2, which jumped into the human population in late 2019 from a currently uncharacterised animal reservoir. Due to this recent association with humans, SARS-CoV-2 may not yet be fully adapted to its human host. This has led to speculations that SARS-CoV-2 may be evolving towards higher transmissibility. The most plausible mutations under putative natural selection are those which have emerged repeatedly and independently (homoplasies). Here, it was formally tested whether any homoplasies observed in SARS-CoV-2 to date are significantly associated with increased viral transmission. To do so, it was developed a phylogenetic index to quantify the relative number of descendants in sister clades with and without a specific allele. This index was applied to a curated set of recurrent mutations identified within a dataset of 46,723 SARS-CoV-2 genomes isolated from patients worldwide. It was not identify a single recurrent mutation in this set convincingly associated with increased viral transmission. Instead, recurrent mutations currently in circulation appear to be evolutionary neutral and primarily induced by the human immune system *via* RNA editing, rather than being signatures of adaptation. At this stage we find no evidence for significantly more transmissible lineages of SARS-CoV-2 due to recurrent mutations.

Reference

https://www.nature.com/articles/s41467-020-19818-2

Progenitor identification and SARS-CoV-2 infection in human distal lung organoids

Abstract

The distal lung contains terminal bronchioles and alveoli that facilitate gas exchange. Three-dimensional *in vitro* human distal lung culture systems would strongly facilitate investigation of pathologies including interstitial lung disease, cancer, and SARS-CoV-2-associated COVID-19 pneumonia. A long-term feeder-free, chemically defined culture of distal lung progenitors was generated as organoids derived from single adult human alveolar epithelial type II (AT2) or KRT5+ basal cells. AT2 organoids exhibited AT1 transdifferentiation potential while basal cell organoids developed lumens lined by differentiated club and ciliated cells. Single cell analysis of basal organoid KRT5+ cells revealed a distinct ITGA6+ITGB4+ mitotic population whose proliferation further segregated to a TNFRSF12Ahi subfraction comprising ~10% of KRT5+ basal cells, residing in clusters within terminal bronchioles and exhibiting enriched clonogenic organoid growth activity. Distal lung organoids were created with apical-out polarity to display ACE2 on the exposed external surface, facilitating SARS-CoV-2 infection of AT2 and basal cultures and identifying club cells as a novel target population. This long-term, feeder-free organoid culture of human distal lung, coupled with single cell analysis, identifies unsuspected basal cell functional heterogeneity and establishes a facile *in vitro* organoid model for human distal lung infections including COVID-19-associated pneumonia.

Reference

https://www.nature.com/articles/s41586-020-3014-1

Science communication as a preventative tool in the COVID19 pandemic

Abstract

Humans have witnessed epidemics and pandemics periodically throughout history. Often, such infectious outbreaks have resulted in entire civilisations struggling against possible extinction. Despite recent clinical advancements and technological

developments, issues of neglected sustainability and lax health hygiene practices, among others, have provided a context for the emergence of the COVID19 pandemic. Against such a backdrop, scientific communication using diversified tools could play a significant role in efforts towards preparedness and control, as well as the initiation of immediate remedial measures in the fight against epidemics and pandemics. These tools could help to increase understanding of the scientific solutions to minimise the outbreaks of infectious diseases, thereby strengthening societal immunity. This paper considers the history of epidemics/pandemics to draw attention to their occurrence, effects and potential impacts on human societies. In addition, it defines the major factors underpinning the various infectious outbreaks over the last three decades. Constructive preparation and preventative stages for authorities, scientists and researchers to check and diminish the impact of epidemics and pandemics during and post-outbreak are suggested while focusing on the need for science communication in the healthcare system. The paper also reviews recent empirical studies and WHO guidelines. Communication through appropriate communicators may help cut through the noise, share facts and boost confidence in science and governance. The impact of science communication on the interplay between government–expert–public or society could help promote positive behavioural change as well as overcome linguistic barriers.

Reference

https://www.nature.com/articles/s41599-020-00645-1

Publication Date: Nov 24, 2020

Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2

Abstract

A long-standing question in infectious disease dynamics concerns the role of transmission heterogeneities, driven by demography, behavior and interventions. Based on detailed patient and contact tracing data in Hunan, China we find 80% of secondary infections traced back to 15% of SARS-CoV-2 primary infections, indicating substantial transmission heterogeneities. Transmission risk scales positively with the duration of exposure and the closeness of social interactions and is modulated by demographic and clinical factors. The lockdown period increases transmission risk in the family and

households, while isolation and quarantine reduce risks across all types of contacts. The reconstructed infectiousness profile of a typical SARS-CoV-2 patient peaks just before symptom presentation. Modeling indicates SARS-CoV-2 control requires the synergistic efforts of case isolation, contact quarantine, and population-level interventions, owing to the specific transmission kinetics of this virus.

Reference

https://science.sciencemag.org/content/early/2020/11/23/science.abe2424

A multivariate data analysis approach for investigating daily statistics of countries affected with COVID-19 pandemic

Abstract

Background: To understand the impact and volume of coronavirus (COVID-19) crisis, univariate analysis is tedious for describing the datasets reported daily. However, to capture the full picture and be able to compare situations and consequences for different countries, multivariate analytical models are suggested in order to visualize and compare the situation of different countries more accurately and precisely.

Aims: It was- aimed to utilize data analysis tools that display the relative positions of data points in fewer dimensions while keeping the variation of the original data set as much as possible, and cluster countries according to their scores on the formed dimensions.

Methods: Principal component analysis (PCA) and Partitioning around medoids (PAM) clustering algorithms were used to analyze data of 56 countries, 82 countries and 91 countries with COVID-19 at three time points, eligible countries included in the analysis are those with total cases of 500 or more with no missing data.

Results: After performing PCA, we generated two scores: Disease Magnitude score that represents total cases, total deaths, total actives cases, and critically ill cases, and Mortality Recovery Ratio score that represents the ratio between total deaths to total recoveries in any given country.

Conclusion: Accurate multivariate analyses can be of great value as they can simplify difficult concepts, explore and communicate findings from health datasets, and support the decision-making process.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)32418-X

SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain

Abstract

Reports indicate an association between COVID-19 and anosmia, as well as the presence of SARS-CoV-2 virions in the olfactory bulb. To test whether the olfactory neuroepithelium may represent a target of the virus, we generated RNA-seq libraries from human olfactory neuroepithelia, in which we found substantial expression of the genes coding for the virus receptor angiotensin-converting enzyme-2 (ACE2), and for the virus internalization enhancer TMPRSS2. We analyzed a human olfactory single-cell RNA-seq dataset and determined that sustentacular cells, which maintain the integrity of olfactory sensory neurons, express ACE2 and TMPRSS2. ACE2 protein was highly expressed in a subset of sustentacular cells in human and mouse olfactory tissues. Finally, we found ACE2 transcripts in specific brain cell types, both in mice and humans. Sustentacular cells thus represent a potential entry door for SARS-CoV-2 in a neuronal sensory system that is in direct connection with the brain.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(20)31036-1

A systematic review of contamination (aerosol, splatter and droplet generation) associated with oral surgery and its relevance to COVID-19

Abstract

Introduction: The current COVID-19 pandemic caused by the SARS-CoV-2 virus has impacted the delivery of dental care globally and has led to re-evaluation of infection

control standards. However, lack of clarity around what is known and unknown regarding droplet and aerosol generation in dentistry (including oral surgery and extractions), and their relative risk to patients and the dental team, necessitates a review of evidence relating to specific dental procedures. This review is part of a wider body of research exploring the evidence on bioaerosols in dentistry and involves detailed consideration of the risk of contamination in relation to oral surgery.

Methods: A comprehensive search of Medline (OVID), Embase (OVID), Cochrane Central Register of Controlled Trials, Scopus, Web of Science, LILACS and ClinicalTrials.Gov was conducted using key terms and MeSH (Medical Subject Headings) words relating to the review questions. Methodological quality including sensitivity was assessed using a schema developed to measure quality aspects of studies using a traffic light system to allow inter- and intra-study overview and comparison. A narrative synthesis was conducted for assessment of the included studies and for the synthesis of results.

Results: Eleven studies on oral surgery (including extractions) were included in the review. They explored microbiological (bacterial and fungal) and blood (visible and/or imperceptible) contamination at the person level (patients, operators and assistants) and/or at a wider environmental level, using settle plates, chemiluminescence reagents or air samplers; all within 1 m of the surgical site. Studies were of generally low to medium quality and highlighted an overall risk of contaminated aerosol, droplet and splatter generation during oral surgery procedures, most notably during removal of impacted teeth using rotatory handpieces. Risk of contamination and spread was increased by factors, including proximity to the operatory site, longer duration of treatment, higher procedural complexity, non-use of an extraoral evacuator and areas involving more frequent contact during treatment.

Conclusion: A risk of contamination (microbiological, visible and imperceptible blood) to patients, dental team members and the clinical environment is present during oral surgery procedures, including routine extractions. However, the extent of contamination has not been explored fully in relation to time and distance. Variability across studies with regards to the analysis methods used and outcome measures makes it difficult to

draw robust conclusions. Further studies with improved methodologies, including higher test sensitivity and consideration of viruses, are required to validate these findings.

Reference

https://www.nature.com/articles/s41405-020-00053-2

Factors associated with acute cardiac injury and their effects on mortality in patients with COVID-19

Abstract

To determine the incidence of acute cardiac injury (ACI), the factors associated with ACI and the in-hospital mortality in patients with COVID-19, especially in severe patients. All consecutive in-patients with laboratory-confirmed COVID-19 from Tongji Hospital in Wuhan during February 1 and March 29, 2020 were included. The demographic, clinical characteristics, laboratory, radiological and treatment data were collected. Univariate and Firth logistic regression analyses were used to identify factors associated with ACI and in-hospital mortality, and Kaplan–Meier method was used to estimate cumulative in-hospital mortality. Among 1031 patients included, 215 (20.7%) had ACI and 501 (48.6%) were severe cases. Overall, 165 patients died; all were from the severe group, and 131 (79.39%) had ACI. ACI ($OR = 2.34$, $P = 0.009$), male gender ($OR = 2.58$, $P = 0.001$), oximeter oxygen saturation ($OR = 0.90$, $P < 0.001$), lactate dehydrogenase ($OR = 3.26$, $P < 0.001$), interleukin-6 (IL-6) ($OR = 8.59$, $P < 0.001$), high sensitivity C-reactive protein (hs-CRP) ($OR = 3.29$, $P = 0.016$), N-terminal pro brain natriuretic peptide (NT-proBNP) ($OR = 2.94$, $P = 0.001$) were independent risk factors for the in-hospital mortality in severe patients. The mortality was significantly increased among severe patients with elevated hs-CRP, IL-6, hs-cTnI, and/or NT-proBNP. Moreover, the mortality was significantly higher in patients with elevation of both hs-cTnI and NT proBNP than in those with elevation of either of them. ACI develops in a substantial proportion of patients with COVID-19, and is associated with the disease severity and in-hospital mortality. A combination of hs-cTnI and NT-proBNP is valuable in predicting the mortality.

Reference

https://www.nature.com/articles/s41598-020-77172-1

Influence of social isolation caused by coronavirus disease 2019 (COVID-19) on the psychological characteristics of hospitalized schizophrenia patients: A case-control study

Abstract

Coronavirus disease 2019 (COVID-19) has been classified as a pandemic, and mental hospitals located in epidemic centers have been affected. Social isolation is an important and irreplaceable measure to control the spread of the epidemic. In this study, schizophrenic patients who were subjected to social isolation after close contact with COVID-19 patients were used as participants to explore the impact of social isolation on common inflammatory indicators and psychological characteristics. A total of 30 patients with schizophrenia were recruited from Wuhan Mental Health Center. In addition, 30 ordinary schizophrenic patients were matched with the isolation group and were recruited from another branch of Wuhan Mental Health Center as controls. We compared the differences in common inflammatory indicators and psychological characteristics between the isolated group and the control group, and longitudinal comparison of the differences in the above indicators before and after isolation among the isolation group. The Chinese Perceived Stress Scale (CPSS) score, Hamilton Depression Scale (HAMD) score and Hamilton Anxiety Scale (HAMA) score of the isolation group were significantly higher than those of the control group ($p = 0.00$, 0.00, 0.00, respectively). The C-reactive protein (CRP) level, CPSS score, HAMA score and Pittsburgh sleep quality index (PSQI) score of the isolation group were significantly higher after isolation ($p = 0.01$, 0.00, 0.00, 0.00, 0.00, respectively). Inpatients of schizophrenia suffered from social isolation due to COVID-19 have a severe psychological burden. Social isolation caused patients to develop a weak inflammatory state and led to worse anxiety and sleep quality.

Reference

https://www.nature.com/articles/s41398-020-01098-5

Establishment of an African green monkey model for COVID-19 and protection against re-infection

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for an unprecedented global pandemic of COVID-19. Animal models are urgently needed to study the pathogenesis of COVID-19 and to screen vaccines and treatments. It was shown that African green monkeys (AGMs) support robust SARS-CoV-2 replication and develop pronounced respiratory disease, which may more accurately reflect human COVID-19 cases than other nonhuman primate species. SARS-CoV-2 was detected in mucosal samples, including rectal swabs, as late as 15 days after exposure. Marked inflammation and coagulopathy in blood and tissues were prominent features. Transcriptome analysis demonstrated stimulation of interferon and interleukin-6 pathways in bronchoalveolar lavage samples and repression of natural killer cell- and T cell–associated transcripts in peripheral blood. Despite a slight waning in antibody titers after primary challenge, enhanced antibody and cellular responses contributed to rapid clearance after re-challenge with an identical strain. These data support the utility of AGM for studying COVID-19 pathogenesis and testing medical countermeasures.

Reference

https://www.nature.com/articles/s41590-020-00835-8

Publication Date: Nov 23, 2020

Insulin treatment is associated with increased mortality in patients with COVID-19

Abstract

COVID-19 caused by SARS-COV2 infection can lead to multi-organ injuries and significant mortality in severe and critical patients, especially among those individuals with type 2 diabetes (T2D) as a comorbidity. While attenuated mortality was observed with aggressive glucose control, it was unclear whether therapeutic regiments including insulin treatment was beneficial for patients with COVID-19 and T2D. This retrospective study investigated 689 patients with COVID-19 and T2D from a cohort of 3,305 cases from Wuhan, China. Unexpectedly, we found that insulin treatment for patients with

COVID-19 and T2D was associated with a significant increase in mortality [27.2% vs. 3.5%; adjusted HR, 5.38 (2.75-10.54)]. Further analysis showed that insulin treatment was associated with enhanced systemic inflammation and aggravated injuries of vital organs. Therefore, insulin treatment for patients with COVID-19 and T2D should be used with caution.

Reference

https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30647-1

Targeted intracellular degradation of SARS-CoV-2 *via* computationally optimized peptide fusions

Abstract

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has elicited a global health crisis of catastrophic proportions. With only a few vaccines approved for early or limited use, there is a critical need for effective antiviral strategies. In this study, a unique antiviral platform was reported, through computational design of ACE2-derived peptides which both target the viral spike protein receptor binding domain (RBD) and recruit E3 ubiquitin ligases for subsequent intracellular degradation of SARS-CoV-2 in the proteasome. Our engineered peptide fusions demonstrate robust RBD degradation capabilities in human cells and are capable of inhibiting infection-competent viral production, thus prompting their further experimental characterization and therapeutic development.

Reference

https://www.nature.com/articles/s42003-020-01470-7

Virtual screening of anti-HIV1 compounds against SARS-CoV-2: machine learning modeling, chemoinformatics and molecular dynamics simulation based analysis

Abstract

COVID-19 caused by the SARS-CoV-2 is a current global challenge and urgent discovery of potential drugs to combat this pandemic is a need of the hour. 3-chymotrypsin-like cysteine protease (3CLpro) enzyme is the vital molecular target

against the SARS-CoV-2. Therefore, in the present study, 1528 anti-HIV1compounds were screened by sequence alignment between 3CLpro of SARS-CoV-2 and avian infectious bronchitis virus (avian coronavirus) followed by machine learning predictive model, drug-likeness screening and molecular docking, which resulted in 41 screened compounds. These 41 compounds were re-screened by deep learning model constructed considering the IC_{50} values of known inhibitors which resulted in 22 hit compounds. Further, screening was done by structural activity relationship mapping which resulted in two structural clefts. Thereafter, functional group analysis was also done, where cluster 2 showed the presence of several essential functional groups having pharmacological importance. In the final stage, Cluster 2 compounds were re-docked with four different PDB structures of 3CLpro, and their depth interaction profile was analyzed followed by molecular dynamics simulation at 100 ns. Conclusively, 2 out of 1528 compounds were screened as potential hits against 3CLpro which could be further treated as an excellent drug against SARS-CoV-2.

Reference

https://www.nature.com/articles/s41598-020-77524-x

Publication Date: Nov 21, 2020

SARS-CoV-2 mRNA vaccines foster potent antigen-specific germinal center responses associated with neutralizing antibody generation

Abstract

The deployment of effective vaccines against SARS-CoV-2 is critical to eradicate the COVID-19 pandemic. Many licensed vaccines confer protection by inducing long-lived plasma cells (LLPC) and memory B cells (MBC), cell types canonically generated during germinal center (GC) reactions. Here, two vaccine platforms −mRNA vaccines were directly compared and a recombinant protein formulated with an MF59-like adjuvant− for their ability to quantitatively and qualitatively shape SARS-CoV-2-specific primary GC responses over time. It was demonstrated that a single immunization with SARS-CoV-2 mRNA, but not with the recombinant protein vaccine, elicited potent SARS-CoV-2-specific GC B and T follicular helper (Tfh) cell responses as well as LLPC and MCB. Importantly, GC responses strongly correlated with neutralizing antibody production.

mRNA vaccines more efficiently induced key regulators of the Tfh cell program and influenced the functional properties of Tfh cells. Overall, this study identifies SARS-CoV-2 mRNA vaccines as strong candidates for promoting robust GC-derived immune responses.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(20)30496-9

Newcastle disease virus (NDV) expressing the spike protein of SARS-CoV-2 as a live virus vaccine candidate

Abstract

Background: Due to the lack of protective immunity of humans towards the newly emerged SARS-CoV-2, this virus has caused a massive pandemic across the world resulting in hundreds of thousands of deaths. Thus, a vaccine is urgently needed to contain the spread of the virus.

Methods: Here, Newcastle disease virus (NDV) vector vaccines were described expressing the spike protein of SARS-CoV-2 in its wild type format or a membrane-anchored format lacking the polybasic cleavage site. All described NDV vector vaccines grow to high titers in embryonated chicken eggs. In a proof of principle mouse study, the immunogenicity and protective efficacy of these NDV-based vaccines were investigated.

Findings: It was reported that the NDV vector vaccines elicit high levels of antibodies that are neutralizing when the vaccine is given intramuscularly in mice. Importantly, these COVID-19 vaccine candidates protect mice from a mouse-adapted SARS-CoV-2 challenge with no detectable viral titer and viral antigen in the lungs.

Interpretation: The results suggested that the NDV vector expressing either the wild type S or membrane-anchored S without the polybasic cleavage site could be used as live vector vaccine against SARS-CoV-2.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30508-9/fulltext

Structure-based drug designing of naphthalene based SARS-CoV PLpro inhibitors for the treatment of COVID-19

Abstract

The emergence of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has imposed a greater challenge for the world. Coronavirus has infected over 38.3 million people and caused millions of deaths worldwide. The COVID-19 outbreak has accentuated the need for additional efforts to develop broad-spectrum therapeutics to combat SARS-CoV-2 infection. In the current investigation, an attempt was made to design potential SARS-CoV PLpro inhibitors containing naphthalene and 3,4-dihydro-2H-pyran moieties connected via -NHCO- linker. The ligands obeyed Lipinski's rule and were found to have good drug-likeness and ADMET properties. Docking simulations confirmed strong binding affinity and inhibition potential of the designed ligands against the receptor SARS CoV-2 Papain-like protease (PLpro). LigandL10 incorporating the oxadiazole ring system displayed better binding affinity than the control 5-acetamido-2-methyl-N-[(1R)-1-naphthalen-1-ylethyl]benzamide. Further, the docked complex of LigandL10 was subjected to molecular dynamics (MD) simulation to examine the molecular mechanisms of protein-ligand interactions. The results of the present study are encouraging. Ligand L10 emerged as the most potent ligand in the series and could be considered for further research for the development of potential therapeutics for the treatment of COVID-19.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)32401-4

Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19

Abstract

Background: Hydroxychloroquine (HC) ± azithromycin (AZ) is widely used for Covid-19. The Qatar Prospective RCT of Expediting Coronavirus Tapering (Q-PROTECT) aimed to assess virologic cure rates of HC±AZ in cases of low-acuity Covid-19.

Methods: Q-PROTECT employed a prospective, placebo-controlled design with blinded randomization to three parallel arms: placebo, oral HC (600 mg daily for one week), or oral HC plus oral AZ (500 mg day one, 250 mg daily on days two through five). At enrollment, non-hospitalized participants had mild or no symptoms and were within a day of Covid-19 positivity by polymerase chain reaction (PCR). After six days, intent-to-treat (ITT) analysis of the primary endpoint of virologic cure was assessed using binomial exact 95% confidence intervals (CIs) and $\chi 2$ testing. (ClinicalTrials.gov NCT04349592, trial status closed to new participants.)

Findings: The study enrolled 456 participants (152 in each of three groups: HC+AZ, HC, placebo) between 13 April and 1 August 2020. HC+AZ, HC, and placebo groups had 6 (3·9%), 7 (4·6%), and 9 (5·9%) participants go off study medications before completing the medication course (p = 0·716). Day six PCR results were available for all 152 HC+AZ participants, 149/152 (98·0%) HC participants, and 147/152 (96·7%) placebo participants. Day six ITT analysis found no difference (p = 0·821) in groups' proportions achieving virologic cure: HC+AZ 16/152 (10·5%), HC 19/149 (12·8%), placebo 18/147 (12·2%). Day 14 assessment also showed no association (p = 0·072) between study group and viral cure: HC+AZ 30/149 (20·1%,), HC 42/146 (28·8%), placebo 45/143 (31·5%). There were no serious adverse events.

Interpretation: HC±AZ does not facilitate virologic cure in patients with mild or asymptomatic Covid-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30389-8/fulltext

Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis

Abstract

Background: Studies have suggested that there is increased risk of thromboembolism (TE) associated with coronavirus disease 2019 (COVID-19). However, overall arterial and venous TE rates of COVID-19 and effect of TE on COVID-19 mortality is unknown.

Methods: We did a systematic review and meta-analysis of studies evaluating TE in COVID-19. We searched PubMed, Cochrane, and Embase for studies published up to June 12, 2020. Random effects models were used to produce summary TE rates and odds ratios (OR) of mortality in COVID-19 patients with TE compared to those without TE. Heterogeneity was quantified with I2.

Findings: Of 425 studies identified, 42 studies enrolling 8271 patients were included in the meta-analysis. Overall venous TE rate was 21% (95% CI:17–26%): ICU, 31% (95% CI: 23–39%). Overall deep vein thrombosis rate was 20% (95% CI: 13–28%): ICU, 28% (95% CI: 16–41%); postmortem, 35% (95% CI:15–57%). Overall pulmonary embolism rate was 13% (95% CI: 11–16%): ICU, 19% (95% CI:14–25%); postmortem, 22% (95% CI:16–28%). Overall arterial TE rate was 2% (95% CI: 1–4%): ICU, 5% (95%CI: 3–7%). Pooled mortality rate among patients with TE was 23% (95%CI:14–32%) and 13% (95% CI:6–22%) among patients without TE. The pooled odds of mortality were 74% higher among patients who developed TE compared to those who did not (OR, 1.74; 95%CI, 1.01–2.98; P = 0.04).

Interpretation: TE rates of COVID-19 are high and associated with higher risk of death. Robust evidence from ongoing clinical trials is needed to determine the impact of thromboprophylaxis on TE and mortality risk of COVID-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30383-7/fulltext

Adverse impact of renin–angiotensin system blockade on the clinical course in hospitalized patients with severe COVID-19: A retrospective cohort study

Abstract

The association between angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) and the risk of mortality in hospitalized patients with severe coronavirus disease 2019 (COVID-19) was investigated. This retrospective cohort study was performed in all hospitalized patients with COVID-19 in tertiary hospitals in Daegu, Korea. Patients were classified based on whether they received ACE-I or ARB before COVID-19 diagnosis. The analysis of the primary outcome, in-hospital mortality, was performed using the Cox proportional hazards regression model.

Of 130 patients with COVID-19, 30 (23.1%) who received ACE-I or ARB exhibited an increased risk of in-hospital mortality (adjusted hazard ratio, 2.20; 95% confidence interval [CI], 1.10–4.38; P = 0.025). ACE-I or ARB was also associated with severe complications, such as acute respiratory distress syndrome (ARDS) (adjusted odds ratio [aOR], 2.58; 95% CI, 1.02–6.51; P = 0.045) and acute kidney injury (AKI) (aOR, 3.06; 95% CI, 1.15–8.15; P = 0.026). Among the patients with ACE-I or ARB therapy, 8 patients (26.7%) used high equivalent doses of ACE-I or ARB and they had higher in-hospital mortality and an increased risk of ARDS and AKI (all, P < 0.05). ACE-I or ARB therapy in patients with severe COVID-19 was associated with the occurrence of severe complications and increased in-hospital mortality. The potentially harmful effect of ACE-I or ARB therapy may be higher in patients who received high doses.

Reference

https://www.nature.com/articles/s41598-020-76915-4

Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China

Abstract

Stringent COVID-19 control measures were imposed in Wuhan between January 23 and April 8, 2020. Estimates of the prevalence of infection following the release of restrictions could inform post-lockdown pandemic management. Here, we describe a city-wide SARS-CoV-2 nucleic acid screening programme between May 14 and June 1, 2020 in Wuhan. All city residents aged six years or older were eligible and 9,899,828 (92.9%) participated. No new symptomatic cases and 300 asymptomatic cases (detection rate 0.303/10,000, 95% CI 0.270–0.339/10,000) were identified. There were no positive tests amongst 1,174 close contacts of asymptomatic cases. 107 of 34,424 previously recovered COVID-19 patients tested positive again (re-positive rate 0.31%, 95% CI 0.423–0.574%). The prevalence of SARS-CoV-2 infection in Wuhan was therefore very low five to eight weeks after the end of lockdown.

Reference

https://www.nature.com/articles/s41467-020-19802-w

Streamlined inactivation, amplification, and Cas13-based detection of SARS-CoV-2

Abstract

The COVID-19 pandemic has highlighted that new diagnostic technologies are essential for controlling disease transmission. Here, it was developed SHINE (Streamlined Highlighting of Infections to Navigate Epidemics), a sensitive and specific diagnostic tool that can detect SARS-CoV-2 RNA from unextracted samples. It was identified the optimal conditions to allow RPA-based amplification and Cas13-based detection to occur in a single step, simplifying assay preparation and reducing run-time. It was improved HUDSON to rapidly inactivate viruses in nasopharyngeal swabs and saliva in 10 min. SHINE's results can be visualized with an in-tube fluorescent readout — reducing contamination risk as amplification reaction tubes remain sealed — and interpreted by a companion smartphone application. It was validated SHINE on 50 nasopharyngeal patient samples, demonstrating 90% sensitivity and 100% specificity compared to RT-qPCR with a sample-to-answer time of 50 min. SHINE has the potential to be used outside of hospitals and clinical laboratories, greatly enhancing diagnostic capabilities.

Reference

https://www.nature.com/articles/s41467-020-19097-x

Publication Date: Nov 19, 2020

SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: A systematic review and meta-analysis

Abstract

Background: Viral load kinetics and duration of viral shedding are important determinants for disease transmission. It was aimed to characterise viral load dynamics, duration of viral RNA shedding, and viable virus shedding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in various body fluids, and to compare SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) viral dynamics.

Methods: In this systematic review and meta-analysis, we searched databases, including MEDLINE, Embase, Europe PubMed Central, medRxiv, and bioRxiv, and the grey literature, for research articles published between Jan 1, 2003, and June 6, 2020. We included case series (with five or more participants), cohort studies, and randomised controlled trials that reported SARS-CoV-2, SARS-CoV, or MERS-CoV infection, and reported viral load kinetics, duration of viral shedding, or viable virus. Two authors independently extracted data from published studies, or contacted authors to request data, and assessed study quality and risk of bias using the Joanna Briggs Institute Critical Appraisal Checklist tools. We calculated the mean duration of viral shedding and 95% CIs for every study included and applied the random-effects model to estimate a pooled effect size. A weighted meta-regression was used with an unrestricted maximum likelihood model to assess the effect of potential moderators on the pooled effect size. This study is registered with PROSPERO, CRD42020181914.

Findings: 79 studies (5340 individuals) on SARS-CoV-2, eight studies (1858 individuals) on SARS-CoV, and 11 studies (799 individuals) on MERS-CoV were included. Mean duration of SARS-CoV-2 RNA shedding was 17·0 days (95% CI 15·5–18·6; 43 studies, 3229 individuals) in upper respiratory tract, 14·6 days (9·3–20·0; seven studies, 260 individuals) in lower respiratory tract, 17·2 days (14·4–20·1; 13 studies, 586 individuals) in stool, and 16·6 days (3·6–29·7; two studies, 108 individuals) in serum samples. Maximum shedding duration was 83 days in the upper respiratory tract, 59 days in the lower respiratory tract, 126 days in stools, and 60 days in serum. Pooled mean SARS-CoV-2 shedding duration was positively associated with age (slope 0·304 [95% CI 0·115–0·493]; p=0·0016). No study detected live virus beyond day 9 of illness, despite persistently high viral loads, which were inferred from cycle threshold values. SARS-CoV-2 viral load in the upper respiratory tract appeared to peak in the first week of illness, whereas that of SARS-CoV peaked at days 10–14 and that of MERS-CoV peaked at days 7–10.

Interpretation: Although SARS-CoV-2 RNA shedding in respiratory and stool samples can be prolonged, duration of viable virus is relatively short-lived. SARS-CoV-2 titres in the upper respiratory tract peak in the first week of illness. Early case finding and isolation, and public education on the spectrum of illness and period of infectiousness are key to the effective containment of SARS-CoV-2.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30172-5/fulltext

Multi-center nationwide comparison of seven serology assays reveals a SARS-CoV-2 non-responding seronegative subpopulation

Abstract

Background: An Israeli national taskforce performed a multi-center clinical and analytical validation of seven serology assays to determine their utility and limitations for SARS-CoV-2 diagnosis.

Methods: Serology assays from Roche, Abbott, Diasorin, BioMerieux, Beckman-Coulter, Siemens, and Mt.-Sinai ELISA were included. Negative samples from 2391 individuals representative of the Israeli population, and 698 SARS-CoV-2 PCR positive patients, collected between March and May 2020, were analyzed.

Findings: Immunoassays sensitivities between 81.5%-89.4% and specificities between 97.7%-100% resulted in a profound impact on the expected Positive Predictive Value (PPV) in low (<15%) prevalence scenarios. No meaningful increase was detected in the false positive rate in children compared to adults. A positive correlation between disease severity and antibody titers, and no decrease in antibody titers in the first 8 weeks after PCR positivity was observed. We identified a subgroup of symptomatic SARS-CoV-2 positive patients (~5% of patients), who remained seronegative across a wide range of antigens, isotypes, and technologies.

Interpretation: The commercially available automated immunoassays exhibit significant differences in performance and expected PPV in low prevalence scenarios. The low false-positivity rate in under 20′s suggests that cross-reactive immunity from previous CoV strains is unlikely to explain the milder disease course in children. Finding no decrease in antibody titers in the first 8 weeks is in contrast to some reports of short half-life for SARS-CoV-2 antibodies. The ~5% who were seronegative non-responders, using multiple assays in a population-wide manner, represents the proportion of patients that may be at risk for re-infection.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30395-3/fulltext

A serological assay to detect SARS-CoV-2 antibodies in at-home collected finger-prick dried blood spots

Abstract

Accurate surveillance of coronavirus disease 2019 (COVID-19) incidence requires large-scale testing of the population. Current testing methods require in-person collection of biospecimens by a healthcare worker, limiting access of individuals who do not have access to testing facilities while placing both patients and healthcare workers at risk of exposure to infection. It was reported that the development and validation of a at-home finger-prick dried blood spot collection kit and an analysis method. We demonstrated 100% sensitivity and specificity using at-home collected specimens across the US. Such methods may facilitate the conduct of unbiased serosurveys within hard to reach populations and help reduce the sample collection burden of serological testing on both health care systems and individuals alike.

Reference

https://www.nature.com/articles/s41598-020-76913-6

Thrombocytopathy and endotheliopathy: Crucial contributors to COVID-19 thromboinflammation

Abstract

The core pathology of coronavirus disease 2019 (COVID-19) is infection of airway cells by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that results in excessive inflammation and respiratory disease, with cytokine storm and acute respiratory distress syndrome implicated in the most severe cases. Thrombotic complications are a major cause of morbidity and mortality in patients with COVID-19. Patients with pre-existing cardiovascular disease and/or traditional cardiovascular risk factors, including obesity, diabetes mellitus, hypertension and advanced age, are at the highest risk of death from COVID-19. In this Review, it was summarized that new lines of evidence that point to both platelet and endothelial dysfunction as essential

components of COVID-19 pathology and describe the mechanisms that might account for the contribution of cardiovascular risk factors to the most severe outcomes in COVID-19. We highlight the distinct contributions of coagulopathy, thrombocytopathy and endotheliopathy to the pathogenesis of COVID-19 and discuss potential therapeutic strategies in the management of patients with COVD-19. Harnessing the expertise of the biomedical and clinical communities is imperative to expand the available therapeutics beyond anticoagulants and to target both thrombocytopathy and endotheliopathy. Only with such collaborative efforts can we better prepare for further waves and for future coronavirus-related pandemics.

Reference

https://www.nature.com/articles/s41569-020-00469-1

Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers

Abstract

COVID-19 is characterized by marked variability in clinical severity. Vitamin D had recently been reviewed as one of the factors that may affect the severity in COVID-19. The objective of current study is to analyze the vitamin D level in COVID-19 patients and its impact on the disease severity. After approval from Ethics Committee, M.L.B Medical College the current study was undertaken as continuous prospective observational study of 6 weeks. Participants were COVID-19 patients of age group 30–60 years admitted during the study period of 6 weeks. Study included either asymptomatic COVID-19 patients (Group A) or severely ill patients requiring ICU admission (Group B). Serum concentration of 25 (OH)D, were measured along with serum IL-6; TNFα and serum ferritin. Standard statistical analysis was performed to analyze the differences. Current Study enrolled 154 patients, 91 in Group A and 63 patients in Group B. The mean level of vitamin D (in ng/mL) was 27.89 ± 6.21 in Group A and 14.35 ± 5.79 in Group B, the difference was highly significant. The prevalence of vitamin D deficiency was 32.96% and 96.82% respectively in Group A and Group B. Out of total 154 patients, 90 patients were found to be deficient in vitamin D (Group A: 29; Group B: 61). Serum level of inflammatory markers was found to be higher in vitamin D deficient COVID-19 patients viz. IL-6 level (in pg/mL) 19.34 ± 6.17 vs 12.18 ± 4.29;

Serum ferritin 319.17 ± 38.21 ng/mL vs 186.83 ± 20.18 ng/mL; TNFα level (in pg/mL) 13.26 ± 5.64 vs 11.87 ± 3.15. The fatality rate was high in vitamin D deficient (21% vs 3.1%). Vitamin D level is markedly low in severe COVID-19 patients. Inflammatory response is high in vitamin D deficient COVID-19 patients. This all translates into increased mortality in vitamin D deficient COVID-19 patients. As per the flexible approach in the current COVID-19 pandemic authors recommend mass administration of vitamin D supplements to population at risk for COVID-19.

Reference

https://www.nature.com/articles/s41598-020-77093-z

Ocular surface manifestation of COVID-19 and tear film analysis

Abstract

To evaluate the ocular manifestation in patients hospitalized with coronavirus disease 2019 (COVID-19) and to search for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in tears. This study was conducted in 29 hospitalized patients who were admitted to the COVID center at the Policlinic Hospital of the University of Messina, Italy. All patients underwent an ophthalmologic assessment comprising a Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire, anterior segment, and the ocular surface examination of both eyes using a portable slit lamp. The Schirmer I test was performed, and the filter paper strip was used to search for the presence of SARS-CoV-2 on the ocular surface by real-time quantitative polymerase chain reaction (RT-qPCR). A total of 10 patients reported ocular symptoms; in particular, four reported eye burning, three reported foreign body sensation, and three reported tearing. Moreover, seven patients presented conjunctival hyperemia and/or chemosis, eleven patients presented blepharitis signs such as lid margin hyperemia and/or telangiectasia, crusted eyelashes, and meibomian orifices alterations. Tear analysis did not reveal the presence of SARS-CoV-2. Ocular symptoms are common in patients with COVID-19; although, tear analysis did not reveal the presence of SARS-CoV-2.

Reference

https://www.nature.com/articles/s41598-020-77194-9

PERSPECTIVE

Publication Date: Nov 25, 2020

SARS-CoV-2 infection: Can ferroptosis be a potential treatment target for multiple organ involvement?

Since the outbreak of the new coronavirus in 2019 (SARS-CoV-2), many studies have been performed to better understand the basic mechanisms and clinical features of the disease. However, uncertainties of the underlying mechanisms of multiple organ involvement remain. A substantial proportion of severe coronavirus disease 2019 (COVID-19) patients have lymphopenia, low serum iron levels, and multiple organ involvement. Several therapeutic agents have been used for different stages of the disease, but the treatment for severe disease is still suboptimal. Understanding the mechanism of programmed cell death in COVID-19 may lead to better therapeutic strategies for these patients. On the basis of observations of basic science studies and clinical researches on COVID-19, it was hypothesized that ferroptosis, a novel programmed cell death, may be an important cause of multiple organ involvement in COVID-19 and it might serve as a new treatment target. In spite of the existing findings on the involvement of ferroptosis in SARS-CoV-2 infection, there is no reported study to uncover how does ferroptosis acts in SARS-CoV-2 infection yet. Uncovering the role of ferroptosis in SARS-CoV-2 infection is essential to develop new treatment strategies for COVID-19. Intracellular cell iron depletion or new generation of ferroptosis inhibitors might be potential drug candidates for COVID-19. It was hoped that this hypothesis may launch a new wave of studies to uncover the association of ferroptosis and SARS-CoV-2 infection *in vitro* and *in vivo*.

Reference

https://www.nature.com/articles/s41420-020-00369-w

Leukocyte trafficking to the lungs and beyond: Lessons from influenza for COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19). Understanding of the fundamental processes underlying the versatile clinical manifestations of COVID-19 is incomplete without comprehension of how different immune cells are recruited to various compartments of virus-infected lungs, and how this recruitment differs among individuals with different levels of disease severity. As in other respiratory infections, leukocyte recruitment to the respiratory system in people with COVID-19 is orchestrated by specific leukocyte trafficking molecules, and when uncontrolled and excessive it results in various pathological complications, both in the lungs and in other organs. In the absence of experimental data from physiologically relevant animal models, our knowledge of the trafficking signals displayed by distinct vascular beds and epithelial cell layers in response to infection by SARS-CoV-2 is still incomplete. However, SARS-CoV-2 and influenza virus elicit partially conserved inflammatory responses in the different respiratory epithelial cells encountered early in infection and may trigger partially overlapping combinations of trafficking signals in nearby blood vessels. Here, we review the molecular signals orchestrating leukocyte trafficking to airway and lung compartments during primary pneumotropic influenza virus infections and discuss potential similarities to distinct courses of primary SARS-CoV-2 infections. We also discuss how an imbalance in vascular activation by leukocytes outside the airways and lungs may contribute to extrapulmonary inflammatory complications in subsets of patients with COVID-19. These multiple molecular pathways are potential targets for therapeutic interventions in patients with severe COVID-19.

Reference

https://www.nature.com/articles/s41577-020-00470-2

HIGHLIGHTS

Publication Date: Nov 24, 2020

Host genetics of coronavirus infection

Characterizing the role of host genetics in SARS coronavirus 2 (SARS-CoV-2) infection may help to understand the diverse clinical outcomes of infected individuals, as well as providing mechanistic information on host–virus interactions and potential drug targets. Two new reports in Cell use genome-wide CRISPR screens to uncover host determinants of coronavirus infection, identifying potential leads for antiviral therapeutics.

In their study, Daniloski, Jordan *et al*. used human A549 alveolar lung cancer cells ectopically overexpressing the SARS-CoV-2 entry receptor, ACE2. They infected these cells with a pooled genome-wide CRISPR library, with each construct encoding a Cas9 nuclease and a guide RNA (gRNA) to direct the disruption of each human target gene. The authors then infected the CRISPR-perturbed cells with SARS-CoV-2 and identified gRNA constructs that were enriched; the targets of these gRNAs are potential infectivity-enhancing genes, the knockout of which protects from cytotoxic SARS-CoV-2 infection.

In a separate study, Wei *et al.* used genome-wide CRISPR screening but sought to understand host susceptibility across all the major recent human outbreak coronaviruses: SARS-CoV, MERS-CoV and SARS-CoV-2. The authors chose a cell line from *Chlorocebus sabaeus* monkeys that has endogenous expression of ACE2 (the receptor for both SARS-CoV and SARS-CoV-2) and DPP4 (the receptor for MERS-CoV). CRISPR reagents were delivered in two steps: first Cas9 and then a genome-wide library of C. sabaeus-targeted gRNAs. Following infection with each single coronavirus, cells were analysed for the most enriched and depleted gRNAs. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41576-020-00310-y

Battle at the entrance gate: CIITA as a weapon to prevent the internalization of SARS-CoV-2 and Ebola viruses

In a recent paper in Science, Bruchez *et al.* provide new insights how host cells can fight virus infection. They show that an MHC class II transactivator (CIITA)—which normally operates as part of the interferon (IFN)-stimulated immune response—is also involved in an antiviral response, beyond its well-known function of antigen presentation. For more details, read the link given below.

Reference

https://www.nature.com/articles/s41392-020-00405-2

NEWSLETTER

Publication Date: Nov 20, 2020

COVID research updates: Immune responses to coronavirus persist beyond 6 months

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

Immune responses to coronavirus persist beyond 6 months (20 November 2020):

The immune system's memory of the new coronavirus lingers for at least six months in most people. Sporadic accounts of coronavirus reinfection and reports of rapidly declining antibody levels have raised concerns that immunity to SARS-CoV-2 could dwindle within weeks of recovery from infection. Shane Crotty at the La Jolla Institute for Immunology in California and his colleagues analysed markers of the immune response in blood samples from 185 people who had a range of COVID-19 symptoms; 41 study participants were followed for at least 6 months (J. M. Dan *et al.* Preprint at bioRxiv https://doi.org/ghkc5k; 2020). The team found that participants' immune responses varied widely. But several components of immune memory of SARS-CoV-2 tended to persist for at least 6 months. Among the persistent immune defenders were memory B cells, which jump-start antibody production when a pathogen is re-encountered, and two important classes of T cell: memory CD4+ and memory CD8+ T cells. The results have not yet been peer-reviewed.

The coronavirus mutates rapidly as it races through mink farms (19 November 2020):

The coronavirus is adapting to its mink hosts, suggests a genetic analysis of farmed animals infected with SARS-CoV-2. Outbreaks of coronavirus have been reported on farms breeding mink (Neovison vison and Mustela lutreola) across Europe and the United States since April. François Balloux at University College London and his colleagues studied 239 viral genomes isolated from farmed animals in the Netherlands and Denmark (L. van Dorp *et al.* Preprint at bioRxiv https://doi.org/fjj6; 2020). The team identified at least seven separate instances in which the virus had jumped from people infected with SARS-CoV-2 to mink. The researchers also found 23 mutations that had

arisen independently at least twice, suggesting that the virus was rapidly adapting to its new host. Some of these frequent mutations appeared in regions of the genome that encode the spike protein that coronaviruses use to infect cells. But researchers say there is no evidence that these changes in mink will affect SARS-CoV-2's ability to spread in people if it jumps back to humans. The findings have not yet been peer reviewed.

Reference

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

COMMENT

Publication Date: Nov 20, 2020

SARS-CoV-2 and the human-animal interface: Outbreaks on mink farms

On Nov 5, the Ministry of Environment and Food of Denmark announced the culling of all mink in the country, estimated to total approximately 17 million animals. The circulation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had already been observed several months earlier, but the reason for the policy change was an alert from the Danish National Institute of Public Health, which found that viruses had spilled back from mink farms into the community, and that during the passage through mink the virus had accumulated mutations in the spike protein gene. Spike mutations are scrutinised because the spike is crucial for docking of SARS-CoV-2 to human cells and therefore a key target for vaccines and therapeutic antibodies. Preliminary analyses suggested that SARS-CoV-2 isolated from mink in Denmark was less easily neutralised by antibodies in two of nine humans that had been infected with SARS-CoV-2 without the mutations. The effect was small but caused widespread concern in the media, suggesting that the vaccines under development would potentially be rendered useless. Following review of the evidence, the European Centre for Disease Prevention and Control and WHO concluded that the risk for the population at large was not increased, but stressed the importance of surveillance at the human–animal interface and rapid exchange of information between virologists and epidemiologists to track possible viral changes that could be of concern. The example of Denmark is a warning: spillover of SARS-CoV-2 from humans to mink and minks to humans is not a new finding. It was first reported in the Netherlands in April, and since has been found in Spain, Italy, the USA, Sweden, and Greece. In most countries, the first infections on mink farms were identified through contact tracing following confirmation of COVID-19 in symptomatic humans.

Mink belong to the Mustelidae family, which includes ferrets that have been used as an animal model owing to their susceptibility to SARS-CoV-2. Efficient transmission between ferrets has been shown in experimental infections, with spread to naive animals through direct contact but also through indirect airborne spread. According to

the European Centre for Disease Prevention and Control, Europe has an estimated 2750 mink farms and produces more than 27 million pelts per year. As farmed minks are kept in large groups and housed in pens in wire cages with bedding that generates a lot of dust, there is ample opportunity for transmission once the virus is introduced on the farms. Introduction and spread might go unnoticed as infected farms have been detected through serosurveys, suggesting that disease might be mild or inapparent, although upper and lower respiratory tract infection and symptoms have been documented as well. There is some evidence that susceptibility differs depending on breed, suggesting a genetic susceptibility factor that could be worth exploring. Once introduced, experience in Denmark and the Netherlands has shown that it might be difficult to stop transmission. Ongoing farm-to-farm transmission has been observed, and investigations are exploring the modes of transmission between farms. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30912-9/fulltext