新型冠状病毒信息简报

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上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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1. 2020 年 7 月 9 日疫情

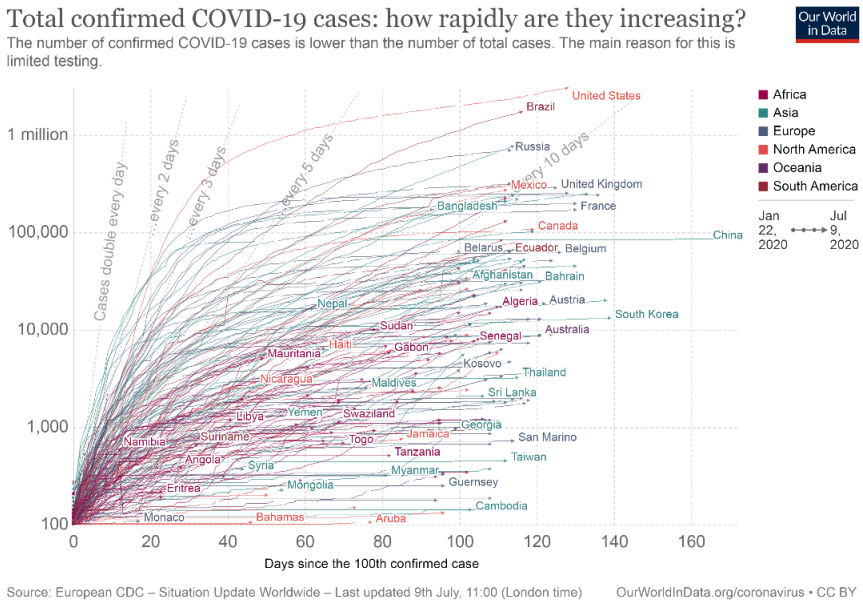
数据来源：WHO

发布时间：2020 年 7 月 9 日北京时间下午 4 点

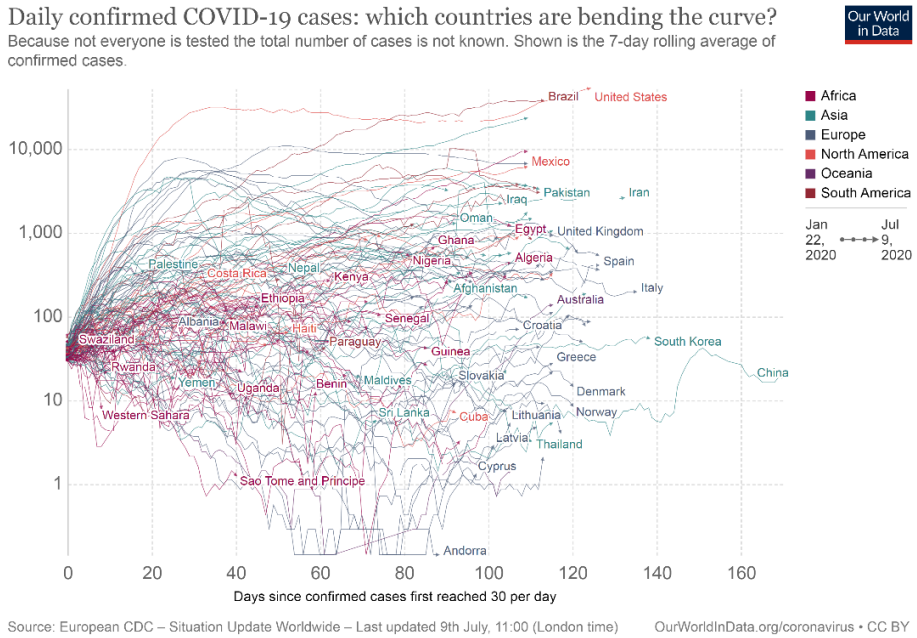
链接：https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

根据 WHO 提供的数据，2020 年 7 月 9 日全球累计确诊新型冠状病毒病人 **11874226** 例，当日新增确诊 **204967** 例，累计死亡 **545481** 例，当日新增死亡 5575。

中国累计确诊 85399 例，累计死亡 4648 例，当日新增确诊 33 例，新增死亡 0 例。



重点国家确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases，数据截止 7 月 10 日北京时间下午 2 点）



重点国家每日新增确诊数量曲线（https://ourworldindata.org/covid-

cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases，数据截止 7 月 10 日北京时间下午 2 点）

全国新型冠状病毒肺炎新增确诊病例分布图（7 月 9 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 中国海关总署：从厄瓜多尔冻南美白虾外包装检出新冠病毒

北京日报于 7 月 10 日报道了海关总署对进口冷链食品开展了新冠病毒风险进行检测，截止 7 月 9 日 24 时，全国海关共抽样检测样本 227934 个，其中产品样本 43964 个，内外包装样本 147568 个，环境样本 36402 个。并分别从大连和厦门入关的厄瓜多尔冻南美白虾外包装检出新冠病毒。海关总署已经暂停厄瓜多尔相关企业产品的进口，对暂扣的货物采取退货、销毁等处理措施

链接：http://www.xinhuanet.com/politics/2020-07/10/c_1126222032.htm

3. 根据 3 月 23 到 5 月 3 日之间对美国 6 个不同地点的血清学检测表明美国真实感染人数可能是报道感染人数的 10 倍

Seroprevalence of Antibodies to SARS-CoV-2 in Six Sites in the United States, March 23-May 3, 2020

根据美国疾控中心联合商业临床检测公司对 3 月 23 到 5 月 3 日之间对美国 6 个不同临床检测点的剩余血进行了 SARS-CoV-2 的血清学检测，检测结果表明真实感染人数可能是报道感染人数的 10 倍。

CDC 报道链接:

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/commercial-lab-surveys.html

该研究的预印本文章链接：

https://www.medrxiv.org/content/10.1101/2020.06.25.20140384v1.full.pdf

该研究对 6 个州的 6 个不同检测点的商业临床检测公司在 3 月 23 到 5 月 3 日间剩余下来的血样（这些血样来源于进行常规临床检测比如血脂检测和临床管理的病人）进行了 COVID-19 的抗体检测。研究者们发现血清学阳性的比率是当时报道的病例数的 10 倍。

Findings: We tested 11,933 residual clinical specimens. We estimate that from 1.1% of persons in the Puget Sound to 6.9% in New York City (collected March 23-April 1) had detectable antibodies. Estimates ranged from 1.9% in south Florida to 4.9% in Connecticut with specimens collected during intervals from April 6-May 3. Six to 24 times more infections were estimated per site with seroprevalence than with case report data.

4. 美国国立卫生研究员 NIH 宣布了一个用来检测 COVID-19 疫苗和其他防治方法的临床试验网络

NIH launches clinical trials network to test COVID-19 vaccines and other prevention tools

链接：https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trials-network-test-covid-19-vaccines-other-prevention-tools

根据美国国立卫生研究院（NIH）官方网站 7 月 8 日的消息。美国国立卫生研究院的国家过敏和传染病研究所（NIAID），建立了一个新的临床试验网络。该临床试验网络旨在招募成千上万的志愿者到大型的临床试验中测试一系列不同的针对 COVID-19 的在研疫苗和的单克隆抗体。

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, has established a new clinical trials network that aims to enroll thousands of volunteers in large-scale clinical trials testing a variety of investigational vaccines and monoclonal antibodies intended to protect people from COVID-19.

5. 西班牙 SARS-CoV-2 流行率(ENE-COVID)：基于全国人群的血清流行病学研究

Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study

来源：The Lancet

发布时间：2020-07-06

链接：https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31483-5/fulltext

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DOI 或 PUBMED ID：https://doi.org/10.1016/S0140-6736(20)31483-5

编译者：宋张悦

中文摘要：

背景：西班牙是受 COVID-19 疫情影响最严重的欧洲国家之一。由于存在无症状感染病例，而且诊断测试有限，血清学调查是评估流行病程度的宝贵工具。这项以全国人口为基础的研究旨在评估西班牙国家和地区层面的 SARS-CoV-2 感染的血清感染情况。

方法：采用按省、市规模分层的两阶段随机抽样方法，从市户籍中选取 35,883 户，邀请所有居民参与。从 2020 年 4 月 27 日到 5 月 11 日，61,075 名参与者(75.1%的个人在选择的家庭户中)回答一份调查问卷，关于 COVID-19 历史症状和风险因素，收到一个即时抗体测试，如果同意，捐赠一份血液样本用于额外的化学发光微粒免疫测定。使用取样重量和分层后校

正 IgG 抗体的患病率，考虑到年龄组、性别和人口普查收入的无反应率差异。利用两种试验的结果，我们计算了一个血清阳性率范围，使特异性(两项测试均为阳性)或敏感性(两项测试其一为阳性)最大化。

发现：通过即时检测血清阳性率为 5.0% (95% CI 4.7-5.4)，通过免疫测定血清阳性率为 4.6%(4.3 - 5.0),特异性敏感性范围为 3.7%(3.3 - 4.0,两项测试均为阳性)至 6.2%(5.8-6.6，两项测试其一为阳性)，在性别上没有差异，10 岁以下儿童的血清亲合率较低(即时检测< 3.1%)。存在很大的地理差异，在马德里附近患病率较高(10%)，在沿海地区患病率较低(3%)。195 名在研究访问前 14 天以上 PCR 阳性的参与者血清亲和力范围为 87.6%(81.1 - 92.1；两项测试均呈阳性)至 91.8%(86.3 - 95.3；两项测试其一呈阳性)。在 7273 名嗅觉缺失或至少有三种症状的患者中，血清反应率从 15.3%(13.8 - 16.8)到 19.3%(17.7-21.0)不等。大约三分之一的血清阳性者无症状，范围从 21.9%(19.1-24.9)到 35.8%(33.1-38.5)。仅有 19.5%(16.3-23.2)的经即时检测和免疫测定均呈血清阳性的症状性参与者报告先前有经 PCR 检测。

解释：大多数西班牙人对 SARS-CoV-2 感染呈血清阴性，即使在热点地区也是如此。大多数经 PCR 确诊的病例都有可检测到的抗体，但相当一部分症状与 COVID-19 相符的人没有进行 PCR 检测，而且至少三分之一的血清学确诊的感染是无症状的。这些结果强调了维持公共卫生措施以避免新的流行病浪潮的必要性。

资金：西班牙卫生部、Carlos III 卫生研究所和西班牙国家卫生系统。

Abstract:

Background Spain is one of the European countries most affected by the COVID-19 pandemic. Serological surveys are a valuable tool to assess the extent of the epidemic, given the existence of asymptomatic cases and little access to diagnostic tests. This nationwide population-based study aims to estimate the seroprevalence of SARS-CoV-2 infection in Spain at national and regional level.

Methods 35 883 households were selected from municipal rolls using two-stage random sampling stratified by province and municipality size, with all residents invited to participate. From April 27 to May 11, 2020, 61 075 participants (75·1% of all contacted individuals within selected households) answered a questionnaire on history of symptoms compatible with COVID-19 and risk factors, received a point-of-care antibody test, and, if agreed, donated a blood sample for additional testing with a chemiluminescent microparticle immunoassay. Prevalences of IgG antibodies were adjusted using sampling weights and post-stratification to allow for differences in non-response rates based on age group, sex, and census-tract income. Using results for both tests, we calculated a seroprevalence range maximising either specificity (positive for both tests) or sensitivity (positive for either test).

Findings Seroprevalence was 5.0% (95% CI 4.7–5.4) by the point-of-care test and 4.6% (4.3–5.0) by immunoassay, with a specificity–sensitivity range of 3.7% (3.3–4.0; both tests positive) to 6.2% (5.8–6.6; either test positive), with no differences by sex and lower seroprevalence in children younger than 10 years (<3.1% by the point-of-care test). There was substantial geographical variability, with higher prevalence around Madrid (>10%) and lower in coastal areas (<3%). Seroprevalence among 195 participants with positive PCR more than 14 days before

the study visit ranged from 87.6% (81.1–92.1; both tests positive) to 91.8% (86.3–95.3; either test positive). In 7273 individuals with anosmia or at least three symptoms, seroprevalence ranged from 15.3% (13.8–16.8) to 19.3% (17.7–21.0). Around a third of seropositive participants were asymptomatic, ranging from 21.9% (19.1–24.9) to 35.8% (33.1–38.5). Only 19.5% (16.3–23.2) of symptomatic participants who were seropositive by both the point-of-care test and immunoassay reported a previous PCR test.

Interpretation The majority of the Spanish population is seronegative to SARS-CoV-2 infection, even in hotspot areas. Most PCR-confirmed cases have detectable antibodies, but a substantial proportion of people with symptoms compatible with COVID-19 did not have a PCR test and at least a third of infections determined by serology were asymptomatic. These results emphasize the need for maintaining public health measures to avoid a new epidemic wave.

Funding Spanish Ministry of Health, Institute of Health Carlos III, and Spanish National Health System.

6. 新的 SARS-CoV-2 特异性抗体和中和试验显示，在 COVID-19 期间广泛的体液免疫反应

Novel SARS-CoV-2 specific antibody and neutralization assays reveal wide range of humoral immune response during COVID-19

来源：medrxiv
发布时间：2020.07.08
文章链接：https://www.medrxiv.org/content/10.1101/2020.07.07.20148106v1
第一作者：Mikail Dogan
通讯作者：Derya Unutmaz
通讯作者单位：美国杰克逊基因医学实验室，康涅狄格州大学医学院免疫学系
DOI：https://doi.org/10.1101/2020.07.07.20148106
编译者：张怡
中文摘要：

在 SARS-CoV-2 (CoV-2)感染期间开发抗体保护是公共卫生和疫苗开发的迫切问题。我们开发了高灵敏度的 CoV-2 特异性抗体和中和试验。在所有 PCR+受试者中(n=87)均检测到效价大于 1:10 万的 CoV-2 刺突蛋白或核衣壳蛋白特异性 IgG 抗体，阴性对照中未检测到。同时检测到其他同型抗体(IgA、IgG1-4)。刺突蛋白伪型慢病毒(也被中和抗体(NAbs)阻断)，在稀释 1 万倍的 COVID-19 和康复期血浆中测定了 CoV-2 中和作用。与门诊病人或康复的血浆献血者相比，住院病人的抗体和中和效价高出 3000 倍。此外，在确诊 COVID-19 后捐献血浆的受试者，其滴度似乎较低。有趣的是，一些 COVID-19 患者还含有抗 SARS 刺突蛋白假病毒的 NAbs。这些结果显示了检测的高特异性和敏感性，这可能影响对 COVID-19 期间抗体反应的质量或持续时间的了解，以及确定潜在疫苗的有效性。

Abstract

Development of antibody protection during SARS-CoV-2 (CoV-2) infection is a pressing question for public health and for vaccine development. We developed highly sensitive CoV-2-specific antibody and neutralization assays. CoV-2 Spike protein or Nucleocapsid protein specific IgG antibodies at titers more than 1:100,000 were detectable in all PCR+ subjects (n=87) and were absent in the negative controls. Other isotype antibodies (IgA, IgG1-4) were also detected.

CoV-2 neutralization was determined in COVID-19 and convalescent plasma up to 10,000-fold dilution, using Spike protein pseudotyped lentiviruses, which was also blocked by neutralizing antibodies (NAbs). Hospitalized patients had up to 3000-fold higher antibody and neutralization titers compared to outpatients or convalescent plasma donors. Further, subjects who donated plasma further out from the diagnosis of COVID-19 appeared to have lower titers. Interestingly, some COVID-19 patients also contained NAbs against SARS Spike protein pseudovirus. Together these results demonstrate the high specificity and sensitivity of our assays, which may impact understanding the quality or duration of the antibody response during COVID-19 and in determining the effectiveness of potential vaccines.

7. 急性 COVID-19 患者恢复后的持续症状

Persistent Symptoms in Patients After Acute COVID-19

来源：JAMA

发布时间：2020-07-09

链接：

https://jamanetwork.com/journals/jama/fullarticle/2768351?guestAccessKey=692a5e20-fdc4-45b2-bdd4-b78dfc4dcd5f&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=070920

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中文摘要：

该文章评估了 143 名意大利 COVID-19 恢复后出院的患者的持续症状。患者在第一个 COVID-19 症状出现后平均 60.3（标准差，13.6）天进行评估；在评估时，只有 18（12.6%）完全没有任何与 COVID-19 相关的症状，而 32%有 1 或 2 个症状，55%有 3 个或更多症状。这些病人没有发烧或任何急性病的症状或体征。44.1%的患者生活质量恶化。恢复后仍有高比例的人报告疲劳（53.1%）、呼吸困难（43.4%）、关节痛（27.3%）和胸痛（21.7%）。

Abstract:

In Italy, a large proportion of patients with coronavirus disease 2019 (COVID-19) presented with symptoms (71.4% of 31 845 confirmed cases as of June 3, 2020).1 Common symptoms include cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, fatigue), gastrointestinal symptoms, and anosmia/dysgeusia.2-4 However, information is lacking on symptoms that persist after recovery. We assessed persistent symptoms in patients who were discharged from the hospital after recovery from COVID-19…

8. COVID-19 住院患者呼吸道微生物共感染特征分析

Characterization of Microbial Co-infections in the Respiratory Tract of

hospitalized COVID-19 patients
来源：medrxiv
发布时间：2020-07-05
链接：https://www.medrxiv.org/content/10.1101/2020.07.02.20143032v1
第一作者：Huanzi Zhong1, Yanqun Wang, Zhun Shi, Lu Zhang, Huahui Ren1, Weiqun He, Zhaoyong Zhang, Airu Zhu, Jingxian Zhao, Fei Xiao
通讯作者：Xun Xu, Yi-min Li, Junhua Li, Jincun Zhao
通讯作者单位：BGI-Shenzhen, Shenzhen 等等
DOI 或 PUBMED ID：
编译者：王玮
中文摘要：

背景：SARS-CoV-2 已导致 2019 年全球冠状病毒病（COVID-19）大流行。然而，呼吸道和其他受感染组织的微生物组成，以及它们对 COVID-19 不同程度疾病严重程度的患者的致病作用仍不清楚。

方法：在 2020 年 1 月 27 日至 2 月 26 日期间，在中国广东省收集了一系列临床标本（痰、鼻和喉拭子、肛拭子和粪便），其中包括 8 名轻症患者和 15 名重症患者（需要进入 ICU 和机械通气）。提取总 RNA，结合实验室诊断分析进行超深转录组测序。测定这些 COVID-19 患者的共感染率、患病率和微生物群落丰度。

结果：值得注意的是，84.6%的重症患者（11/13）出现呼吸道微生物共感染，测序发现，其中病毒和细菌共感染分别占 30.8%（4/13）和 69.2%（9/13）。另外，23.1%（3/13）的患者经细菌培养也证实了伯克霍尔德菌复合物（BCC）和白色葡萄球菌的细菌共感染。此外，在一名重症患者身上发现了一种具有时间依赖性的、继发性的多重毒力基因表达的新生隐球菌感染，这可能是他入院一个月后病情恶化和死亡的主要原因。

讨论：该研究发现，在住院的 COVID-19 患者中，SARS-CoV-2 和各种呼吸道病原微生物的共同感染模式与疾病严重程度有关。建议对 BCC 相关的医院感染进行检测和跟踪，以改进治疗方案，减少 SARS-CoV-2 感染住院患者的死亡。

Abstract:

Summary Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic of Coronavirus disease 2019 (COVID-19). However, microbial composition of the respiratory tract and other infected tissues, as well as their possible pathogenic contributions to varying degrees of disease severity in COVID-19 patients remain unclear.

Method Between January 27 and February 26, 2020, serial clinical specimens (sputum, nasal and throat swab, anal swab and feces) were collected from a cohort of hospitalized COVID-19 patients, including 8 mildly and 15 severely ill patients (requiring ICU admission and mechanical ventilation), in the Guangdong province, China. Total RNA was extracted and ultra-deep metatranscriptomic sequencing was performed in combination with laboratory diagnostic assays. Co-infection rates, the prevalence and abundance of microbial communities in these COVID-19 patients were determined.

Findings Notably, respiratory microbial co-infections were exclusively found in 84.6% of severely ill patients (11/13), among which viral and bacterial co-infections were detected by sequencing in 30.8% (4/13) and 69.2% (9/13) of the

patients, respectively. In addition, for 23.1% (3/13) of the patients, bacterial co-infections with Burkholderia cepacia complex (BCC) and Staphylococcus epidermidis were also confirmed by bacterial culture. Further, a time-dependent, secondary infection of B. cenocepacia with expressions of multiple virulence genes in one severely ill patient was demonstrated, which might be the primary cause of his disease deterioration and death one month after ICU admission.
Interpretation Our findings identified distinct patterns of co-infections with SARS-CoV-2 and various respiratory pathogenic microbes in hospitalized COVID-19 patients in relation to disease severity. Detection and tracking of BCC-associated nosocomial infections are recommended to improve the pre-emptive treatment regimen and reduce fatal outcomes of hospitalized patients infected with SARS-CoV-2.

9. 血脂水平与 COVID-19 风险的因果关系：孟德尔随机研究

Causally Associations of Blood Lipids Levels with COVID-19 Risk: Mendelian Randomization Study
链接：https://www.medrxiv.org/content/10.1101/2020.07.07.20147926v1
编译者：王玮

西安交通大学的研究者发现血脂异常与 COVID-19 的易感性有关，导致 COVID-19 感染的几率增高 27%（MR-IVW OR=1.27，95%CI:1.08～1.49，p 值=3.18×10-3）。此外，血液总胆固醇水平升高，COVID-19 易感性增加 14%（MR-IVW OR=1.14，95%CI:1.04～1.25，p 值=5.07×10-3）。基因分析表明 ABO 基因与总胆固醇相关，基因集分析发现免疫过程参与总胆固醇的风险效应。

10. 具有神经系统症状的 COVID-19 患者中高频率的脑脊液自身抗体

High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms
来源：medRxiv
发布时间：2020-07-06
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编译者：张鹏伟
中文摘要：
COVID-19 重症监护患者偶尔会出现神经系统症状。大多数脑脊液（CSF）样本中没有 SARS-CoV-2，这表明可能与包括自身免疫在内的其他机制有关。因此，我们确定了十一名患有无法解释的神经系统症状的重症 COVID-19 连续患者中是否存在抗神经胶质或抗神经胶质自身抗体。包括肌阵挛、颅神经受累、动眼神经障碍、谵妄、肌张力障碍和癫痫发作。大多数患者显示出 CSF 炎症迹象和神经丝轻链水平升高。所有患者在血清或脑脊液中都有抗神经元自身抗体，这些抗体是通过基于细胞的分析和小鼠脑切片上的间接免疫荧光来评估与中枢神

经系统疾病相关的细胞内和表面抗原。抗原包括临床上已确定的蛋白质，如 Yo 或 NMDA 受体，也包括脑切片上的各种特异性未确定表位。包括基底节、海马或嗅球的血管内皮细胞、星形细胞蛋白和神经鞘膜。在缺乏其他解释的情况下，针对大脑的自身抗体的出现频率很高，这表明与临床症状有因果关系，特别是与高兴奋性（肌阵挛、癫痫发作）有关。虽然一些潜在的自身抗原仍有待于将来的研究鉴定，但自身抗体的存在可以解释 COVID-19 多器官疾病的某些方面，并可指导选定病例的免疫治疗。

Abstract:
COVID-19 intensive care patients occasionally develop neurological symptoms. The absence of SARS-CoV-2 in most cerebrospinal fluid (CSF) samples suggests the involvement of further mechanisms including autoimmunity. We therefore determined whether anti-neuronal or anti-glial autoantibodies are present in eleven consecutive severely ill COVID-19 patients presenting with unexplained neurological symptoms. These included myoclonus, cranial nerve involvement, oculomotor disturbance, delirium, dystonia and epileptic seizures. Most patients showed signs of CSF inflammation and increased levels of neurofilament light chain. All patients had anti-neuronal autoantibodies in serum or CSF when assessing a large panel of autoantibodies against intracellular and surface antigens relevant for central nervous system diseases using cell-based assays and indirect immunofluorescence on murine brain sections. Antigens included proteins well-established in clinical routine, such as Yo or NMDA receptor, but also a variety of specific undetermined epitopes on brain sections. These included vessel endothelium, astrocytic proteins and neuropil of basal ganglia, hippocampus or olfactory bulb. The high frequency of autoantibodies targeting the brain in the absence of other explanations suggests a causal relationship to clinical symptoms, in particular to hyperexcitability (myoclonus, seizures). While several underlying autoantigens still await identification in future studies, presence of autoantibodies may explain some aspects of multi-organ disease in COVID-19 and can guide immunotherapy in selected cases.

11. 在血液转录组中疾病严重程度特异性中性粒细胞的特征可使 COVID-19 患者分层

Disease severity-specific neutrophil signatures in blood transcriptomes stratify COVID-19 patients

来源：medRxiv

发布时间：2020-07-08

链接：https://www.medrxiv.org/content/10.1101/2020.07.07.20148395v1.full.pdf

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中文摘要：

SARS-CoV-2 大流行目前正在导致世界各地越来越多的 COVID-19 患者。临床表现从无症状、轻度呼吸道感染、到严重的急性呼吸窘迫综合征、呼吸衰竭和死亡。关于严重病例中免疫系统失调的报告要求更好地描述和理解免疫系统的变化。文中作者描述了 39 名 COVID-19 患者和 10 名对照组的全血转录组，从而得出基于分子表型的数据分层。中性粒细胞活化相关特征在严重的患者组中显著富集，这在来自 30 名独立的第二队列的全血转录组以及来自 11 名 COVID-19 患者的第三队列的粒细胞样本中得到证实。将 COVID-19 血液转录组与从 11 种不同的病毒感染、炎症性疾病和独立对照样本中收集的 2600 多个样本进行比较，发现 COVID-19 具有高度特异性的转录组特征。此外，分层转录组数据可预测靶向宿主全身免疫反应失调的特异性候选药物。

Abstract

The SARS-CoV-2 pandemic is currently leading to increasing numbers of COVID-19 patients all over the world. Clinical presentations range from asymptomatic, mild respiratory tract infection, to severe cases with acute respiratory distress syndrome, respiratory failure, and death. Reports on a dysregulated immune system in the severe cases calls for a better characterization and understanding of the changes in the immune system. Here, we profiled whole blood transcriptomes of 39 COVID-19 patients and 10 control donors enabling a data-driven stratification based on molecular phenotype. Neutrophil activation52 associated signatures were prominently enriched in severe patient groups, which was corroborated in whole blood transcriptomes from an independent second cohort of 30 as well as in granulocyte samples from a third cohort of 11 COVID-19 patients. Comparison of COVID-19 blood transcriptomes with those of a collection of over 2,600 samples derived from 11 different viral infections, inflammatory diseases and independent control samples revealed highly specific transcriptome signatures for COVID-19. Further, stratified transcriptomes predicted patient subgroup-specific drug candidates targeting the dysregulated systemic immune response of the host.

12. 严重 COVID-19 患者中 SARS-CoV-2 特异性的功能受限的 T 细胞水平升高

High levels of SARS-CoV-2 specific T-cells with restricted functionality in patients with severe course of COVID-19

来源：medRxiv

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中文摘要：

感染 SARS-CoV-2 病人在疾病的严重程度上是具有一定的差异。文中研究者对不同严重程度的 COVID-19 患者中 SARS-CoV-2 特异性 T 细胞和抗体特征进行了分析。尽管严重的淋巴细胞减少影响所有主要的淋巴细胞亚群，但与恢复期患者相比，COVID-19 重症患者的 SARS-

CoV-2 特异性 T 细胞水平显著升高。SARS-CoV-2 特异性 CD4-T 细胞数目大于 CD8-T 细胞，其与血浆母细胞数量及 SARS-CoV-2 特异性 IgA 和 IgG 水平密切相关。与康复期患者不同，重症患者的 SARS-CoV-2 特异性 T 细胞在表型和功能上表现出明显的变化，这种变化在 CD4-T 细胞和 CD8-T 细胞中也较为显著。尽管在重症患者中强烈的诱导特异性免疫可以控制病毒复制，但为抵消肺部过度的免疫病理情况而需要限制特异性和一般免疫，这可能会导致其功能改变。

Abstract

Patients infected with SARS-CoV-2 differ in the severity of disease. In this study, SARS-CoV-2 specific T-cells and antibodies were characterized in patients with different COVID-19 related disease severity. Despite severe lymphopenia affecting all major lymphocyte subpopulations, patients with severe disease mounted significantly higher levels of SARS-CoV-2 specific T-cells as compared to convalescent individuals. SARS-CoV-2 specific CD4 T-cells dominated over CD8 T-cells and closely correlated with the number of plasma blasts and SARS-CoV-2 specific IgA- and IgG-levels. Unlike in convalescents, SARS-CoV-2 specific T-cells in patients with severe disease showed marked alterations in phenotypical and functional properties, which also extended to CD4 and CD8 T-cells in general. Given the strong induction of specific immunity to control viral replication in patients with severe disease, the functionally altered phenotype may result from the need for contraction of specific and general immunity to counteract excessive immunopathology in the lung.

13. 血液生物标志物评分可在诊断前十年识别出患有严重 COVID-19 的高风险人群：UK Biobank 中 105000 名成年人的代谢谱

Blood biomarker score identifies individuals at high risk for severe COVID-19 a decade prior to diagnosis: metabolic profiling of 105,000 adults in the UK Biobank

来源：medRxiv

发布时间：2020-07-03

链接：https://www.medrxiv.org/content/10.1101/2020.07.02.20143685v1

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DOI 或 PUBMED ID：https://doi.org/10.1101/2020.07.02.20143685

编译者：刘焕珍

中文摘要：

背景：识别严重 COVID-19 高危健康人群是全球卫生工作的重点。我们研究了通过高通量代谢组学测定的血液生物标志物是否可以预测血液采样后数年内重症肺炎和 COVID-19 住院的人群。

方法：利用核磁共振代谢组学对 2007-2010 年期间在英国生物库中收集的 105146 份血浆样本（年龄范围 39-70 岁）进行全面的生物标志物分析。测试的这些生物标志物是否与严重肺炎（2507 例，定义为住院诊断或平均 8.1 年随访期间死亡记录）和严重 COVID-19（195 例，定义为 2020 年 3 月中旬至 6 月中旬在医院诊断）的相关性。根据一半的研究人群得出了预测重症肺炎的多生物标志物评分，并在另一半人群中进行了验证。我们探讨了该生物标志物

评分与严重 COVID-19 风险的关系。
研究结果：具有严重 COVID-19 风险的生物标志物关联遵循总体模式，类似于具有严重肺炎风险的关联（相关系数 0.83）。多生物标志物评分由 25 种血液生物标志物组成，包括炎症蛋白、脂肪酸、氨基酸和先进的血脂测定，与严重肺炎的风险密切相关（比值比为 1.67 / SD [95％置信区间 1.59-1.76]；最高五分位值相对于最低五分位值个体的风险增加 3.8 倍）。多生物标志物评分还与严重 COVID-19 的风险相关（比值比为 1.33/SD[1.17－1.53]；最高五分位值个体是最低五分位风险的 2.5 倍），这些差异在调整体重指数、吸烟和现有的呼吸和心脏代谢疾病后仍然显著。模拟从血液取样到 COVID-19 的十年时间间隔，在 7-11 年后发生的严重肺炎事件与多生物标志物评分相关，幅度相似（比值比为 1.43/SD[1.29-1.59]；最高五分位数个体与最低五分位数个体的风险比是 2.6）。再加上今天的筛查方案，多生物标志物评分的关联度是重症肺炎短期风险的 3 倍（比值比为 2.21 / SD [1.95-2.50]；血液采样后的前 2 年中的事件分析中的最高五分位数是最低五分位数风险的 8.0 倍）。
解释：在英国生物库 10 年前的血液样本中，通过高通量代谢组学测量的多生物标志物评分表明存在严重 COVID-19 的风险。生物标志物变化的分子特征反映出严重 COVID-19 的风险与重症肺炎的风险相似，尤其是考虑到 COVID-19 大流行的时间滞后。生物标志物评分与严重肺炎的 2 年风险的关联性更大，这为筛选鉴定可能罹患严重 COVID-19 的高危人群提供了可能性。

Abstract:
Background: Identification of healthy people at high risk for severe COVID-19 is a global health priority. We investigated whether blood biomarkers measured by high-throughput metabolomics could be predictive of severe pneumonia and COVID-19 hospitalisation years after the blood sampling.
Methods: Nuclear magnetic resonance metabolomics was used to quantify a comprehensive biomarker profile in 105 146 plasma samples collected in the UK Biobank during 2007－2010 (age range 39－70). The biomarkers were tested for association with severe pneumonia (2507 cases, defined as diagnosis in hospital or death record occurring during a median of 8.1-year follow-up) and with severe COVID-19 (195 cases, defined as diagnosis in hospital between mid-March to mid-June 2020). A multi-biomarker score was derived for prediction of severe pneumonia based on half of the study population and validated in the other half. We explored how this biomarker score relates to the risk of severe COVID-19.
Findings: The biomarker associations with risk of severe COVID-19 followed an overall pattern similar to associations with risk of severe pneumonia (correlation 0.83). The multi-biomarker score, comprised of 25 blood biomarkers including inflammatory proteins, fatty acids, amino acids and advanced lipid measures, was strongly associated with risk of severe pneumonia (odds ratio 1.67 per SD [95% confidence interval 1.59－1.76]; 3.8-fold risk increase for individuals in upper vs lower quintile). The multi-biomarker score was also associated with risk of severe COVID-19 (odds ratio 1.33 per SD [1.17－1.53]; 2.5-fold risk for upper vs lower quintile) and remained significant when adjusting for body mass index, smoking, and existing respiratory and cardiometabolic diseases. Mimicking the decade lag from blood sampling to COVID-19, severe pneumonia events occurring after 7－11 years associated with the multi-biomarker score to a similar magnitude (odds ratio 1.43 per SD [1.29－

1.59]; 2.6-fold risk for upper vs lower quintile) as for severe COVID-19. Interpolating to a screening scenario today, the magnitude of association of the multi-biomarker score was 3 times higher for short-term risk of severe pneumonia (odds ratio 2.21 per SD [1.95–2.50]; 8.0-fold risk for upper vs lower quintile in analysis of events during first 2 years after blood sampling).
Interpretation: In decade-old blood samples from the UK Biobank, a multi-biomarker score measured by highthroughput metabolomics is indicative of the risk for severe COVID-19. The molecular signature of biomarker changes reflective of risk for severe COVID-19 is similar to that for severe pneumonia, in particular when accounting for the time lag to the COVID-19 pandemic. The even stronger association of the biomarker score with 2-year risk for severe pneumonia lends support to promising screening possibilities for identifying people at high risk for severe COVID-19.

14. IL-3 是 SARS-CoV-2 感染严重程度和预后的一个预测指标

Interleukin-3 is a predictive marker for severity and outcome during SARS-CoV-2 infections

链接：https://www.biorxiv.org/content/10.1101/2020.07.02.184093v1.full.pdf
编译者：张丽双
德国研究人员发现，IL-3 通过促进肺 $CD123^+$上皮细胞分泌 CXCL12 来招募抗病毒循环 pDC 进入气道，低血浆 IL-3（ <20 pg/ml）与 SARS-CoV-2 感染者重症和死亡增加有关。

15. 儿童多系统炎症综合征（MIS-C）全身炎症和抗体反应的研究

Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C)
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发布时间：2020-07-06
链接：https://www.medrxiv.org/content/10.1101/2020.07.04.20142752v1
第一作者：Conor Gruber
通讯作者：Dusan Bogunovic
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DOI 或 PUBMED ID：https://doi.org/10.1101/2020.07.04.20142752
编译者：刘焕珍
中文摘要：
最初，由严重急性呼吸系统综合症冠状病毒 2 型（SARS-CoV-2）引起的全球 COVID-19 暴发使儿童免于重症。然而，在最初的感染浪潮之后，据报道在 SARS-CoV-2 持续流行的地区出现了一种新型的高炎症性疾病。尽管其临床特征逐渐清晰，但其病理生理学尚不清楚。在此，我们报告了 8 例儿童多系统炎症综合征（MIS-C）的免疫图谱。我们记录所有 MIS-C 患者都有先前接触过 SARS-CoV-2 的证据，并具有正常的同种型转换和中和能力的抗体反应。我们进一步通过高维细胞因子检测法分析了分泌的免疫反应，该方法确定了炎症反应（IL-18 和 IL-6）、淋巴细胞和髓细胞趋化性和激活（CCL3，CCL4 和 CDCP1）以及粘膜免疫失调（IL-17A、CCL20、CCL28）的升高特征。外周血的质谱免疫分型显示 mDC1 和非经典单核细胞以及 NK 和 T 淋巴细胞的减少，这表明其渗入了受影响的组织。活化的髓系功能的标志物也很明显，包

括中性粒细胞和非经典单核细胞中 ICAM1 和 FcgR1 的上调，在自身炎症和自身免疫中有充分的证据表明抗原递呈和 Fc 介导的反应增强。最后，为了评估继发于感染的自身免疫反应的作用，我们分析了 MIS-C 血浆的自身抗原反应性，这揭示了已知的疾病相关自身抗体（anti-La）和识别内皮细胞、胃肠道和免疫细胞抗原的新候选物。所有患者均接受抗 IL-6R 抗体或 IVIG 治疗，使炎症标志物正常化，从而实现快速疾病解决追踪。

一句话总结：这项研究描绘了与 SARS-CoV-2 相关的新型儿科炎症综合征的细胞和血清学免疫功能障碍。

Abstract:

Initially, the global outbreak of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spared children from severe disease. However, after the initial wave of infections, clusters of a novel hyperinflammatory disease have been reported in regions with ongoing SARS-CoV-2 epidemics. While the characteristic clinical features are becoming clear, the pathophysiology remains unknown. Herein, we report on the immune profiles of eight Multisystem Inflammatory Syndrome in Children (MIS-C) cases. We document that all MIS-C patients had evidence of prior SARS-CoV-2 exposure, mounting an antibody response with normal isotype-switching and neutralization capability. We further profiled the secreted immune response by high-dimensional cytokine assays, which identified elevated signatures of inflammation (IL-18 and IL-6), lymphocytic and myeloid chemotaxis and activation (CCL3, CCL4, and CDCP1) and mucosal immune dysregulation (IL-17A, CCL20, CCL28). Mass cytometry immunophenotyping of peripheral blood revealed reductions of mDC1 and non-classical monocytes, as well as both NK- and T- lymphocytes, suggesting extravasation to affected tissues. Markers of activated myeloid function were also evident, including upregulation of ICAM1 and FcgR1 in neutrophil and non-classical monocytes, well-documented markers in autoinflammation and autoimmunity that indicate enhanced antigen presentation and Fc-mediated responses. Finally, to assess the role for autoimmunity secondary to infection, we profiled the auto-antigen reactivity of MIS-C plasma, which revealed both known disease-associated autoantibodies (anti-La) and novel candidates that recognize endothelial, gastrointestinal and immune-cell antigens. All patients were treated with anti- IL6R antibody or IVIG, which led to rapid disease resolution tracking with normalization of inflammatory markers.

One Sentence Summary: This study maps the cellular and serological immune dysfunction underlying a novel pediatric inflammatory syndrome associated with SARS-CoV-2.

16. 葡萄糖-6-磷酸脱氢酶（G6PD）缺乏在沙特阿拉伯的一家儿童医院中 COVID-19 儿童病人中呈现异常高比例

G6PD Deficiency Overrepresented Among Pediatric COVID-19 Cases in One Saudi Children Hospital

链接：https://www.medrxiv.org/content/10.1101/2020.07.08.20148700v1

沙特阿拉伯的一家医院发现儿童 COVID-19 病人中葡萄糖-6-磷酸脱氢酶（G6PD）缺乏的比例明显高于该地人群中葡萄糖-6-磷酸脱氢酶（G6PD）缺乏的比例。

Fluorescent spot test for glucose-6-phosphate dehydrogenase (G6PD) deficiency was performed in 5 boys and 14 girls who had confirmed COVID-19. Out of those, 4 (80%) boys and 5 (36%) girls were found to be G6PD deficient.

17. COVID-19 住院病人中的消化道症状

Digestive Manifestations in Patients Hospitalized with COVID-19
链接：https://www.medrxiv.org/content/10.1101/2020.07.07.20143024v1
美国南卡罗来纳州医科大学等单位对 36 个中心的 1992 位 COVID-19 病人进行了研究，发 COVID-19 病人中常见胃肠道系统症状以及肝功能测试不正常，不过觉大多数症状轻微，这些症状和更重的临床特征不相关。
Conclusions: Among patients hospitalized with COVID-19, gastrointestinal symptoms and liver test abnormalities were common but the majority were mild and their presence was not associated with a more severe clinical course.

18. 在致死性 COVID-19 病例中组织特异性的病毒耐受

Tissue-specific tolerance in fatal Covid-19
来源：medrxiv
发布时间：2020-07-04
链接:https://www.medrxiv.org/content/10.1101/2020.07.02.20145003v1
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通讯作者：David A Dorward, Christopher D Lucas
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编译者：蒋立春
宿主能成功地抵抗一个病原物可以是通过抗性或者耐受来实现，宿主要在抗微生物和免疫调节的策略之间进行优先选择。COVID-19 中的超炎反应和更差的临床结果相关。
地塞米松能减少危重 COVID-19 病人死亡提示炎症反应是病人的死亡原因之一。
我们还不知道这个有害的免疫反应是对 SARS-CoV-2 的存在需要加强抵抗的反应，还是为了增强耐受的一个独立的免疫病理过程。研究这们报告了 11 例致死性 COVID-19 病例中发现了主要集中于肺部和网状内皮组织系统的不正常的免疫反应，和病毒的存在没有明显的拓扑相关性，提示存在组织特异性的 SARS-CoV-2 耐受。
不管是在组织间还是组织内，在致死性 COVID-19 病例中的炎症和器官功能受累和广泛分布的 SARS-CoV-2 病毒 RNA 和蛋白的分布不一致。
在肺部发现了富含单核细胞和髓系细胞的脉管炎，有大量得巨噬细胞和单核细胞进入到肺实质。此外，在淋巴组织中发现了刻板的非正常的网状内皮组织反应（反应性血浆细胞增多和载铁巨噬細胞），这和淋巴组织中病毒的分布不相关联。
研究者们认为这些结果支持独立于病毒的病理性免疫反应可能是 COVID-19 的一个主要的致死机制。该研究支持对没有发生损伤的器官特异性的病毒耐受机制进行更好的研究和理解，将优先考虑靶向非正常的巨噬细胞和浆细胞反应的病毒耐受作为 COVID-19 治疗的策略。
Successful host defence against a pathogen can involve resistance or tolerance, with implications for prioritising either antimicrobial or immunomodulatory therapeutic approaches. Hyper-inflammation occurs in Covid-19 and is associated with worse outcomes. The efficacy of dexamethasone in preventing mortality in critical Covid-19 suggests that inflammation has a causal role in death. Whether this deleterious inflammation is primarily a direct response to the presence of

SARS-CoV-2 requiring enhanced resistance, or an independent immunopathologic process necessitating enhanced tolerance, is unknown. Here we report an aberrant immune response in fatal Covid-19, principally involving the lung and reticuloendothelial system, that is not clearly topologically associated with the virus, indicating tissue-specific tolerance of SARS-CoV-2. We found that inflammation and organ dysfunction in fatal Covid-19 did not map to the widespread tissue and cellular distribution of SARS-CoV-2 RNA and protein, both between and within tissues. A monocyte/myeloid-rich vasculitis was identified in the lung, along with an influx of macrophages/monocytes into the parenchyma. In addition, stereotyped abnormal reticulo-endothelial responses (reactive plasmacytosis and iron-laden macrophages) were present and dissociated from the presence of virus in lymphoid tissues. Our results support virus-independent immunopathology being one of the primary mechanisms underlying fatal Covid-19. This supports prioritising pathogen tolerance as a therapeutic strategy in Covid-19, by better understanding non-injurious organ-specific viral tolerance mechanisms and targeting aberrant macrophage and plasma cell responses.

19. 合成痘病毒 SARS-CoV-2 疫苗的开发

Development of a Synthetic Poxvirus-Based SARS-CoV-2 Vaccine

来源：biorxiv

发布时间：2020.07.02

文章链接：https://www.biorxiv.org/content/10.1101/2020.07.01.183236v1

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DOI：https://doi.org/10.1101/2020.07.01.183236

编译者：张怡

中文摘要：

改良牛痘安卡拉(MVA)是一种高度减毒的痘病毒载体，广泛用于研制传染病和癌症疫苗。作者开发了一种基于独特的三质粒系统的新型疫苗平台，以有效地从化学合成的 DNA 生成重组 MVA 载体。为了应对目前由 SARS 冠状病毒-2 (SARS-CoV-2)引起的全球大流行，作者利用这种新型疫苗平台快速合成了共表达 SARS-CoV-2 刺突蛋白和核衣壳抗原的完整合成 MVA (sMVA)载体，这两种免疫显性抗原涉及保护性免疫。用这些 sMVA 载体免疫的小鼠产生了 SARS-CoV-2 抗原特异性的体液和细胞免疫反应，包括有效的中和抗体。这些结果证明了一种基于合成 DNA 的新型疫苗平台的潜力，它可以有效地生成重组 MVA 载体，并快速开发一种多抗原的基于痘病毒的 SARS-CoV-2 候选疫苗。

Abstract

Modified Vaccinia Ankara (MVA) is a highly attenuated poxvirus vector that is widely used to develop vaccines for infectious diseases and cancer. We developed a novel vaccine platform based on a unique three-plasmid system to efficiently generate recombinant MVA vectors from chemically synthesized DNA. In response to the ongoing global pandemic caused by SARS coronavirus-2 (SARS-CoV-2), we used this novel vaccine platform to rapidly produce fully synthetic MVA (sMVA) vectors co-expressing SARS-CoV-2 spike and nucleocapsid antigens, two immunodominant

antigens implicated in protective immunity. Mice immunized with these sMVA vectors developed robust SARS-CoV-2 antigen-specific humoral and cellular immune responses, including potent neutralizing antibodies. These results demonstrate the potential of a novel vaccine platform based on synthetic DNA to efficiently generate recombinant MVA vectors and to rapidly develop a multi-antigenic poxvirus-based SARS-CoV-2 vaccine candidate.

20. 一种快速适应 SARS-CoV-2 的生物材料疫苗

A rapidly adaptable biomaterial vaccine for SARS-CoV-2

来源：bioRxiv

发布时间：2020-07-07

链接：https://www.biorxiv.org/content/10.1101/2020.07.07.192203v1

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DOI 或 PUBMED ID：https://www.biorxiv.org/content/10.1101/2020.07.07.192203v1

编译者：刘焕珍

中文摘要：

全球 COVID-19 大流行促使人们加快研究开发安全有效的疫苗。为了满足这一需求，我们利用了一种生物材料疫苗技术，该技术由介孔二氧化硅棒（MSR）组成，该技术可提供粒细胞-巨噬细胞集落刺激因子（GM-CSF）和佐剂的持续释放，以浓缩和成熟抗原提呈细胞。在这里，我们探讨了使用单磷酸脂 A（MPLA）作为佐剂，以 SARS-CoV-2 刺突蛋白 S1、S2、核衣壳蛋白（N）和受体结合域（RBD）作为靶抗原所引起的体液反应。在这些研究中，我们探讨了抗原剂量和疫苗制备与及时装载抗原的影响。单次注射 MSR 疫苗即使不使用增强剂，也能诱导对所提抗原的快速而强健的抗体滴度，并且来自接种动物的血清显示出对 SARS-CoV-2 假病毒的中和活性。总的来说，这些结果表明 MSR 疫苗系统在用于呈现 SARS-CoV-2 抗原时可以提供强有力的保护性免疫。

Abstract:

The global COVID-19 pandemic motivates accelerated research to develop safe and efficacious vaccines. To address this need, we leveraged a biomaterial vaccine technology that consists of mesoporous silica rods (MSRs) that provide a sustained release of granulocyte-macrophage colony-stimulating factor (GM-CSF) and adjuvants to concentrate and mature antigen-presenting cells at the vaccine site. Here we explored the humoral responses resulting from the use of monophosphoryl lipid A (MPLA) as the adjuvant and SARS-CoV-2 spike proteins S1, S2, the nucleocapsid (N) protein, and receptor binding domain (RBD) as the target antigens. The dose of antigen and impact of pre-manufacturing of vaccines as versus loading antigen just-in-time was explored in these studies. Single shot MSR vaccines induced rapid and robust antibody titers to the presented antigens, even without the use of a boost, and sera from vaccinated animals demonstrated neutralizing activity against a SARS-CoV-2 pseudovirus. Overall, these results suggest the MSR vaccine system may provide potent protective immunity when utilized to present SARS-CoV-2 antigens.

21. SARS 冠状病毒 RNA 合成复合物的荧光高通量筛选方法

A Fluorescence-based High Throughput-Screening assay for the SARS-CoV RNA synthesis complex

来源：bioRxiv

发布时间：2020-07-7

链接：https://www.biorxiv.org/content/10.1101/2020.07.07.192005v1

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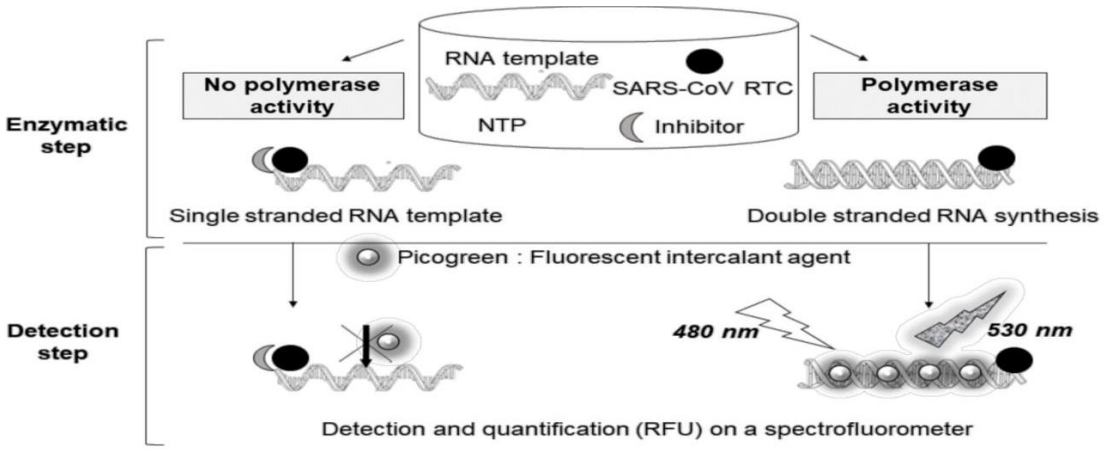
DOI 或 PUBMED ID：https://doi.org/10.1101/2020.07.07.192005

编译者：张鹏伟

中文摘要：

当前严重急性呼吸综合征冠状病毒 2 型（SARS-CoV-2）大流行揭示了一种新的病原体，其 RNA 合成机制与 SARS-CoV 高度同源（>96%aa 特性）。这种系统发育的相关性突出了保守复制酶的潜在用途，以发现针对这种重要病原体的抑制剂，这反过来又有助于科学防范新出现的病毒。在这里，我们报道了一种纯化的高活性 SARS 冠状病毒复制/转录复合物（RTC）的应用，建立了一种高通量筛选冠状病毒 RNA 合成抑制剂的方法。对 FDA 批准药物的一个小的（1520 个化合物）化学文库的筛选证明了我们的检测方法的稳健性，并将加速针对 SARS-CoV-2 的药物重新定位或新药物的发现。



Principle of SARS-CoV RNA synthesis detection by a fluorescence-based high throughput screening assay

Abstract:

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) emergence in 2003 introduced the first serious human coronavirus pathogen to an unprepared world. To control emerging viruses, existing successful anti(retro)viral therapies can inspire antiviral strategies, as conserved viral enzymes (eg., viral proteases and RNA-dependent RNA polymerases) represent targets of choice. Since 2003, much effort has been expended in the characterization of the SARS-CoV replication/transcription machinery. Until recently, a pure and highly active preparation of SARS-CoV recombinant RNA synthesis machinery was not available, impeding target-based high throughput screening of drug candidates against this viral family. The current Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-

CoV-2) pandemic revealed a new pathogen whose RNA synthesis machinery is highly (>96% aa identity) homologous to SARS-CoV. This phylogenetic relatedness highlights the potential use of conserved replication enzymes to discover inhibitors against this significant pathogen, which in turn, contributes to scientific preparedness against emerging viruses. Here, we report the use of a purified and highly active SARS-CoV replication/transcription complex (RTC) to set-up a high-throughput screening of Coronavirus RNA synthesis inhibitors. The screening of a small (1,520 compounds) chemical library of FDA-approved drugs demonstrates the robustness of our assay and will allow to speed-up drug repositioning or novel drug discovery against the SARS-CoV-2.

22. 皮质类固醇对纽约都会区 COVID-19 肺炎非重症监护病房患者的疗效

Efficacy of Corticosteroids in Non-Intensive Care Unit Patients with COVID-19 Pneumonia from the New York Metropolitan region

链接：https://www.medrxiv.org/content/10.1101/2020.07.02.20145565v1

编译者：张丽双

纽约研究者发现，在非 ICU 住院的 COVID-19 肺炎并发 AHRF 的非 ICU 患者中，使用皮质类固醇治疗与 ICU 转移，插管或住院死亡的主要复合终点风险显著降低。

23. SARS-CoV-2 的全身炎症反应对洛匹那韦(LPV)和羟氯喹(HCQ)血浆浓度的影响

Effect of Systemic Inflammatory Response to SARS-CoV-2 on Lopinavir and Hydroxychloroquine Plasma Concentrations

链接：https://www.medrxiv.org/content/10.1101/2020.07.05.20146878v1

编译者：张丽双

瑞士学者关注到 SARS-CoV-2 导致炎性细胞因子释放，可下调代谢酶的表达。这种级联影响血浆中的药物浓度。临床数据表明急性期炎症标志物 C 反应蛋白（CRP）与血浆中 LPV 显著正相关，但与 HCQ 血浆浓度不相关。

24. 一个依赖 pH 调控的开关可介导 SARS-CoV-2 Spike 蛋白的构象屏蔽

A pH-dependent switch mediates conformational masking of SARS-CoV-2 spike

来源：bioRxiv

发布时间：2020-07-04

链接：https://www.biorxiv.org/content/10.1101/2020.07.04.187989v1

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通讯作者：

通讯作者单位：

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

SARS-CoV-2 病毒引发的疫情已在全球范围传播，因此针对 Spike 蛋白三聚体的疫苗研发工作就显得犹未紧急。然而，却有部分抗体无法起到中和病毒的作用，例如与 Spike 隐藏表位的亲和力为纳摩尔级的 CR3022。这说明，存在一种由 Spike 蛋白导致的抗体中和逃逸途径。本文中作者发现，在生理 pH 下，SARS-CoV-2 Spike 蛋白的展开焓是球状蛋白的 10%；

而在内体 pH 下的展开焓则提高了 10 倍多。同时，在生理 pH 下，Spike 蛋白可以被如 CR3022 的抗体特异性识别；而在内体 pH 下，抗体则会脱落。这说明 Spike 蛋白通过一种受 pH 调节的构象屏蔽机制来逃避潜在的中和抗体。为了研究 Spike 蛋白与 ACE2 受体的相互作用和逃逸机制的兼容性，作者分别在生理 pH 和内体 pH 下，测定了 Spike 与 ACE2 的结合能力，并利用 cryo-EM 技术解析了 Spike 蛋白与 1 至 3 个 ACE2 分子结合后的复合物结构。在没有 ACE2 的条件下，对 cryo-EM 数据的分析表明，较低的 pH 值可降低蛋白构象的差异性。在 pH 5.5 的情况下，三聚体中的一个受体结合结构域（RBD）打开的构象是主要成分。在更低的 pH 条件下，随着 RBD 的下降和受 pH 调控的开关结构的重新折叠，蛋白被锁定在了一个全关闭的构象。值得注意的是，在新出现的存在 Asp614Gly 突变的毒株中，将 RDB 锁定在关闭构象的开关结构会部分受到突变的影响而不稳定，从而提高了 Spike 与 ACE2 的有效相互作用，同时也降低了由于构象屏蔽而造成的逃逸。

译者注：作者未在预印本中提供 PDB ID 或 EMDB ID

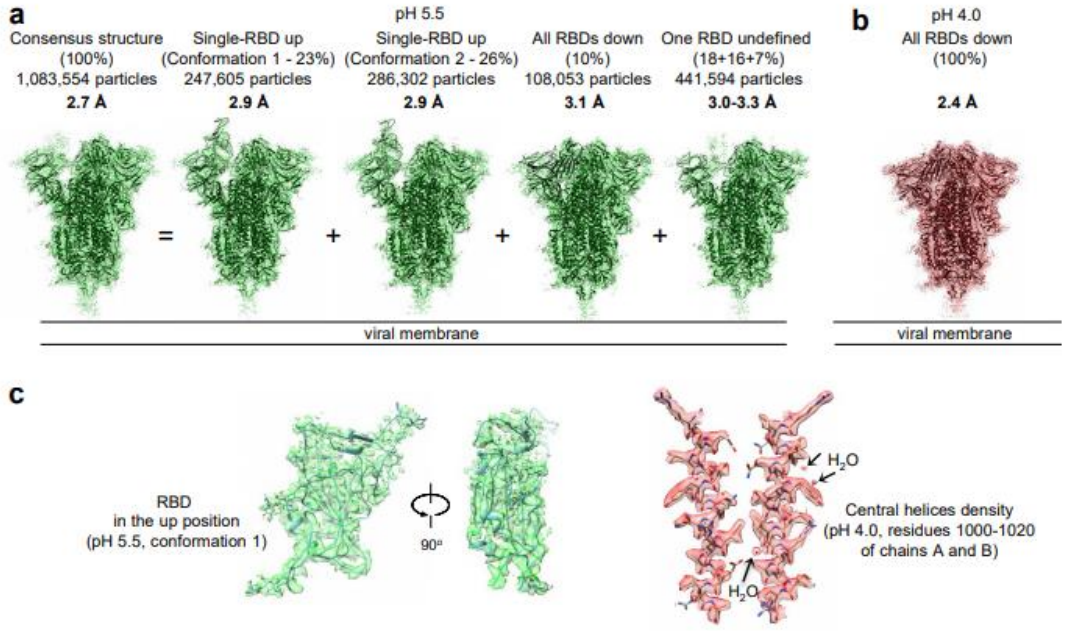

Figure 3 | Cryo-EM analyses reveal lower pH to reduce spike-conformational heterogeneity culminating in an all RBDdown conformation at pH 4.0. a, Structures at pH 5.5 with particle prevalence and resolution of determined structures. **b**, High resolution structure of spike at pH 4.0. **c**, Examples of reconstruction density. The single-up RBD in the pH 5.5 conformation 1 with density is shown to the left, and a region at the central helices of the pH 4.0 structure is shown with well-defined water molecules to the right.

Abstract:

SARS-CoV-2 has emerged as a global pathogen, sparking urgent vaccine development efforts with the trimeric spike. However, the inability of antibodies like CR3022, which binds a cryptic spike epitope with nanomolar affinity, to neutralize virus, suggests a spike-based means of neutralization escape. Here, we show the SARS-CoV-2 spike to have 10% the unfolding enthalpy of a globular protein at physiological pH, where it is recognized by antibodies like CR3022, and up to 10-times more unfolding enthalpy at endosomal pH, where it sheds such antibodies, suggesting that the spike evades potentially neutralizing antibody through a pH-

dependent mechanism of conformational masking. To understand the compatibility of this mechanism with ACE2-receptor interactions, we carried out binding measurements and determined cryo-EM structures of the spike recognizing up to three ACE2 molecules at both physiological and endosomal pH. In the absence of ACE2, cryo-EM analyses indicated lower pH to reduce conformational heterogeneity. Single-receptor binding domain (RBD)-up conformations dominated at pH 5.5, resolving into a locked all-down conformation at lower pH through lowering of RBD and refolding of a pH-dependent switch. Notably, the emerging Asp614Gly strain partially destabilizes the switch that locks RBD down, thereby enhancing functional interactions with ACE2 while reducing evasion by conformational masking.

25. SARS-CoV-2 Nsp1 与核糖体 mRNA 通道结合从而抑制翻译过程

SARS-CoV-2 Nsp1 binds ribosomal mRNA channel to inhibit translation

来源：bioRxiv

发布时间：2020-07-07

链接：https://www.biorxiv.org/content/10.1101/2020.07.07.191676v1

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DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

非结构蛋白 1（Nsp1），也被称为宿主关闭因子，是在 SARS-CoV-2 病毒感染人类细胞后合成的第一个病毒蛋白，能够抑制宿主的天然免疫功能。本文中，作者结合 cryo-EM 技术和生化实验，发现 SARS-CoV-2 Nsp1 与包含了 43S 预启动复合物的核糖体复合物中的人源 40S 亚结构结合。Nsp1 的 C 端结构域插入 mRNA 通道的入口，干扰 mRNA 的结合。作者发现，在人源细胞的裂解物中，Nsp1 的存在可以有效抑制翻译过程。基于高分辨率的 40S-Nsp1 复合物结构，作者确定了 Nsp1 中抑制翻译过程的关键残基。作者还进一步发现，病毒 mRNA 的全长 5’端非翻译区能够在体外实验中刺激翻译过程，这说明 SARS-CoV-2 通过 Nsp1 抑制宿主的翻译功能，并结合病毒 mRNA 的高效翻译过程，来共同实现病毒基因的表达。

结构文件：

	40S-Nsp1 complex	40S body	40S head-Nsp1
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RCSB PDB ID	6ZOJ	6ZOK	6ZOL

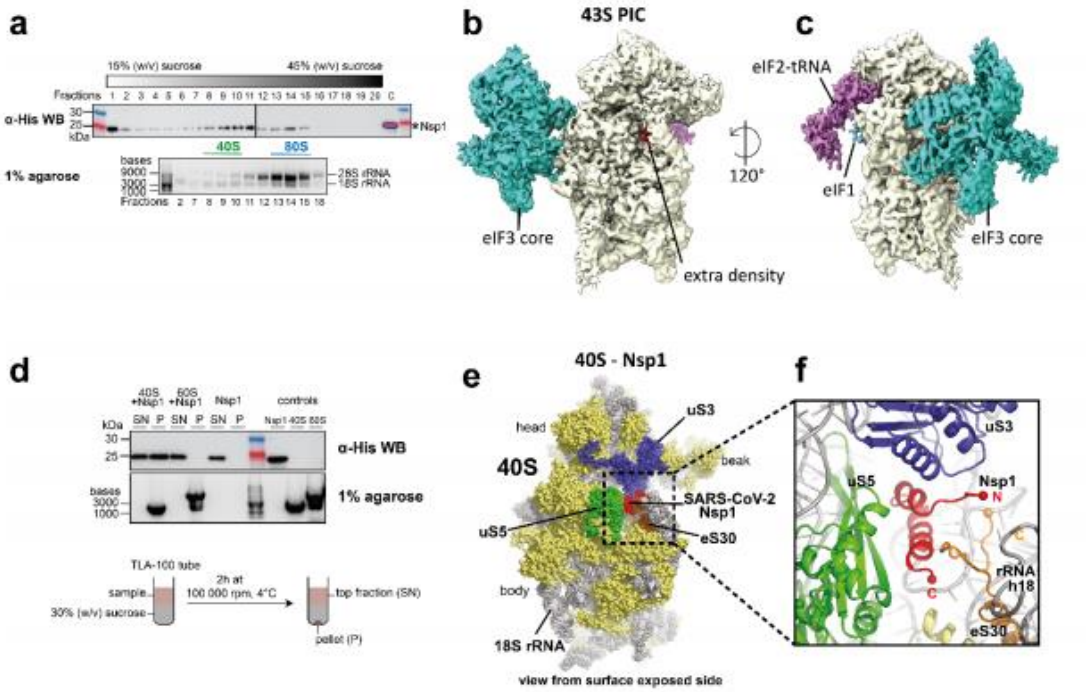

Figure 1: Structures of ribosomal complexes inhibited by SARS-CoV-2 Nsp1 solved by cryo-EM. **(a)** Sucrose gradient fractionation of HEK lysate supplemented with Nsp1. Nsp1 co-migrates with 40S and 80S ribosomal particles in a 15-45% (w/v) sucrose gradient. His6-tagged Nsp1 is visualized by Western blot using an α-His antibody, while the rRNA content in corresponding fractions is monitored on an agarose gel. All samples for the Western blot derive from the same experiment and the blots were processed in parallel. **(b-c)** Overview of Nsp1 (red) binding to a 43S PIC containing the core of initiation factor eIF3 (cyan), eIF1 (blue) and the eIF2-tRNA ternary complex (magenta). **(d)** In the in vitro binding assay, WT Nsp1 was added to 40S and 60S ribosomal SU and loaded on a 30% (w/v) sucrose cushion. Unbound proteins remained in the supernatant (SN), while bound Nsp1 co-pelleted with 40S (P). **(e)** Overview of Nsp1 binding to the small ribosomal subunit. Nsp1 (red) binds close to the mRNA entry site and contacts uS3 (blue) from the ribosomal 40S head as well as uS5 (green), the C-terminus of uS30 (orange) and h18 of the 18S rRNA (grey) of the 40S body. **(f)** Zoomed view of the area of Nsp1 binding as highlighted in (e).

Abstract:

The non-structural protein 1 (Nsp1), also referred to as the host shutoff factor, is the first viral protein that is synthesized in SARS-CoV-2 infected human cells to suppress host innate immune functions. By combining cryo-electron microscopy and biochemical experiments, we show that SARS-CoV-2 Nsp1 binds to the human 40S subunit in ribosomal complexes including the 43S pre-initiation complex. The protein inserts its C-terminal domain at the entrance to the mRNA channel where it interferes with mRNA binding. We observe potent translation inhibition in the presence of Nsp1 in lysates from human cells. Based on the high-resolution structure of the 40S-Nsp1 complex, we identify residues of Nsp1 crucial for mediating translation inhibition. We further show that the full-length 5′ untranslated region of the genomic viral mRNA stimulates translation in vitro,

suggesting that SARS-CoV-2 combines inhibition of translation by Nsp1 with efficient translation of the viral mRNA to achieve expression of viral genes.

26. 人类诱导多能干细胞来源的心肌细胞易受 SARS-CoV-2 的感染

Human iPSC-Derived Cardiomyocytesare Susceptible to SARS-CoV-2 Infection

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编译者：孔娟
中文摘要：

COVID-19 是由呼吸系统症状定义，但是心脏并发症包括病毒性心肌炎也很普遍。尽管 COVID-19 引起的缺血性和炎性反应会对心脏功能产生不利影响，但 SARS-CoV-2 的感染对人类心肌细胞的直接影响尚不清楚。文中研究者利用人类诱导多能干细胞来源的心肌细胞(hiPSC-CMs)作为模型来检测心肌细胞特异性感染 SARS-CoV-2 的机制。显微镜学和 RNA 测序证明 SARS-CoV-2 可以通过 ACE2 进入单核细胞-巨噬细胞。感染 SARS-CoV-2 病毒 72 小时后，病毒复制和细胞病变效应诱导 hiPSC-CM 凋亡和停止跳动。SARS-CoV-2 的感染激活了免疫应答和抗病毒清除基因的信号通路，同时抑制了代谢途径和 ACE2 的表达。这些研究表明，SARS-CoV-2 可在体外感染人巨细胞病毒，为阐明感染机制建立了研究模型，为进一步建立心脏特异性抗病毒药物筛选平台奠定了一定的研究基础。

Abstarct:

Coronavirus disease 2019 (COVID-19) is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is defined by respiratory symptoms, but cardiac complications including viral myocarditis are also prevalent. Although ischemic and inflammatory responses caused by COVID-19 can detrimentally affect cardiac function, the direct impact of SARS-CoV-2 infection on human cardio myocytes is not well-understood. Here, we utilize human induced pluripotent stem cell-derived cardio myocytes (hiPSC-CMs) as a model to examine the mechanisms of cardio myocyte-specific infection by SARS-CoV-2. Microscopy and RNA-sequencing demonstrate that SARS-CoV-2 can enter hiPSC-CMs via ACE2. Viral replication and cytopathic effect induce hiPSC-CM apoptosis and cessation of beating after 72hours of infection. SARS-CoV-2 infection active tesinnate immune response and antiviral clearance gene pathways, while inhibiting metabolic pathways and suppressingACE2expression. These studies show that SARS-CoV-2 can infect hiPSC-CMsin vitro, establishing a model for elucidating infection mechanisms and potentially a cardiac-specific antiviral drug screening platform.

27. SARS-CoV-2 刺突蛋白的 D614G 变异增加了病毒的感染力，不改变对靶向受体结合域的敏感度

SARS-CoV-2 Spike protein variant D614G increases infectivity and retains sensitivity to antibodies that target the receptor binding domain

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在疫情爆发的过程中，病毒基因组变异可以用于追踪病毒从一个易感宿主传播到另一个易感宿主的传播轨迹。虽然变异一般没有功能上的意义，偶尔它们也可能让病毒传播得更快、改变病症严重程度或者对抗病毒治疗产生抗性。从 SARS-CoV-2 被发现是 COVID-19 的病原物之后，这个病毒已经扩散到了全世界。已经测序的 SARS-CoV-2 基因组已经成千上万计了。对于 RNA 病毒而言，SARS-CoV-2 的变异速率不算快，不过在人群里的大规模传播已经给 SARS-CoV-2 的病毒变异进行筛选提供了充分的机会。在这些被筛选出的变异中，有一个并不存在于可能的动物来源病毒的共同祖先的刺突蛋白变异 D614G。该变异于 1 月份在德国和中国病人中首次发现。D614G 变异在人群中的概率一直在稳步增加，现在在世界范围内已经占到所分离病毒的 97%。这个观察让人们提出一个问题：D614G 是否促进了 SARS-CoV-2 的复制。结构模型预测显示 D614G 可能会干扰 S1 和 S2 结构域的接触，会导致构象的显著变化。用单环载体，研究者们发现 D614G 的感染力在人肺细胞系、结肠细胞系中是其祖先基因型的 3 到 9 倍。在其他异位表达人 ACE2 和 TMPRSS2 或者穿山甲、猪、狗以及猫的 ACE2 基因的其他人细胞系中也得到了同样的结论。尽管如此，靶向刺突蛋白的受体结合域的单克隆抗体仍然对包含该变异的病毒具备完全的中和效应。这些结果提示 D614G 因为能增加人到人的传播受到正向选择，让 SARS-CoV-2 更快地扩散到世界各地，但是该变异对针对刺突蛋白受体结合域的抗病毒治疗不产生耐受和抗性。

Virus genome sequence variants that appear over the course of an outbreak can be exploited to map the trajectory of the virus from one susceptible host to another. While such variants are usually of no functional significance, in some cases they may allow the virus to transmit faster, change disease severity, or confer resistance to antiviral therapies. Since the discovery of SARS-CoV-2 as the cause of COVID-19, the virus has spread around the globe, and thousands of SARS-CoV-2 genomes have been sequenced. The rate of sequence variation among SARS-CoV-2 isolates is modest for an RNA virus but the enormous number of human-to-human transmission events has provided abundant opportunity for selection of sequence variants. Among these, the SARS-CoV-2 Spike protein variant, D614G, was not present in the presumptive common ancestor of this zoonotic virus but was first detected in late January in Germany and China. The D614G variant steadily increased in frequency and now constitutes >97% of isolates world-wide, raising the question whether D614G confers a replication advantage to SARS-CoV-2. Structural models predict that D614G would disrupt contacts between the S1 and S2 domains of the Spike protein and cause significant shifts in conformation. Using single-cycle vectors we showed that D614G is three to nine-fold more

infectious than the ancestral form on human lung and colon cell lines, as well as on other human cell lines rendered permissive by ectopic expression of human ACE2 and TMPRSS2, or by ACE2 orthologues from pangolin, pig, dog, or cat. Nonetheless, monoclonal antibodies targeting the receptor binding domain of the SARS-CoV-2 Spike protein retain full neutralization potency. These results suggest that D614G was selected for increased human-to-human transmission, that it contributed to the rapidity of SARS-CoV-2 spread around the world, and that it does not confer resistance to antiviral therapies targeting the receptor binding domain.

28. 转基因和腺病毒 hACE2 小鼠模型感染 SARS-CoV-2 的比较

Comparison of Transgenic and Adenovirus hACE2 Mouse Models for SARS-CoV-2 Infection

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中文摘要：

SARS-CoV-2 目前在世界范围内引起了一场高发病率和高死亡率的大流行。开发 COVID-19 的动物模型对于评估疫苗和抗病毒药物以及了解疾病的发病机制至关重要。SARS-CoV-2 已被证明使用与 SARS-CoV-1 相同的进入受体，即人血管紧张素转换酶 2（hACE2）。由于小鼠和 hACE2 的氨基酸差异，近交系小鼠不能支持 SARS-CoV-2 病毒的高滴度复制。因此，已经开发出许多转基因和敲入小鼠模型以及病毒载体介导的 hACE2 传递系统。该文章比较了 K18-hACE2 转基因模型和腺病毒介导的 hACE2 向小鼠肺的传递。发现 K18-hACE2 小鼠在肺和脑中病毒高滴度复制，导致小鼠死亡。相反，腺病毒介导的病毒低滴度复制仅限于肺部，并且在激发剂量为 104 孔斑形成单位（PFU）时没有出现感染的临床症状。K18-hACE2 模型提供了一个严格的模型，用于测试疫苗和抗病毒药物预防疾病的能力，而腺病毒传递系统具有灵活性，可用于多种基因背景和改良的小鼠品系。

Abstract:

Severe acute respiratory syndrome CoV-2 (SARS-CoV-2) is currently causing a worldwide pandemic with high morbidity and mortality. Development of animal models that recapitulate important aspects of coronavirus disease 2019 (COVID-19) is critical for the evaluation of vaccines and antivirals, and understanding disease pathogenesis. SARS-CoV-2 has been shown to use the same entry receptor as SARS-CoV-1, human angiotensin-converting enzyme 2 (hACE2)(1-3). Due to amino acid differences between murine and hACE2, inbred mouse strains fail to support

high titer viral replication of SARS-CoV-2 virus. Therefore, a number of transgenic and knock-in mouse models, as well as viral vector-mediated hACE2 delivery systems have been developed. Here we compared the K18-hACE2 transgenic model to adenovirus-mediated delivery of hACE2 to the mouse lung. We show that K18-hACE2 mice replicate virus to high titers in both the lung and brain leading to lethality. In contrast, adenovirus-mediated delivery results in viral replication to lower titers limited to the lung, and no clinical signs of infection with a challenge dose of 104 plaque forming units. The K18-hACE2 model provides a stringent model for testing the ability of vaccines and antivirals to protect against disease, whereas the adenovirus delivery system has the flexibility to be used across multiple genetic backgrounds and modified mouse strains.

29. 动物模型预筛选：SARS-CoV-2 的预先暴露对 NHP 模型反应的影响

Animal Model Prescreening: Pre-exposure to SARS-CoV-2 impacts responses in the NHP model

链接：https://www.biorxiv.org/content/10.1101/2020.07.06.189803v1

编译者：王玮

美国研究者发现预先暴露于 SARS-CoV-2 会影响动物模型中的生物标志物反应，说明动物模型的综合预筛选的重要性。

30. 仓鼠模型中的法匹拉韦和 SARS-CoV-2

Favipiravir and severe acute respiratory syndrome coronavirus 2 in hamster model

链接：https://www.biorxiv.org/content/10.1101/2020.07.07.191775v1

编译者：张丽双

法国研究者发现，在仓鼠模型中，高剂量（700-1400mg/kg/天）法匹拉韦可显著减少肺部病毒复制，并伴随该疾病的临床缓解。但是，这些高剂量与仓鼠的明显毒性有关。