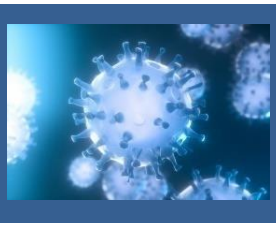
COVID-19

Aug 19 – 25, 2021



RESEARCH PUBLICATIONS

Publication Date: Aug 25, 2021

Comprehensive mapping of SARS-CoV-2 interactions *in vivo* reveals functional virus-host interactions

Abstract

SARS-CoV-2 is a major threat to global health. Here, the RNA structure and RNA-RNA interactions of wildtype (WT) and a mutant (Δ382) SARS-CoV-2 in cells were investigated using Illumina and Nanopore platforms. It was identified that twelve potentially functional structural elements within the SARS-CoV-2 genome, observe that subgenomic RNAs can form different structures, and that WT and Δ382 virus genomes fold differently. Proximity ligation sequencing identify hundreds of RNA-RNA interactions within the virus genome and between the virus and host RNAs. SARS-CoV-2 genome binds strongly to mitochondrial and small nucleolar RNAs and is extensively 2'-O-methylated. 2'-O-methylation sites are enriched in viral untranslated regions, associated with increased virus pair-wise interactions, and are decreased in host mRNAs upon virus infection, suggesting that the virus sequesters methylation machinery from host RNAs towards its genome. These studies deepen our understanding of the molecular and cellular basis of SARS-CoV-2 pathogenicity and provide a platform for targeted therapy.

Reference

https://www.nature.com/articles/s41467-021-25357-1

Homology between SARS CoV-2 and human proteins

Abstract

An extremely high contagiousness of SARS CoV-2 indicates that the virus developed the ability to deceive the innate immune system. The virus could have included in its outer protein domains some motifs that are structurally similar to those that the potential victim's immune system has learned to ignore. The similarity of the primary structures of the viral and human proteins can provoke an autoimmune process. Using an open-access protein database Uniprot, the SARS CoV-2 proteome was compared with those of other organisms. In the SARS CoV-2 spike (S) protein molecule, we have localized more than two dozen hepta- and octamers homologous to human proteins. They are scattered along the entire length of the S protein molecule, while some of them fuse into sequences of considerable length. Except for one, all these n-mers project from the virus particle and therefore can be involved in providing mimicry and misleading the immune system. All hepta- and octamers of the envelope (E) protein, homologous to human proteins, are located in the viral transmembrane domain and form a 28-mer protein E14-41 VNSVLLFLAFVVFLLVTLAILTALRLCA. The involvement of the protein E in provoking an autoimmune response (after the destruction of the virus particle) seems to be highly likely. Some SARS CoV-2 nonstructural proteins may also be involved in this process, namely ORF3a, ORF7a, ORF7b, ORF8, and ORF9b. It is possible that ORF7b is involved in the dysfunction of olfactory receptors, and the S protein in the dysfunction of taste perception.

Reference

https://www.nature.com/articles/s41598-021-96233-7

A high-resolution temporal atlas of the SARS-CoV-2 translatome and transcriptome

Abstract

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which infected >200 million people resulting in >4 million deaths. However, temporal landscape of the SARS-CoV-2 translatome and its impact on the human genome remain unexplored. Here, a high-resolution atlas of the translatome and transcriptome

of SARS-CoV-2 was reported for various time points after infecting human cells. Intriguingly, substantial amount of SARS-CoV-2 translation initiates at a novel translation initiation site (TIS) located in the leader sequence, termed TIS-L. Since TIS-L is included in all the genomic and subgenomic RNAs, the SARS-CoV-2 translatome may be regulated by a sophisticated interplay between TIS-L and downstream TISs. TIS-L functions as a strong translation enhancer for ORF S, and as translation suppressors for most of the other ORFs. The global temporal atlas provides compelling insight into unique regulation of the SARS-CoV-2 translatome and helps comprehensively evaluate its impact on the human genome.

Reference

https://www.nature.com/articles/s41467-021-25361-5

ACE2-targeting monoclonal antibody as potent and broad-spectrum coronavirus blocker

Abstract

The evolution of coronaviruses, such as SARS-CoV-2, makes broad-spectrum coronavirus preventional or therapeutical strategies highly sought after. Here it was reported that a human angiotensin-converting enzyme 2 (ACE2)-targeting monoclonal antibody, 3E8, blocked the S1-subunits and pseudo-typed virus constructs from multiple coronaviruses including SARS-CoV-2, SARS-CoV-2 mutant variants (SARS-CoV-2-D614G, B.1.1.7, B.1.351, B.1.617.1, and P.1), SARS-CoV and HCoV-NL63, without markedly affecting the physiological activities of ACE2 or causing severe toxicity in ACE2 “knock-in” mice. 3E8 also blocked live SARS-CoV-2 infection *in vitro* and in a prophylactic mouse model of COVID-19. Cryo-EM and “alanine walk” studies revealed the key binding residues on ACE2 interacting with the CDR3 domain of 3E8 heavy chain. Although full evaluation of safety in non-human primates is necessary before clinical development of 3E8, a potentially potent and “broad-spectrum” management strategy was provided against all coronaviruses that utilize ACE2 as entry receptors and disclosed an anti-coronavirus epitope on human ACE2.

Reference

https://www.nature.com/articles/s41392-021-00740-y

Comparative transcriptomic analysis of SARS-CoV-2 infected cell model systems reveals differential innate immune responses

Abstract

The transcriptome of SARS-CoV-2-infected cells that reflects the interplay between host and virus has provided valuable insights into mechanisms underlying SARS-CoV-2 infection and COVID-19 disease progression. In this study, it was shown that SARS-CoV-2 can establish a robust infection in HEK293T cells that overexpress human angiotensin-converting enzyme 2 (hACE2) without triggering significant host immune response. Instead, endoplasmic reticulum stress and unfolded protein response-related pathways are predominantly activated. By comparing the data with published transcriptome of SARS-CoV-2 infection in other cell lines, we found that the expression level of hACE2 directly correlates with the viral load in infected cells but not with the scale of immune responses. Only cells that express high level of endogenous hACE2 exhibit an extensive immune attack even with a low viral load. Therefore, the infection route may be critical for the extent of the immune response, thus the severity of COVID-19 disease status.

Reference

https://www.nature.com/articles/s41598-021-96462-w

Applications of laboratory findings in the prevention, diagnosis, treatment, and monitoring of COVID-19

Abstract

The worldwide pandemic of coronavirus disease 2019 (COVID-19) presents us with a serious public health crisis. To combat the virus and slow its spread, wider testing is essential. There is a need for more sensitive, specific, and convenient detection methods of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Advanced detection can greatly improve the ability and accuracy of the clinical diagnosis of COVID-19, which is conducive to the early suitable treatment and supports precise prophylaxis. In this article, the latest laboratory diagnostic technologies and methods for SARS-CoV-2 were combined and presented to identify the technical characteristics, considerations, biosafety requirements, common problems with testing

and interpretation of results, and coping strategies of commonly used testing methods. The gaps were highlighted in current diagnostic capacity and propose potential solutions to provide cutting-edge technical support to achieve a more precise diagnosis, treatment, and prevention of COVID-19 and to overcome the difficulties with the normalization of epidemic prevention and control.

Reference

https://www.nature.com/articles/s41392-021-00731-z

Pooled RT-qPCR testing for SARS-CoV-2 surveillance in schools - A cluster randomised trial

Abstract

Background: The extent to which children and adolescents contribute to SARS-CoV-2 transmission remains not fully understood. Novel high-capacity testing methods may provide real-time epidemiological data in educational settings helping to establish a rational approach to prevent and minimize SARS-CoV-2 transmission. It was investigated that whether pooling of samples for SARS-CoV-2 detection by RT-qPCR is a sensitive and feasible high-capacity diagnostic strategy for surveillance of SARS-CoV-2 infections in schools.

Methods: In this study, students and school staff of 14 educational facilities in Germany were tested sequentially between November 9 and December 23, 2020, two or three times per week for at least three consecutive weeks. Participants were randomized for evaluation of two different age adjusted swab sampling methods (oropharyngeal swabs or buccal swabs compared to saliva swabs using a ‘lolli method’). Swabs were collected and pooled for SARS-CoV-2 RT-qPCR. Individuals of positive pooled tests were retested by RT-qPCR the same or the following day. Positive individuals were quarantined while the SARS-CoV-2 negative individuals remained in class with continued pooled RT-qPCR surveillance. The study is registered with the German Clinical Trials register (registration number: DRKS00023911).

Findings: 5,537 Individuals were eligible and 3970 participants were enroled and included in the analysis. In students, a total of 21,978 swabs were taken and combined in 2218 pooled RT-qPCR tests. We detected 41 positive pooled tests (1·8%) leading to

36 SARS-CoV-2 cases among students which could be identified by individual re-testing. The cumulative 3-week incidence for primary schools was 564/100,000 (6/1064, additionally 1 infection detected in week 4) and 1249/100,000 (29/2322) for secondary schools. In secondary schools, there was no difference in the number of SARS-CoV-2 positive students identified from pooled oropharyngeal swabs compared to those identified from pooled saliva samples (lolli method) (14 vs. 15 cases; 1·3% vs. 1·3%; OR 1.1; 95%-CI 0·5–2·5). A single secondary school accounted for 17 of 36 cases (47%) indicating a high burden of asymptomatic prevalent SARS-CoV-2 cases in the respective school and community.

Interpretation: In educational settings, SARS-CoV-2 screening by RT-qPCR-based pooled testing with easily obtainable saliva samples is a feasible method to detect incident cases and observe transmission dynamics.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00362-X/fulltext

Immunological evaluation of an inactivated SARS-CoV-2 vaccine in rhesus macaques

Abstract

Because of the relatively limited understanding of COVID-19 pathogenesis, immunological analysis for vaccine development is needed. Mice and macaques were immunized with an inactivated SARS-CoV-2 vaccine prepared by two inactivators. Various immunological indexes were tested, and viral challenges were performed on day 7 or 150 after booster immunization in monkeys. This inactivated SARS-CoV-2 vaccine was produced by sequential inactivation with formaldehyde followed by propiolactone. The various antibody responses and specific T cell responses to different viral antigens elicited in immunized animals were maintained for longer than 150 days. This comprehensive immune response could effectively protect vaccinated macaques by inhibiting viral replication in macaques and substantially alleviating immunopathological damage, and no clinical manifestation of immunopathogenicity was observed in immunized individuals during viral challenge. This candidate inactivated vaccine was identified as being effective against SARS-CoV-2 challenge in rhesus macaques.

Reference

https://www.cell.com/molecular-therapy-family/methods/fulltext/S2329-0501(21)00131-5

Single cell transcriptome identifies FCGR3B upregulated subtype of alveolar macrophages in patients with critical COVID-19

Abstract

Understanding host cell heterogeneity is critical for unravelling disease mechanism. Utilizing large scale single-cell transcriptomics, multiple tissue specimens were analyzed from patients with life-threatening COVID-19 pneumonia, compared with healthy controls. A subtype of monocyte-derived alveolar macrophages (MoAM) were identified where genes associated with severe COVID-19 comorbidities are significantly upregulated in broncho-alveolar lavage fluid (BALF) of critical cases. FCGR3B consistently demarcated MoAM subset in different samples from severe COVID-19 cohorts and in CCL3L1-upregulated cells from nasopharyngeal swabs. *In silico* findings were validated by upregulation of FCGR3B in nasopharyngeal swabs of severe ICU COVID-19 cases, particularly in older patients and those with comorbidities. Additional lines of evidence from transcriptomic data and *in vivo* of severe COVID-19 cases suggest that FCGR3B may identify a specific subtype of MoAM in patients with severe COVID-19 that may present a novel biomarker for screening and prognosis as well as a potential therapeutic target.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00998-6

Publication Date: Aug 24, 2021

The structure of a dimeric form of SARS-CoV-2 polymerase

Abstract

The coronavirus SARS-CoV-2 uses an RNA-dependent RNA polymerase (RdRp) to replicate and transcribe its genome. Previous structures of the RdRp revealed a monomeric enzyme composed of the catalytic subunit nsp12, two copies of subunit nsp8, and one copy of subunit nsp7. Here an alternative, dimeric form of the enzyme was reported and its structure, at 5.5 Å resolution, was resolved. In this structure, the

two RdRps contain only one copy of nsp8 each and dimerize via their nsp7 subunits to adopt an antiparallel arrangement. It was speculated that the RdRp dimer facilitates template switching during production of sub-genomic RNAs.

Reference

https://www.nature.com/articles/s42003-021-02529-9

A non-enzymatic, isothermal strand displacement and amplification assay for rapid detection of SARS-CoV-2 RNA

Abstract

The current nucleic acid signal amplification methods for SARS-CoV-2 RNA detection heavily rely on the functions of biological enzymes which imposes stringent transportation and storage conditions, high cost and global supply shortages. Here, a non-enzymatic whole genome detection method based on a simple isothermal signal amplification approach is developed for rapid detection of SARS-CoV-2 RNA and potentially any types of nucleic acids regardless of their size. The assay, termed non-enzymatic isothermal strand displacement and amplification (NISDA), is able to quantify 10 RNA copies.μL−1. In 164 clinical oropharyngeal RNA samples, NISDA assay is 100 % specific, and it is 96.77% and 100% sensitive when setting up in the laboratory and hospital, respectively. The NISDA assay does not require RNA reverse-transcription step and is fast (<30 min), affordable, highly robust at room temperature (>1 month), isothermal (42 °C) and user-friendly, making it an excellent assay for broad-based testing.

Reference

https://www.nature.com/articles/s41467-021-25387-9

Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19

Abstract

Neutralizing autoantibodies against type I interferons (IFNs) have been found in some patients with critical coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, the

prevalence of these antibodies, their longitudinal dynamics across the disease severity scale, and their functional effects on circulating leukocytes remain unknown. Here, in 284 patients with COVID-19, type I IFN-specific autoantibodies were found in peripheral blood samples from 19% of patients with critical disease and 6% of patients with severe disease. No type I IFN autoantibodies were found in individuals with moderate disease. Longitudinal profiling of over 600,000 peripheral blood mononuclear cells using multiplexed single-cell epitope and transcriptome sequencing from 54 patients with COVID-19 and 26 non-COVID-19 controls revealed a lack of type I IFN-stimulated gene (ISG-I) responses in myeloid cells from patients with critical disease. This was especially evident in dendritic cell populations isolated from patients with critical disease producing type I IFN-specific autoantibodies. Moreover, we found elevated expression of the inhibitory receptor leukocyte-associated immunoglobulin-like receptor 1 (LAIR1) on the surface of monocytes isolated from patients with critical disease early in the disease course. LAIR1 expression is inversely correlated with ISG-I expression response in patients with COVID-19 but is not expressed in healthy controls. The deficient ISG-I response observed in patients with critical COVID-19 with and without type I IFN-specific autoantibodies supports a unifying model for disease pathogenesis involving ISG-I suppression through convergent mechanisms.

Reference

https://www.science.org/doi/10.1126/scitranslmed.abh2624

Publication Date: Aug 23, 2021

Characterization of SARS-CoV-2 and host entry factors distribution in a COVID-19 autopsy series

Abstract

Background: SARS-CoV-2 is a highly contagious virus that causes the disease COVID-19. It was recently reported that androgens regulate the expression of SARS-CoV-2 host entry factors ACE2 and TMPRSS2, and androgen receptor (AR) in lung epithelial cells. It was also demonstrated that the transcriptional repression of the AR enhanceosome inhibited SARS-CoV-2 infection *in vitro*.

Methods: To better understand the various sites of SARS-CoV-2 infection, and presence of host entry factors, the tissue distribution and localization of SARS-CoV-2 virus, viral replication, and host entry factors were extensively characterized in various anatomical sites sampled *via* autopsy. RNA *in-situ*-hybridization (RNA-ISH), immunohistochemistry (IHC) and quantitative reverse transcription polymerase chain reaction (qRT-PCR) approaches were applied. Histopathological changes in SARS-CoV-2 infected tissues were also assessed.

Results: SARS-CoV-2 virus and viral replication were detected in pulmonary tissues by RNA-ISH and IHC and a variety of non-pulmonary tissues including kidney, heart, liver, spleen, thyroid, lymph node, prostate, uterus, and colon by qRT-PCR. We observe heterogeneity in viral load and viral cytopathic effects among various organ systems, between individuals and within the same patient. In a patient with a history of kidney transplant and under immunosuppressant therapy, we observe an unusually high viral load in lung tissue by RNA-ISH, IHC and qRT-PCR. SARS-CoV-2 virus is also detected in this patent's kidney, liver and uterus. ACE2, TMPRSS2 and AR expression were found to overlap with the infection sites.

Conclusions: This study portrays the impact of dispersed SARS-CoV-2 infection in diverse organ systems, thereby facilitating avenues for systematic therapeutic approaches.

Reference

https://www.nature.com/articles/s43856-021-00025-z

Cryo-EM and antisense targeting of the 28-kDa frameshift stimulation element from the SARS-CoV-2 RNA genome

Abstract

Drug discovery campaigns against COVID-19 are beginning to target the SARS-CoV-2 RNA genome. The highly conserved frameshift stimulation element (FSE), required for balanced expression of viral proteins, is a particularly attractive SARS-CoV-2 RNA target. Here, a 6.9 Å resolution cryo-EM structure of the FSE (88 nucleotides, ~28 kDa) was presented and validated through an RNA nanostructure tagging method. The tertiary structure presents a topologically complex fold in which the 5′ end is threaded

through a ring formed inside a three-stem pseudoknot. Guided by this structure, we develop antisense oligonucleotides that impair FSE function in frameshifting assays and knock down SARS-CoV-2 virus replication in A549-ACE2 cells at 100 nM concentration.

Reference

https://www.nature.com/articles/s41594-021-00653-y

Factors associated with SARS-COV-2 infection in Bogotá, Colombia: Results from a large epidemiological surveillance study

Abstract

Background: Epidemiologic surveillance of COVID-19 is essential to collect and analyse data to improve public health decision making during the pandemic. There are few initiatives led by public-private alliances in Colombia and Latin America. The CoVIDA project contributed with RT-PCR tests for SARS-CoV-2 in mild or asymptomatic populations in Bogotá. The present study aimed to determine the factors associated with SARS-CoV-2 infection in working adults.

Methods: COVID-19 intensified sentinel epidemiological surveillance study, from April 18, 2020, to March 29, 2021. The study included people aged 18 years or older without a history of COVID-19. Two main occupational groups were included: healthcare and essential services workers with high mobility in the city. Social, demographic, and health-related factors were collected *via* phone survey. Afterwards, the molecular test was conducted to detect SARS-CoV-2 infection.

Findings: From the 58,638 participants included in the study, 3,310 (5·6%) had a positive result. A positive result was associated with the age group (18-29 years) compared with participants aged 60 or older, participants living with more than three cohabitants, living with a confirmed case, having no affiliation to the health system compared to those with social health security, reporting a very low socioeconomic status compared to those with higher socioeconomic status, and having essential occupations compared to healthcare workers.

Interpretation: The CoVIDA study showed the importance of intensified epidemiological surveillance to identify groups with increased risk of infection. These groups should be

prioritised in the screening, contact tracing, and vaccination strategies to mitigate the pandemic.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00040-5/fulltext

A SARS-CoV-2 antibody broadly neutralizes SARS-related coronaviruses and variants by coordinated recognition of a virus vulnerable site

Abstract

Potently neutralizing SARS-CoV-2 antibodies often target the spike protein receptor binding site (RBS), but the variability of RBS epitopes hampers broad neutralization of multiple sarbecoviruses and drifted viruses. Here, using humanized mice, an RBS antibody was identified with a germline VH gene that potently neutralized SARS-related coronaviruses including SARS-CoV and SARS-CoV-2 variants. X-ray crystallography revealed coordinated recognition by the heavy chain of non-RBS conserved sites and the light chain of RBS with a binding angle mimicking the ACE2 receptor. The minimum footprints in the hypervariable region of RBS contributed to the breadth of neutralization, which was enhanced by IgG3 class switching. The coordinated binding resulted in broad neutralization of SARS-CoV and emerging SARS-CoV-2 variants of concern. Low dose therapeutic antibody treatment in hamsters reduced the virus titers and morbidity during SARS-CoV-2 challenge. The structural basis for broadly neutralizing activity may inform the design of broad spectrum of therapeutics and vaccines.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00359-9

Repeat positive SARS-CoV-2 RNA testing in nursing home residents during the initial 9 months of the COVID-19 pandemic: An observational retrospective analysis

Abstract

Background: Nursing homes are high-risk COVID-19 settings with residents who are typically older and have multiple comorbidities. SARS-CoV-2 testing occurs frequently in nursing homes, with public health guidance suggesting that repeat testing is generally not warranted in the 90 days following initial positive test results. Interpretation of repeat positive tests beyond 90 days is challenging and the consequences of decisions following these tests are significant.

Methods: A surveillance system for COVID-19 was utilized to identify Connecticut nursing home residents who tested positive for SARS-CoV-2 by RNA-based testing ≥ 90 days after initial positive results. Statewide nursing home testing data was analyzed over a 9-month period, from the first Connecticut nursing home case identified on March 15 through December 15, 2020, when nursing home COVID-19 vaccinations began in Connecticut.

Findings: 156 Residents (median age 75 years) were identified with positive RNA-based PCR tests occurring ≥90 days after an initial positive test. Residents with repeat positives tests represented approximately 2.6% (156/6,079) of nursing home residents surviving beyond 90 days of their initial SARS-CoV-2 diagnosis statewide since the start of the pandemic, with a median time to repeat positivity of 135 days (range 90–245 days). Deaths were reported in 12.8% (20/156) of residents following the repeat positive test, with 80% (16/20) having one or more intervening negative RT-PCR tests prior to the repeat positive test.

Interpretation: The analysis suggested that repeat positive testing in nursing home populations may exceed those reported in younger age groups. Repeat positive tests beyond 90 days may accompany severe outcomes, and should be prospectively investigated with genomic, virologic and additional data, when feasible. Data shed light on the duration of protective immunity following natural infection in this subset of largely elderly and medically frail individuals.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00046-6/fulltext

Human small intestinal infection by SARS-CoV-2 is characterized by a mucosal infiltration with activated CD8+ T cells

Abstract

The SARS-CoV-2 pandemic has so far claimed over three and a half million lives worldwide. Though the SARS-CoV-2 mediated disease COVID-19 has first been characterized by an infection of the upper airways and the lung, recent evidence suggests a complex disease including gastrointestinal symptoms. Even if a direct viral tropism of intestinal cells has recently been demonstrated, it remains unclear, whether gastrointestinal symptoms are caused by direct infection of the gastrointestinal tract by SARS-CoV-2 or whether they are a consequence of a systemic immune activation and subsequent modulation of the mucosal immune system. To better understand the cause of intestinal symptoms we analyzed biopsies of the small intestine from SARS-CoV-2 infected individuals. Applying qRT-PCR and immunohistochemistry, we detected SARS-CoV-2 RNA and nucleocapsid protein in duodenal mucosa. In addition, applying imaging mass cytometry and immunohistochemistry, histomorphological changes of the epithelium were identified, which were characterized by an accumulation of activated intraepithelial $CD8^+$ T cells as well as epithelial apoptosis and subsequent regenerative proliferation in the small intestine of COVID-19 patients. In summary, the findings indicated that intraepithelial $CD8^+$ T cells are activated upon infection of intestinal epithelial cells with SARS-CoV-2, providing one possible explanation for gastrointestinal symptoms associated with COVID-19.

Reference

https://www.nature.com/articles/s41385-021-00437-z

mRNA-1273 protects against SARS-CoV-2 beta infection in nonhuman primates

Abstract

B.1.351 is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant most resistant to antibody neutralization. It was demonstrated how the dose and number of immunizations influence protection. Nonhuman primates received two doses of 30 or 100 μg of Moderna's mRNA-1273 vaccine, a single immunization of 30 μg, or no vaccine. Two doses of 100 μg of mRNA-1273 induced 50% inhibitory reciprocal serum dilution neutralizing antibody titers against live SARS-CoV-2 p.Asp614Gly and B.1.351 of 3,300 and 240, respectively. Higher neutralizing responses against B.1.617.2 were also observed after two doses compared to a single dose. After challenge with B.1.351, there was ~4- to 5-log10 reduction of viral subgenomic RNA and low to undetectable replication in bronchoalveolar lavages in the two-dose vaccine groups, with a 1-log10 reduction in nasal swabs in the 100-μg group. These data establish that a two-dose regimen of mRNA-1273 will be critical for providing upper and lower airway protection against major variants of concern.

Reference

https://www.nature.com/articles/s41590-021-01021-0

Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: A randomised, controlled, multinational, open-label meta-trial

Abstract

Background: Awake prone positioning has been reported to improve oxygenation for patients with COVID-19 in retrospective and observational studies, but whether it improves patient-centred outcomes is unknown. It was aimed to evaluate the efficacy of awake prone positioning to prevent intubation or death in patients with severe COVID-19 in a large-scale randomised trial.

Methods: In this prospective, a priori set up and defined, collaborative meta-trial of six randomised controlled open-label superiority trials, adults who required respiratory support with high-flow nasal cannula for acute hypoxaemic respiratory failure due to

COVID-19 were randomly assigned to awake prone positioning or standard care. Hospitals from six countries were involved: Canada, France, Ireland, Mexico, USA, Spain. Patients or their care providers were not masked to allocated treatment. The primary composite outcome was treatment failure, defined as the proportion of patients intubated or dying within 28 days of enrolment. The six trials are registered with ClinicalTrials.gov, NCT04325906, NCT04347941, NCT04358939, NCT04395144, NCT04391140, and NCT04477655.

Findings: Between April 2, 2020 and Jan 26, 2021, 1126 patients were enrolled and randomly assigned to awake prone positioning (n=567) or standard care (n=559). 1121 patients (excluding five who withdrew from the study) were included in the intention-to-treat analysis. Treatment failure occurred in 223 (40%) of 564 patients assigned to awake prone positioning and in 257 (46%) of 557 patients assigned to standard care (relative risk 0·86 [95% CI 0·75−0·98]). The hazard ratio (HR) for intubation was 0·75 (0·62−0·91), and the HR for mortality was 0·87 (0·68−1·11) with awake prone positioning compared with standard care within 28 days of enrolment. The incidence of prespecified adverse events was low and similar in both groups.

Interpretation: Awake prone positioning of patients with hypoxaemic respiratory failure due to COVID-19 reduces the incidence of treatment failure and the need for intubation without any signal of harm. These results support routine awake prone positioning of patients with COVID-19 who require support with high-flow nasal cannula.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00356-8/fulltext

Epitope diversity of SARS-CoV-2 hyperimmune intravenous human immunoglobulins and neutralization of variants of concern

Abstract

Hyperimmune immunoglobulin (hCoV-2IG) generated from SARS-CoV-2 convalescent plasma (CP) are under evaluation in clinical trials. Here the antibody epitope repertoire, and virus neutralizing capacity of six hCoV-2IG batches as well as nine CP against SARS-CoV-2 and emerging variants of concern (VOCs) were explored. Epitope-mapping by gene-fragment phage display library spanning the SARS-CoV-2 spike

demonstrated broad recognition of multiple antigenic sites spanning the entire spike that was higher for hCoV-2IG than CP, with predominant binding to the fusion peptide. In the pseudovirus neutralization assay and in the wild-type SARS-CoV-2 PRNT assay, hCoV-2IG lots showed higher titers against the WA-1 strain compared with CP. Neutralization of VOCs were reduced to different extent by hCoV-2IG lots but were higher than CP. Significant reduction of hCoV-2IG binding was observed to RBD-E484K followed by RBD-N501Y (but not RBD-K417N). This study suggested that post-exposure treatment with hCoV-2IG could be preferable to CP.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00974-3

The neutralization potency of anti-SARS-CoV-2 therapeutic human monoclonal antibodies is retained against viral variants

Abstract

A wide range of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing monoclonal antibodies (mAbs) have been reported, most of which target the spike glycoprotein. Therapeutic implementation of these antibodies has been challenged by emerging SARS-CoV-2 variants harboring mutated spike versions. Consequently, re-assessment of previously identified mAbs is of high priority. Four previously selected mAbs targeting non-overlapping epitopes are now evaluated for binding potency to mutated RBD versions, reported to mediate escape from antibody neutralization. In vitro neutralization potencies of these mAbs, and two NTD-specific mAbs, are evaluated against two frequent SARS-CoV-2 variants of concern, the B.1.1.7 Alpha and the B.1.351 Beta. Furthermore, therapeutic potential of three selected mAbs was demonstrated by treatment of K18-human angiotensin-converting enzyme 2 (hACE2) transgenic mice 2 days post-infection with each virus variant. Thus, despite the accumulation of spike mutations, the highly potent MD65 and BL6 mAbs retain their ability to bind the prevalent viral mutants, effectively protecting against B.1.1.7 and B.1.351 variants.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01123-2

Spatiotemporal invasion dynamics of SARS-CoV-2 lineage B.1.1.7 emergence

Abstract

Understanding the causes and consequences of the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern is crucial to pandemic control yet difficult to achieve because they arise in the context of variable human behavior and immunity. The spatial invasion dynamics of lineage B.1.1.7 were investigated by jointly analyzing UK human mobility, virus genomes, and community-based polymerase chain reaction data. A multistage spatial invasion process was identified in which early B.1.1.7 growth rates were associated with mobility and asymmetric lineage export from a dominant source location, enhancing the effects of B.1.1.7's increased intrinsic transmissibility. It was further explored how B.1.1.7 spread was shaped by nonpharmaceutical interventions and spatial variation in previous attack rates. The findings showed that careful accounting of the behavioral and epidemiological context within which variants of concern emerge is necessary to interpret correctly their observed relative growth rates.

Reference

https://www.science.org/doi/10.1126/science.abj0113

Publication Date: Aug 19, 2021

A glycan gate controls opening of the SARS-CoV-2 spike protein

Abstract

SARS-CoV-2 infection is controlled by the opening of the spike protein receptor binding domain (RBD), which transitions from a glycan-shielded 'down' to an exposed 'up' state to bind the human angiotensin-converting enzyme 2 receptor and infect cells. While snapshots of the 'up' and 'down' states have been obtained by cryo-electron microscopy and cryo-electron tomagraphy, details of the RBD-opening transition evade experimental characterization. Here over 130 μs of weighted ensemble simulations of the fully glycosylated spike ectodomain allow us to characterize more than 300 continuous, kinetically unbiased RBD-opening pathways. Together with ManifoldEM analysis of cryo-electron microscopy data and biolayer interferometry experiments, we reveal a gating role for the N-glycan at position N343, which facilitates RBD opening.

Residues D405, R408 and D427 also participate. The atomic-level characterization of the glycosylated spike activation mechanism provided herein represents a landmark study for ensemble pathway simulations and offers a foundation for understanding the fundamental mechanisms of SARS-CoV-2 viral entry and infection.

Reference

https://www.nature.com/articles/s41557-021-00758-3

Effects of a large-scale social media advertising campaign on holiday travel and COVID-19 infections: A cluster randomized controlled trial

Abstract

During the Coronavirus Disease 2019 (COVID-19) epidemic, many health professionals used social media to promote preventative health behaviors. A randomized controlled trial of the effect of a Facebook advertising campaign was conducted, consisting of short videos recorded by doctors and nurses to encourage users to stay at home for the Thanksgiving and Christmas holidays (NCT04644328 and AEARCTR-0006821). Counties were randomly assigned to high intensity ($n = 410$ (386) at Thanksgiving (Christmas)) or low intensity ($n = 410$ (381)). The intervention was delivered to a large fraction of Facebook subscribers in 75% and 25% of randomly assigned zip codes in high- and low-intensity counties, respectively. In total, 6,998 (6,716) zip codes were included, and 11,954,109 (23,302,290) users were reached at Thanksgiving (Christmas). The first two primary outcomes were holiday travel and fraction leaving home, both measured using mobile phone location data of Facebook users. Average distance traveled in high-intensity counties decreased by −0.993 percentage points (95% confidence interval (CI): –1.616, −0.371; $P = 0.002$) for the 3 days before each holiday compared to low-intensity counties. The fraction of people who left home on the holiday was not significantly affected (adjusted difference: 0.030; 95% CI: −0.361, 0.420; $P = 0.881$). The third primary outcome was COVID-19 infections recorded at the zip code level in the 2-week period starting 5 days after the holiday. Infections declined by 3.5% (adjusted 95% CI: −6.2%, −0.7%; $P = 0.013$) in intervention compared to control zip codes. Social media messages recorded by health professionals before the winter holidays in the United States led to a significant reduction in holiday travel and subsequent COVID-19 infections.

Reference

https://www.nature.com/articles/s41591-021-01487-3

Fine-grained data reveal segregated mobility networks and opportunities for local containment of COVID-19

Abstract

Deriving effective mobility control measures is critical for the control of COVID-19 spreading. In response to the COVID-19 pandemic, many countries and regions implemented travel restrictions and quarantines to reduce human mobility and thus reduce virus transmission. But since human mobility decreased heterogeneously, we lack empirical evidence of the extent to which the reductions in mobility alter the way people from different regions of cities are connected, and what containment policies could complement mobility reductions to conquer the pandemic. Here, individual movements in 21 of the most affected counties in the United States were examined, showing that mobility reduction leads to a segregated place network and alters its relationship with pandemic spread. The findings suggested localized area-specific policies, such as geo-fencing, as viable alternatives to city-wide lockdown for conquering the pandemic after mobility was reduced.

Reference

https://www.nature.com/articles/s41598-021-95894-8

Tissue-specific expression of the SARS-CoV-2 receptor, angiotensin-converting enzyme 2, in mouse models of chronic kidney disease

Abstract

Elevated angiotensin-converting enzyme 2 (ACE2) expression in organs that are potential targets of severe acute respiratory syndrome coronavirus 2 may increase the risk of coronavirus disease 2019 (COVID-19) infection. Previous reports show that ACE2 alter its tissue-specific expression patterns under various pathological conditions, including renal diseases. Here, changes in pulmonary ACE2 expression were examined in two mouse chronic kidney disease (CKD) models: adenine-induced (adenine mice) and aristolochic acid-induced (AA mice). It was also investigated changes in pulmonary ACE2 expression due to renin–angiotensin system (RAS) blocker (olmesartan)

treatment in these mice. Adenine mice showed significant renal functional decline and elevated blood pressure, compared with controls. AA mice also showed significant renal functional decline, compared with vehicles; blood pressure did not differ between groups. Renal ACE2 expression was significantly reduced in adenine mice and AA mice; pulmonary expression was unaffected. Olmesartan attenuated urinary albumin excretion in adenine mice, but did not affect renal or pulmonary ACE2 expression levels. The results suggested that the risk of COVID-19 infection may not be elevated in patients with CKD because of their stable pulmonary ACE2 expression. Moreover, RAS blockers can be used safely in treatment of COVID-19 patients with CKD.

Reference

https://www.nature.com/articles/s41598-021-96294-8

SARS-CoV-2 infection initiates interleukin-17-enriched transcriptional response in different cells from multiple organs

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has emerged as a pandemic. Paucity of information concerning the virus and therapeutic interventions have made SARS-CoV-2 infection a genuine threat to global public health. Therefore, there is a growing need for understanding the molecular mechanism of SARS-CoV-2 infection at cellular level. To address this, we undertook a systems biology approach by analyzing publicly available RNA-seq datasets of SARS-CoV-2 infection of different cells and compared with other lung pathogenic infections. Our study identified several key genes and pathways uniquely associated with SARS-CoV-2 infection. Genes such as interleukin (IL)-6, CXCL8, CCL20, CXCL1 and CXCL3 were upregulated, which in particular regulate the cytokine storm and IL-17 signaling pathway. Of note, SARS-CoV-2 infection strongly activated IL-17 signaling pathway compared with other respiratory viruses. Additionally, this transcriptomic signature was also analyzed to predict potential drug repurposing and small molecule inhibitors. In conclusion, our comprehensive data analysis identifies key molecular pathways to reveal underlying pathological etiology and potential therapeutic targets in SARS-CoV-2 infection.

Reference

https://www.nature.com/articles/s41598-021-96110-3

Towards the sustainable discovery and development of new antibiotics

Abstract

An ever-increasing demand for novel antimicrobials to treat life-threatening infections caused by the global spread of multidrug-resistant bacterial pathogens stands in stark contrast to the current level of investment in their development, particularly in the fields of natural-product-derived and synthetic small molecules. New agents displaying innovative chemistry and modes of action are desperately needed worldwide to tackle the public health menace posed by antimicrobial resistance. Here, the consortium presents a strategic blueprint to substantially improve our ability to discover and develop new antibiotics. Both short-term and long-term solutions were proposed to overcome the most urgent limitations in the various sectors of research and funding, aiming to bridge the gap between academic, industrial and political stakeholders, and to unite interdisciplinary expertise in order to efficiently fuel the translational pipeline for the benefit of future generations.

Reference

https://www.nature.com/articles/s41570-021-00313-1

Activation or exhaustion of $CD8^+$ T cells in patients with COVID-19

Abstract

In addition to $CD4^+$ T cells and neutralizing antibodies, $CD8^+$ T cells contribute to protective immune responses against SARS-CoV-2 in patients with coronavirus disease 2019 (COVID-19), an ongoing pandemic disease. In patients with COVID-19, $CD8^+$ T cells exhibiting activated phenotypes are commonly observed, although the absolute number of $CD8^+$ T cells is decreased. In addition, several studies have reported an upregulation of inhibitory immune checkpoint receptors, such as PD-1, and the expression of exhaustion-associated gene signatures in $CD8^+$ T cells from patients with COVID-19. However, whether $CD8^+$ T cells are truly exhausted during COVID-19 has been a controversial issue. In the present review, the current understanding of $CD8^+$ T-cell exhaustion was summarized and the available knowledge was described on the

phenotypes and functions of $CD8^+$ T cells in the context of activation and exhaustion. Recent reports were also summarized regarding phenotypical and functional analyses of SARS-CoV-2-specific $CD8^+$ T cells and discuss long-term SARS-CoV-2-specific $CD8^+$ T-cell memory.

Reference

https://www.nature.com/articles/s41423-021-00750-4

Profile of humoral and cellular immune responses to single doses of BNT162b2 or ChAdOx1 nCoV-19 vaccines in residents and staff within residential care homes (VIVALDI): An observational study

Abstract

Background: Residents of long-term care facilities (LTCFs) have been prioritised for COVID-19 vaccination because of the high COVID-19 mortality in this population. Several countries have implemented an extended interval of up to 12 weeks between the first and second vaccine doses to increase population coverage of single-dose vaccination. It was aimed to assess the magnitude and quality of adaptive immune responses following a single dose of COVID-19 vaccine in LTCF residents and staff.

Methods: From the LTCFs participating in the ongoing VIVALDI study (ISRCTN14447421), staff and residents who had received a first dose of COVID-19 vaccine (BNT162b2 [tozinameran] or ChAdOx1 nCoV-19), had pre-vaccination and post-vaccination blood samples (collected between Dec 11, 2020, and Feb 16, 2021), and could be linked to a pseudoidentifier in the COVID-19 Data Store were included in our cohort. Past infection with SARS-CoV-2 was defined on the basis of nucleocapsid-specific IgG antibodies being detected through a semiquantitative immunoassay, and participants who tested positive on this assay after but not before vaccination were excluded from the study. Processed blood samples were assessed for spike-specific immune responses, including spike-specific IgG antibody titres, T-cell responses to spike protein peptide mixes, and inhibition of ACE2 binding by spike protein from four variants of SARS-CoV-2 (the original strain as well as the B.1.1.7, B.1.351, and P.1 variants). Responses before and after vaccination were compared on the basis of age, previous infection status, role (staff or resident), and time since vaccination.

Findings: The cohort comprised 124 participants from 14 LTCFs: 89 (72%) staff (median age 48 years [IQR 35·5–56]) and 35 (28%) residents (87 years [77–90]). Blood samples were collected a median 40 days (IQR 25–47; range 6–52) after vaccination. 30 (24%) participants (18 [20%] staff and 12 [34%] residents) had serological evidence of previous SARS-CoV-2 infection. All participants with previous infection had high antibody titres following vaccination that were independent of age (rs=0·076, p=0·70). In participants without evidence of previous infection, titres were negatively correlated with age (rs=–0·434, p<0·0001) and were 8·2-times lower in residents than in staff. This effect appeared to result from a kinetic delay antibody generation in older infection-naive participants, with the negative age correlation disappearing only in samples taken more than 42 days post-vaccination (rs=–0·207, p=0·20; n=40), in contrast to samples taken after 0–21 days (rs=–0·774, p=0·0043; n=12) or 22–42 days (rs=–0·437, p=0·0034; n=43). Spike-specific cellular responses were similar between older and younger participants. In infection-naive participants, antibody inhibition of ACE2 binding by spike protein from the original SARS-CoV-2 strain was negatively correlated with age (rs=–0·439, p<0·0001), and was significantly lower against spike protein from the B.1.351 variant (median inhibition 31% [14–100], p=0·010) and the P.1 variant (23% [14–97], p<0·0001) than against the original strain (58% [27–100]). By contrast, a single dose of vaccine resulted in around 100% inhibition of the spike–ACE2 interaction against all variants in people with a history of infection.

Interpretation: History of SARS-CoV-2 infection impacts the magnitude and quality of antibody response after a single dose of COVID-19 vaccine in LTCF residents. Residents who are infection-naive have delayed antibody responses to the first dose of vaccine and should be considered for an early second dose where possible.

Reference

https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(21)00168-9/fulltext

COVID-19 vaccine strategies for Aotearoa New Zealand: A mathematical modelling study

Abstract

Background: COVID-19 elimination measures, including border closures have been applied in New Zealand. The potential effect of vaccination programmes have modelled for opening borders.

Methods: A deterministic age-stratified Susceptible, Exposed, Infectious, Recovered (SEIR) model were used. Spread was minimised by varying the age-stratified vaccine allocation to find the minimum herd immunity requirements (the effective reproduction number Reff<1 with closed borders) under various vaccine effectiveness (VE) scenarios and R0 values. Two-year open-border simulations were run for two vaccine strategies: minimising Reff and targeting high-risk groups.

Findings: Targeting of high-risk groups will result in lower hospitalisations and deaths in most scenarios. Reaching the herd immunity threshold (HIT) with a vaccine of 90% VE against disease and 80% VE against infection requires at least 86•5% total population uptake for R0=4•5 (with high vaccination coverage for 30–49-year-olds) and 98•1% uptake for R0=6. In a two-year open-border scenario with 10 overseas cases daily and 90% total population vaccine uptake (including 0–15 year olds) with the same vaccine, the strategy of targeting high-risk groups is close to achieving HIT, with an estimated 11,400 total hospitalisations (peak 324 active and 36 new daily cases in hospitals), and 1,030 total deaths.

Interpretation: Targeting high-risk groups for vaccination will result in fewer hospitalisations and deaths with open borders compared to targeting reduced transmission. With a highly effective vaccine and a high total uptake, opening borders will result in increasing cases, hospitalisations, and deaths. Other public health and social measures will still be required as part of an effective pandemic response.

Reference

https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(21)00165-6/fulltext

The impact of spike N501Y mutation on neutralizing activity and RBD binding of SARS-CoV-2 convalescent serum

Abstract

Background: Several SARS-CoV-2 lineages with spike receptor binding domain (RBD) N501Y mutation have spread globally. The impact of N501Y was evaluated on neutralizing activity of COVID-19 convalescent sera and on anti-RBD IgG assays.

Methods: The susceptibility to neutralization by COVID-19 patients' convalescent sera from Hong Kong were compared between two SARS-CoV-2 isolates (B117-1/B117-2) from the α-variant with N501Y and 4 non-N501Y isolates. The effect of N501Y on antibody binding was assessed. The performance of commercially-available IgG assays was determined for patients infected with N501Y variants.

Findings: The microneutralization antibody (MN) titers of convalescent sera from 9 recovered COVID-19 patients against B117-1 (geometric mean titer[GMT], 80; 95% CI, 47–136) were similar to those against the non-N501Y viruses. However, MN titer of these serum against B117-2 (GMT, 20; 95% CI, 11–36) was statistically significantly reduced when compared with non-N501Y viruses ($P < 0.01$; one-way ANOVA). The difference between B117-1 and B117-2 was confirmed by testing 60 additional convalescent sera. B117-1 and B117-2 differ by only 3 amino acids (nsp2-S512Y, nsp13-K460R, spike-A1056V). Enzyme immunoassay using 272 convalescent sera showed reduced binding of anti-RBD IgG to N501Y or N501Y-E484K-K417N when compared with that of wild-type RBD (mean difference: 0.1116 and 0.5613, respectively; one-way ANOVA). Of 7 anti-N-IgG positive sera from patients infected with N501Y variants (collected 9-14 days post symptom onset), 6 (85.7%) tested negative for a commercially-available anti-S1-IgG assay.

Interpretation: The importance of using a panel of viruses within the same lineagewas highlighted to determine the impact of virus variants on neutralization. Furthermore, clinicians should be aware of the potential reduced sensitivity of anti-RBD IgG assays.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00337-6/fulltext

Neutralisation titres against SARS-CoV-2 are sustained 6 months after onset of symptoms in individuals with mild COVID-19

Abstract

Background: Given the importance of neutralizing antibodies in protection against SARS-CoV-2 infection, it is critical to assess neutralization persistence long-term following recovery. This study investigated neutralization titres against SARS-CoV-2 up to 6 months post-symptom onset in individuals with mild COVID-19.

Methods: Plasma neutralization titres in convalescent COVID-19 individuals were determined at baseline and 6 months post-symptom onset using a cell culture infectious SARS-CoV-2 assay. Total SARS-CoV-2 spike-specific IgG and IgA binding was measured using a lectin capture ELISA and compared between timepoints and correlated to neutralizing titres.

Findings: All 48 convalescent COVID-19 individuals were found to have detectable SARS-CoV-2 50% inhibitory dilution neutralisation titres (ID50) at baseline and 6 months post-symptom onset with mean ID50 of 1/943 and 1/411, respectively. SARS-CoV-2 neutralisation titres peaked within 1-2 months post-symptom onset. However, 50% of individuals showed comparable ID50 at baseline and 6 months post-symptom onset. Both SARS-CoV-2 spike-specific IgG and IgA levels correlated well with neutralising titres. IgG binding was found to be sustained up to 6 months post-symptom onset, whereas IgA levels declined.

Interpretation: This study demonstrates durability of SARS-CoV-2 spike-specific IgG and neutralisation responses following recovery from mild COVID-19. Thus, all subjects included in this study might potentially have protective levels of neutralising antibodies 6 months post-symptom onset. This study also demonstrates a relationship between spike-specific IgA and neutralisation decline, with implications for long-term protection against SARS-CoV-2 infection.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00312-1/fulltext

REPORT

Publication Date: Aug 20, 2021

Masitinib is a broad coronavirus 3CL inhibitor that blocks replication of SARS-CoV-2

Abstract

There is an urgent need for antiviral agents that treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A library of 1900 clinically safe drugs was screened against OC43, a human beta coronavirus that causes the common cold, and evaluated the top hits against SARS-CoV-2. Twenty drugs significantly inhibited replication of both viruses in cultured human cells. Eight of these drugs inhibited the activity of the SARS-CoV-2 main protease, 3CLpro, with the most potent being masitinib, an orally bioavailable tyrosine kinase inhibitor. X-ray crystallography and biochemistry show that masitinib acts as a competitive inhibitor of 3CLpro. Mice infected with SARS-CoV-2 and then treated with masitinib showed >200-fold reduction in viral titers in the lungs and nose, as well as reduced lung inflammation. Masitinib was also effective in vitro against all tested variants of concern (B.1.1.7, B.1.351, and P.1).

Reference

https://www.science.org/doi/10.1126/science.abg5827