新型冠状病毒信息简报

第 80 期（2020 年 11 月 13 日–11 月 20 日周报）

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

联系人：蒋立春 jianglch@shanghaitech.edu.cn

内容介绍

分类	标题名称
疫情播报	1. 2020 年 11 月 19 日疫情
流行病学	2. 一项大规模的用 T 细胞受体测序检测和追溯在意大利 Vo 镇 SARS-CoV-2 的感染的研究 3. 一位免疫抑制的宿主中持续性存在的 SARS-CoV-2 及病毒的进化 4. 季节性人类冠状病毒抗体在感染 SARS-CoV-2 后增强，但与保护无关 5. 肯尼亚献血者抗 SARS-CoV-2 IgG 抗体的血清阳性率
疾病检测	6. 冠状病毒（COVID-19）更新：FDA 授权首个可在家自我测试的 COVID-19 检测 7. 7 项商用 SARS-CoV-2 快速 Point-of-Care 抗原测试的比较
疾病病理	8. 肠壁屏障完整性破坏加剧了 COVID-19 的严重程度
疫苗研发	9. 11 月 20 日辉瑞递交了的关于 COVID-19 疫苗的紧急使用授权 10. Moderna 的新冠疫苗免疫高效性再次展示 mRNA 技术的广泛应用前景 11. ChAdOx1 nCoV-19 疫苗的安全性和免疫原性年轻人和老年人均采用初免-加强疗法成人（COV002）：单盲，随机，对照，2/3 期试验 12. SARS-CoV-2 mRNA 疫苗的初步研究
基础研究	13. 在 SARS-CoV-2 感染和细胞因子休克综合征中，TNF-α 和 IFN-γ 的协同作用触发炎症细胞死亡、组织损伤和死亡 14. SARS-CoV-2 表位被多种人类 T 细胞受体所识别 15. 慢性炎症失调的新型基因特异性翻译机制揭示了有前景的多方面 COVID-19 治疗手段 16. SARS-CoV-2 病毒颗粒上的 Spike 蛋白的实时构象动力学研究 17. SARS-CoV-2 N 蛋白相分离的磷酸化调控提供了其双重功能的生物物理基础 18. SARS-CoV-2 进入因子在健康人和 COVID-19 患者胰腺中的表达 19. 从水貂分离出的 SARS-CoV-2 基因组中的反复出现的突变指向快速的宿主适应
疾病模型	20. Roborovski 矮仓鼠——一种 SARS-CoV-2 感染后快速致死的模型 21. SARS-CoV-2 在家猫中的传播存在狭窄的瓶颈

1. 2020 年 11 月 19 日疫情

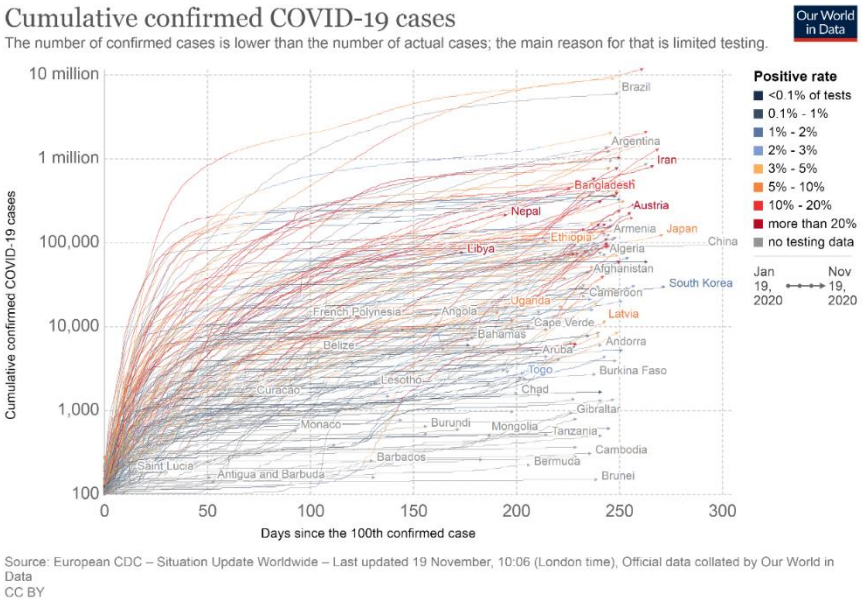
数据来源：WHO

发布时间：2020 年 11 月 19 日北京时间下午 4 点

链接：https://covid19.who.int/

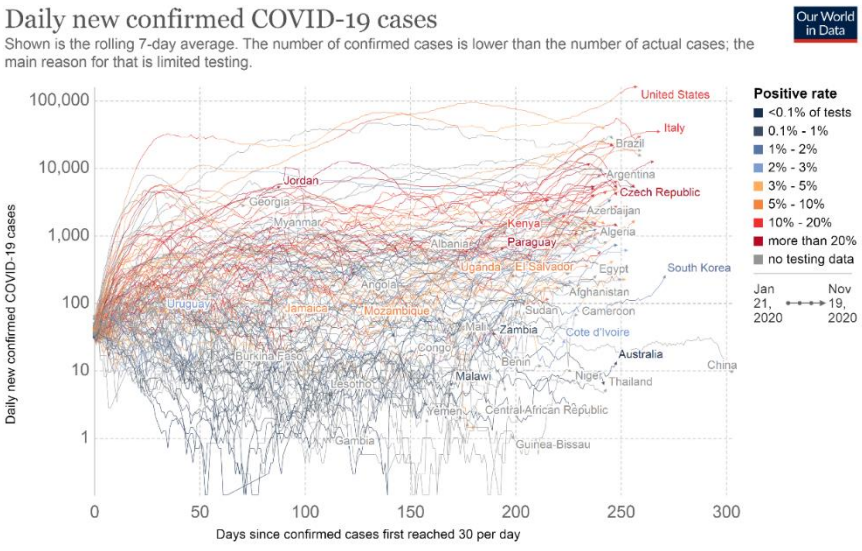
根据 WHO 提供的数据，2020 年 11 月 19 日全球累计确诊新型冠状病毒病人 **55,928,327** 例，当日新增确诊 **594,542** 例，累计死亡 **1,344,003** 例，当日新增死亡 **9,989**。

中国累计确诊 92,513 例，累计死亡 4,749 例，当日新增确诊 23 例，新增死亡 0 例。



Source: European CDC – Situation Update Worldwide – Last updated 19 November, 10:06 (London time), Official data collated by Our World in Data
CC BY

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）



Source: European CDC – Situation Update Worldwide – Last updated 19 November, 10:06 (London time), Official data collated by Our World in Data
CC BY

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）

全国新型冠状病毒肺炎新增确诊病例分布图（11 月 19 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

根据上海发布、新华社等官方公众号的消息，本周内在上海、天津、阜阳等地出现本地新增病人，相关流行病调查工作正在紧急开展中。

2. 一项大规模的用 T 细胞受体测序检测和追溯在意大利 Vo 镇 SARS-CoV-2 的感染的研究

Diagnosis and Tracking of Past SARS-CoV-2 Infection in a Large Study of Vo', Italy Through T-Cell Receptor Sequencing

来源：medrxiv

发布时间：2020-11-12

链接：https://www.medrxiv.org/content/10.1101/2020.11.09.20228023v1

第一作者：Rachel M. Gittelman,

通讯作者：Andrea Crisanti

通讯作者单位：University of Padova, Italy

中文摘要：

对 SARS-CoV-2 感染后的适应性免疫的了解可以增进我们对 COVID-19 的暴露以及未来的保护和免疫力的理解。作者们分析了意大利威尼托大区的 Vò 镇（该镇是意大利首发疫情的小镇）的 2200 个人的 T 细胞和抗体特征。其中的包括了 70 个 PCR 确诊过的 SARS-CoV-2 的病例（24 位症状，37 位有症状，以及 9 位住院病人）。作者们在病人 PCR 确诊后 60 天后进行抽血分析。其中 97%（68/70）的人显示出阳性的 T 细胞结果，比同样样品上进行血清学抗体检测的阳性率高（77%，54/70）。T 细胞反应的深度和广度和病症的严重性相关，有症状以及住院的 COVID-19 病人相比无症状感染者的 T 细胞反应更强。和 T 细胞反应相比，康复期的抗体水平能提供的信息更少，因为它们和之前症状的严重程度不相关。在 2200 个研究对象中，通过 T 细胞反应的检测另外鉴定出 45 个疑似感染—这些人没有明确的 PCR 检测阳性结果。在这些人中，那些曾经有报道过相关症状以及其家庭中曾经有 PCR 确诊过的阳性感染者的 T 细胞反应阳性率更高。

所有这些表明，检测 T 细胞反应是既往 SARS-CoV-2 感染的一个可靠的敏感的持续有效的监测手段。

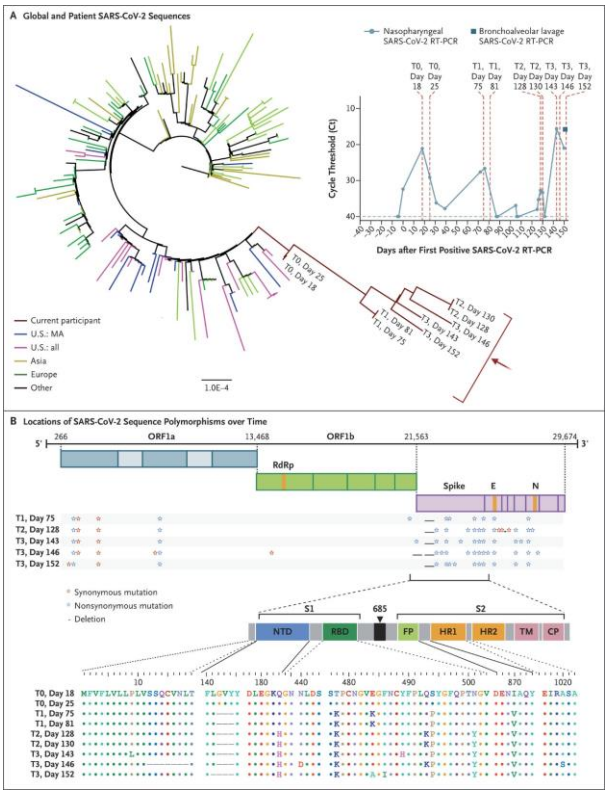
Abstract:
Measuring the adaptive immune response after SARS-CoV-2 infection may improve our understanding of COVID-19 exposure and potential future protection or immunity. We analyzed T-cell and antibody signatures in a large population study of over 2,200 individuals from the municipality of Vo', Italy, including 70 PCR-confirmed SARS-CoV-2 cases (24 asymptomatic, 37 symptomatic, 9 hospitalized). Blood samples taken 60 days after PCR diagnosis demonstrated 97% (68/70) of the latter subjects had a positive T-cell test result, higher than an antibody serology assay (77%; 54/70 of subjects) performed on the same samples. The depth and breadth of the T-cell response was associated with disease severity, with symptomatic and hospitalized COVID-19 cases having significantly higher response than asymptomatic cases. In contrast, antibody levels at this convalescent time point were less informative as they did not correlate with disease severity. 45 additional suspected infections were identified based on T-cell response from the 2,220 subjects without confirmatory PCR tests. Among these, notably, subjects who reported symptoms or had household exposure to a PCR-confirmed infection demonstrated a higher T-cell test positive rate. Taken together, these results establish that T cells are a sensitive, reliable and persistent measure of past SARS-CoV-2 infection.

3. 一位免疫抑制的宿主中持续性存在的 SARS-CoV-2 及病毒的进化

Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host

11 月 11 日的新英格兰医学杂志发表了一个个案报告，报告了一位免疫抑制的宿主中持续性存在的 SARS-CoV-2，并且病毒发生快速突变近乎的案例。

链接：https://www.nejm.org/doi/10.1056/NEJMc2031364



A 45-year-old man with severe antiphospholipid syndrome complicated by diffuse alveolar hemorrhage,1 who was receiving anticoagulation therapy, glucocorticoids, cyclophosphamide, and intermittent rituximab and eculizumab, was admitted to the hospital with fever.

…

Although most immunocompromised persons effectively clear SARS-CoV-2 infection, this case highlights the potential for persistent infection5 and accelerated viral evolution associated with an immunocompromised state

4. 季节性人类冠状病毒抗体在感染 SARS-CoV-2 后增强，但与保护无关

Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection

来源：medRxiv

发布时间：2020-11-10

链接：https://www.medrxiv.org/content/10.1101/2020.11.06.20227215v1

第一作者：Elizabeth M. Anderson

通讯作者：Scott E. Hensley

通讯作者单位： Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

DOI 或 PUBMED ID：preprint

编译者：孔娟

中文摘要：

SARS-CoV-2 在人类中迅速传播,尽管 SARS-CoV-2 是一种新型的冠状病毒,但在大流行之前,大多数人都曾接触过其他抗原性不同的常见季节性人冠状病毒(hCoVs)。文中研究者对 204 名在新冠肺炎大流行前采集的血清样本中的 SARS-CoV-2 及 hCoV 反应性抗体的水平进行了检测。并对另一组 252 名 PCR 检测 SARS-CoV-2 阳性的血清样本中针对大流行前其它冠状病毒抗体水平进行了检测。研究发现大部分个体在发生新冠肺炎大流行之前就具有 hCoV 反应性抗体。有 23%具有与 SARS-CoV-2 S 蛋白和核衣壳蛋白发生交叉反应的非中和抗体。这些抗体与抗 SARS-CoV-2 感染或住院治疗无关，但这些 hCoV 交叉反应抗体在感染 SARS-CoV-2 后增强。还需要进一步的研究来确定季节性人类 β 冠状病毒感染和 SARS-CoV-2 交叉反应性抗体诱导之间的时间关系。

Abstract：

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread within the human population. Although SARS-CoV-2 is a novel coronavirus, most humans had been previously exposed to other antigenically distinct common seasonal human coronaviruses (hCoVs) before the COVID-19 pandemic. Here, we quantified levels of SARS-CoV-2-reactive antibodies and hCoV-reactive antibodies in serum samples collected from 204 humans before the COVID-19 pandemic. We then quantified pre-pandemic antibody levels in serum from a separate cohort of 252 individuals who became PCR-confirmed infected with SARS-CoV-2. Finally, we longitudinally measured hCoV and SARS-CoV-2 antibodies in the serum of hospitalized COVID-19 patients. Our studies indicate that most individuals possessed hCoV-reactive antibodies before the COVID-19 pandemic. We determined that ~23% of these individuals possessed non-neutralizing antibodies that cross-

reacted with SARS-CoV-2 spike and nucleocapsid proteins. These antibodies were not associated with protection against SARS-CoV-2 infections or hospitalizations, but paradoxically these hCoV cross-reactive antibodies were boosted upon SARS-CoV-2 infection.

5. 肯尼亚献血者抗 SARS-CoV-2 IgG 抗体的血清阳性率

Seroprevalence of anti－SARS-CoV-2 IgG antibodies in Kenyan blood donors
来源：science
发布时间：2020.11.11
文章链接：
https://science.sciencemag.org/content/early/2020/11/11/science.abe1916
第一作者：Sophie Uyoga，Ifedayo M. O. Adetifa, Henry K. Karanja，James Nyagwange
通讯作者：Sophie Uyoga
通讯作者单位：肯尼亚基利菲 凯姆里-韦尔科姆信托基金研究项目
DOI: 10.1126/science.abe1916
编译者：张怡
中文摘要：
2020 年 3 月 12 日，肯尼亚报告了第一例 SARS-CoV-2，预计将出现大量病例和死亡，但到 2020 年 7 月 31 日，只有 20,636 例和 341 例死亡。然而，SARS-CoV-2 在社区中的暴露程度仍不清楚。研究者们确定了 2020 年 4-6 月肯尼亚献血者中抗 SARS-CoV-2 IgG 的流行情况。粗血清阳性率为 5.6%(174/3098)。人口加权、试验性能调整的全国血清阳性率为 4.3%(95%可信区间为 2.9-5.8%)，在城市县、，蒙巴萨(8.0%)、内罗毕(7.3%)和基苏木(5.5%)最高。SARS-CoV-2 暴露范围比基于病例的监测所显示的更为广泛，这些结果将有助于指导肯尼亚和整个非洲的大流行应对工作。
Abstract
The first case of SARS-CoV-2 in Kenya was reported on March 12, 2020 and an overwhelming number of cases and deaths were expected but by July 31, 2020 there were only 20,636 cases and 341 deaths. However, the extent of SARS-CoV-2 exposure in the community remains unknown. We determined the prevalence of anti－SARS-CoV-2 IgG among blood donors in Kenya in April-June 2020. Crude seroprevalence was 5.6% (174/3098). Population-weighted, test-performance-adjusted national seroprevalence was 4.3% (95% CI 2.9－5.8%) and was highest in urban counties, Mombasa (8.0%), Nairobi (7.3%) and Kisumu (5.5%). SARS-CoV-2 exposure is more extensive than indicated by case-based surveillance and these results will help guide the pandemic response in Kenya, and across Africa.

6. 冠状病毒（COVID-19）更新：FDA 授权首个可在家自我测试的 COVID-19 检测

Coronavirus (COVID-19) Update: FDA Authorizes First COVID-19 Test for Self-Testing at Home
来源：FDA 新闻稿
链接：https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-covid-19-test-self-testing-home
编译者：雷颖
11 月 17 日美国食品药物管理局（US Food and Drug Administration）发布了紧急使用授

权（EUA），用于第一项可在家中进行自我测试的 COVID-19 诊断测试，并提供了快速的结果。Lucira COVID-19 多合一检测试剂盒是一种分子（实时环路介导的扩增反应）一次性测试，旨在检测引起 COVID-19 的新型冠状病毒 SARS-CoV-2。Lucira COVID-19 多合一测试盒测试已被授权用于被其医疗服务提供者怀疑为 COVID-19 的 14 岁及以上个人的家庭收集的鼻拭子样本的家庭使用。它也被授权用于所有年龄段的即时护理（POC）场所（例如，医生办公室、医院、紧急护理中心和急诊室），但在医院使用该测试时，医疗服务提供者必须收集样本。POC 用于测试 14 岁以下的个人。该检测当前仅授权处方使用。

7. 7 项商用 SARS-CoV-2 快速 Point-of-Care 抗原测试的比较

Comparison of seven commercial SARS-CoV-2 rapid Point-of-Care Antigen tests

来源：medrxiv

发布时间：2020.11.13

文章链接：https://www.medrxiv.org/content/10.1101/2020.11.12.20230292v1

第一作者：Victor M. Corman

通讯作者：Christian Drosten

通讯作者单位：柏林查理大学病毒学研究所，德国感染研究中心

doi: https://doi.org/10.1101/2020.11.12.20230292

编译者：张怡

中文摘要：

背景：抗原的 POCT 可加速 SARS-CoV-2 检测。随着第一个 AgPOCT 的出现，人们对它们的效用和性能越来越感兴趣。

方法:研究者比较了 7 家供应商的 AgPOCT 产品:雅培 Panbio™COVID-19 Ag 快速测试;RapiGEN BIOCREDIT COVID-19 Ag; Healgen®冠状病毒 Ag 快速测试盒(拭子);Coris Bioconcept Covid.19 Ag;R-Biopharm RIDA®快速 SARS-CoV-2 抗原;NAL von minden NADAL COVID19-Ag 检测;以及 Roche/SD 生物传感器 SARS-CoV 快速抗原检测。评估了重组核蛋白、培养流行和新型冠状病毒、存储的已知 SARS-CoV-2 病毒载量的临床样本(n=138)、存储的非 SARS-CoV-2 呼吸制剂患者样本(n=100)以及健康志愿者的自采样拭子(n=35)。

发现：7 个被测产品中有 6 个的检测限为每棉签 2.08×106 至 2.88×107 拷贝，离群值为每棉签 1.58×1010 拷贝。五种产品的特异性在 98.53%到 100%之间，有两种离群值为 94.85%和 88.24%。假阳性结果与任何特定的呼吸制剂无关。由于一些测试的 AgPOCT 是早期生产批次，观察到的特异性问题不太可能持续。

解释：大多数 AgPOCT 的敏感性范围与病毒载量数字重叠，通常在有症状的第一周观察到，这标志着大多数患者的传染期。具有接近患者传染性的病毒浓度的检测极限的 AgPOCT 可能在医疗保健和公共卫生各个领域的决策中提供捷径。

Abstract

Background Antigen point of care tests (AgPOCT) can accelerate SARS-CoV-2 testing. As first AgPOCT are becoming available, there is a growing interest in their utility and performance.

Methods Here we compare AgPOCT products by seven suppliers: the Abbott Panbio™ COVID-19 Ag Rapid Test; the RapiGEN BIOCREDIT COVID-19 Ag; the Healgen® Coronavirus Ag Rapid Test Cassette (Swab); the Coris Bioconcept Covid.19 Ag Respi-Strip; the R-Biopharm RIDA®QUICK SARS-CoV-2 Antigen; the NAL von minden NADAL COVID19-Ag Test; and the Roche/SD Biosensor SARS-CoV Rapid Antigen Test. Tests were evaluated on recombinant nucleoprotein, cultured endemic and emerging

coronaviruses, stored clinical samples with known SARS-CoV-2 viral loads (n=138), stored samples from patients with respiratory agents other than SARS-CoV-2 (n=100), as well as self-sampled swabs from healthy volunteers (n=35).
Findings Limits of detection in six of seven tested products ranged between 2.08 × 106 and 2.88 × 107 copies per swab, the outlier at 1.58 × 1010 copies per swab. Specificities ranged between 98.53% and 100% in five products, with two outliers at 94.85% and 88.24%. False positive results were not associated with any specific respiratory agent. As some of the tested AgPOCT were early production lots, the observed issues with specificity are unlikely to persist.
Interpretation The sensitivity range of most AgPOCT overlaps with viral load figures typically observed during the first week of symptoms, which marks the infectious period in the majority patients. AgPOCTs with a limit of detection that approximates the virus concentration above which patients are infectious may enable shortcuts in decision-making in various areas of healthcare and public health.

8. 肠壁屏障完整性破坏加剧了 COVID-19 的严重程度

Severe COVID-19 Is Fueled by Disrupted Gut Barrier Integrity
来源：medRxiv
发布时间：2020-11-16
链接：https://www.medrxiv.org/content/10.1101/2020.11.13.20231209v1
第一作者：Leila B. Giron
通讯作者：Mohamed Abdel-Mohsen
通讯作者单位：美国威斯塔研究所
DOI 或 PUBMED ID：https://doi.org/10.1101/2020.11.13.20231209
编译者：刘焕珍
中文摘要：
肠道菌群与肺（肠肺轴）之间的串扰被破坏是呼吸相关疾病期间严重程度的驱动因素。肺损伤会引起全身性炎症，从而破坏肠道屏障的完整性，增加对肠道微生物及其产物的渗透性。这会加剧炎症，产生积极的反馈。为了测试肠道破裂导致 COVID-19 严重程度的可能性，我们使用系统生物学方法分析了不同疾病严重程度和对照的 COVID-19 患者的血浆。严重的 COVID-19 与紧密连接渗透性的急剧增加以及细菌和真菌产物向血液中的转运有关。这种肠道破坏和微生物易位与全身炎症增加和补体激活、肠道代谢功能降低和死亡率较高密切相关。我们的研究强调了以前未曾认识到的，具有重要临床意义的因素，即肠屏障完整性的破坏，是导致 COVID-19 严重程度的一种力量。
Abstract:
A disruption of the crosstalk between gut microbiota and the lung (gut-lung axis) has been implicated as a driver of severity during respiratory-related diseases. Lung injury causes systemic inflammation, which disrupts gut barrier integrity, increasing the permeability to gut microbes and their products. This exacerbates inflammation, resulting in positive feedback. To test the possibility that a disrupted gut contributes to Coronavirus disease 2019 (COVID-19) severity, we used a systems biology approach to analyze plasma from COVID-19 patients with varying disease severity and controls. Severe COVID-19 is associated with a

dramatic increase in tight junction permeability and translocation of bacterial and fungal products into blood. This intestinal disruption and microbial translocation correlate strongly with increased systemic inflammation and complement activation, lower gut metabolic function, and higher mortality. Our study highlights a previously unappreciated factor with significant clinical implications, disruption in gut barrier integrity, as a force that contributes to COVID-19 severity.

9. 11 月 20 日辉瑞递交了的关于 COVID-19 疫苗的紧急使用授权

Pfizer Submitted an EUA Request for Its COVID-19 Vaccine

链接：https://www.pfizer.com/news/hot-topics/our_covid_19_vaccine_study_what_s_next

11 月 18 日辉瑞和 BioNTECH 总结说 COVID-19 疫苗 3 期临床达到了所有的主要临床有效性终点

PFIZER AND BIONTECH CONCLUDE PHASE 3 STUDY OF COVID-19 VACCINE CANDIDATE, MEETING ALL PRIMARY EFFICACY ENDPOINTS

链接：https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-submit-emergency-use-authorization

关于主要有效性的分析表明在第一剂之后的 28 天后 BNT162b2 对病毒感染的保护效应达到了 95%。对试验后期 170 个确诊的受试者进行揭盲后，只有 8 个在打过疫苗的组，其他 162 人全部来自于安慰剂组。

疫苗的有效性在不同年龄段、性别、种族以及族群地理分布等中结果一致；根据观察到的结果，对 65 岁以上老年人的保护率高于 94%。

达到了 FDA 关于紧急使用授权的安全要求。

数据显示该疫苗在所有超过 43000 个受试者中良好耐受；没有观察到严重的安全隐患；唯一超过 2%的三级不良反应是疲劳（3.8%）以及头痛（2.0%）。

两家公司计划在近日向 FDA 递交紧急使用授权申请，并将数据分享给全球其他监管部分。

两家公司计划在 2020 年在全球范围内生产 5 千万剂疫苗，以及到 2021 年底到达高达 13 亿剂（该疫苗需要注射 2 剂）。

辉瑞公司表示该公司拥有的丰富经验、人才以及现存的冷链足以将疫苗分发到世界各地（编者注：该疫苗需要负 80 的冷链运输条件）。

Highlights:

Primary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose;170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group.

Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%.

Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved.

Data demonstrate vaccine was well tolerated across all populations with over 43,000 participants enrolled; no serious safety concerns observed; the only Grade 3 adverse event greater than 2% in frequency was fatigue at 3.8% and headache at 2.0%.

Companies plan to submit within days to the FDA for EUA and share data with

other regulatory agencies around the globe.
The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021.
Pfizer is confident in its vast experience, expertise and existing cold-chain infrastructure to distribute the vaccine around the world.

10. Moderna 的新冠疫苗免疫高效性再次展示 mRNA 技术的广泛应用前景

Moderna COVID-19 vaccine validates mRNA platform, suggests success of other vaccines
来源：Biocentury
发布时间：2020-11-16
链接：https://www.biocentury.com/article/632030
作者：STEVE USDIN
编译者：姜连连
中文摘要：
Moderna 宣布其研制的新冠疫苗 III 期临床试验有效性为 94.5%。III 期临床试验共 30000 名志愿者参加，均为 18 岁以上的成年人，疫苗组和安慰剂对照组各有 15000 人。第一个中期结果分析显示 95 人在疫苗二免后两周确诊为感染新冠病毒，其中 90 人来自对照组，5 人来自疫苗免疫组，由此计算得出该疫苗降低了（90-5）/90=94.5%的感染比例，即疫苗有效率约为 94.5%。疫苗安全性较好，受试者对疫苗耐受性良好，其副作用包括轻度或中度的疲劳、肌肉关节疼痛和头痛。另外，对比辉瑞的 mRNA 疫苗超低温（-80℃）储运条件而言，Moderna 公司的疫苗可在-20℃下保存长达六个月，或 2-8℃保存约 1 个月，且使用前无需稀释，因此使用和储运更为方便。mRNA 技术是将 mRNA 直接制剂注射机体，通过胞吞作用 mRNA 进入细胞，合成特定的蛋白，从而刺激机体产生免疫反应。该技术的高效性已在 Moderna 和辉瑞的新冠 mRNA 疫苗 III 临床数据中得以验证和显现。因此，mRNA 疫苗开发是目前最有效和先进的方法之一，具有广泛的应用前景。
Abstract:
Moderna mRNA vaccine was demonstrated 94.5% efficacy in preventing COVID-19 in an interim analysis of the Phase III COVE trial. Moderna are based on 95 cases of COVID-19, of which 90 cases were in the placebo group vs. five cases observed in the mRNA-1273 group, resulting in efficacy of 94.5% ($p < 0.0001$). There were severe adverse events after the second dose in the COVE trial that could cause some people to avoid the vaccine or forgo the second dose. Grade 3, or severe, events that occurred after the second dose included fatigue, which affected 9.7% of trial participants, myalgia (8.9%), arthralgia (5.2%), headache (4.5%) and pain (4.1%). Moderna's vaccine is stable for 30 days at 2° to 8° C in a standard medical refrigerator. In contrast, BioNTech vaccine must be stored at -80° C, creating logistical challenges It can safely remain at room temperature for 24 hours before vaccination and can be stored for up to six months at -20° C. The mRNA platform clearly works with interim data from Phase III trials of the Moderna and Pfizer vaccine candidates. And Moderna vaccine's efficacy in preventing severe disease is "absolutely critical" for assessing its public health value.

11. ChAdOx1 nCoV-19 疫苗的安全性和免疫原性年轻人和老年人均采用初免-加强疗法成人（COV002）：单盲，随机，对照，2/3 期试验

Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial

来源：THE LANCET

发布时间：2020-11-18

链接：https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32466-1/fulltext

第一作者：Maheshi N Ramasamy

通讯作者：Maheshi N Ramasamy

通讯作者单位：Oxford Vaccine Group, Department of Paediatrics

DOI 或 PUBMED ID：https://doi.org/10.1016/S0140-6736(20)32466-1

编译者：张鹏伟

中文摘要：

背景：

如果老年人（年龄≥70 岁）患上 COVID-19，则罹患严重疾病和死亡的风险增加，因此，如果开发出有效的疫苗，则应优先进行免疫。由于老年人的免疫衰老，疫苗的免疫原性通常较差。我们已经报道了新的黑猩猩腺病毒载体疫苗 ChAdOx1 nCoV-19 在年轻人中的免疫原性，现在描述了该疫苗在更广泛的参与者中的安全性和免疫原性，包括 70 岁以上的成年人。

方法：

在这份有关单盲，随机，对照，第 2/3 期试验（COV002）的第 2 阶段组成部分的报告中，年龄在 18 岁以上的健康成年人以年龄递增的方式进入了英国的两家临床研究机构， 分为 18-55 岁，56-69 岁，70 岁及更高年龄的免疫原性亚组。如果参与者没有严重或无法控制的合并症或脆弱性评分较高（年龄≥65 岁），则符合资格。首先，将参与者招募至低剂量队列，并在每个年龄组内，随机分配参与者接受肌肉内 ChAdOx1 nCoV-19（$2.2\times\times10^{10}$病毒颗粒）或对照疫苗 MenACWY，采用区组随机分配和 按以下比率按年龄，剂量组和研究地点进行分层：在 18-55 岁组中，两剂 ChAdOx1 nCoV-19 或两剂 MenACWY 为 1：1；在 56-69 岁年龄组中，一剂 ChAdOx1 nCoV-19，一剂 MenACWY，两剂 ChAdOx1 nCoV-19 或两剂 MenACWY 3：1：3：1； 在 70 岁以上的人群中，一剂 ChAdOx1 nCoV-19，一剂 MenACWY，两剂 ChAdOx1 nCoV-19 或两剂 MenACWY 的比例为 5：1：5：1。初免疗法相隔 28 天。然后将参与者纳入标准剂量队列（ChAdOx1 nCoV-19 的 $3.5-6.5\times10^{10}$病毒颗粒），并遵循相同的随机程序，不同的是将 18-55 岁年龄组以 5：1 分配 分别与两剂 ChAdOx1 nCoV-19 或两剂 MenACWY 的比例成正比。参加者和研究者（而不是管理疫苗的工作人员）被屏蔽了疫苗的分配。本报告的具体目标是评估 55 岁以上成年人单剂量和两剂量方案的安全性，体液和细胞免疫原性。使用内部标准化 ELISA，多重免疫测定和严重急性呼吸系统综合症冠状病毒 2（SARS-CoV-2）微中和测定（MNA80）评估基线和加强免疫后直至每年接种后的体液反应。使用离体 IFN-γ 酶联免疫斑点测定法评估细胞应答。该试验的主要结果是疗效（通过有症状，经病毒学证实的 COVID-19 的病例数来衡量）和安全性（通过严重不良事件的发生来衡量）。按参加疫苗的参与者进行小组分配分析。在这里，我们报告有关安全性，反应原性以及细胞和体液免疫反应的初步发现。这项研究正在进行中，并已在 ClinicalTrials.gov，NCT04400838 和 ISRCTN，15281137 中进行了注册。

发现：

在 2020 年 5 月 30 日至 8 月 8 日之间，共有 560 名参与者参加：160 名 18-55 岁（分配给

ChAdOx1 nCoV-19 的人 100 名，分配给 MenACWY 60 名），160 名 56-69 岁（分配给 ChAdOx1 nCoV-19 的人）：40 个分配给 MenACWY)，以及 240 个 70 岁以上的老人(200 个分配给 ChAdOx1 nCoV-19：40 个分配给 MenACWY)。七名参与者未接受分配的两剂方案的加强剂量，一名参与者接受了错误的疫苗，而三名由于标签错误而被排除在免疫原性分析之外。552 位可分析的参与者中有 280 位（50%）是女性。接受 ChAdOx1 nCoV-19 的参与者的局部和全身反应比接受对照疫苗的参与者更常见，并且本质上与先前报道的相似（注射部位疼痛，发烧，肌肉疼痛，头痛)，但是在老年人(≥56 岁)比年轻人不常见。在接受两次标准剂量的 ChAdOx1 nCoV-19 的那些人群中，初次接种疫苗后，在 18-55 岁组的 49 位参与者中有 43 位（88%）报道了局部反应，在 56-69 岁年龄段的 30 位参与者中有 22 位（73%）报告了局部反应组和 70 岁及以上年龄组的 49 名患者中的 30 名（61%），以及 18-55 岁组中 42 名（86%）参与者的全身反应，56-69 岁组中 23 名(77%)的参与者，以及 70 岁及以上年龄组中有 32 位(65%)。截至 2020 年 10 月 26 日，在研究期间发生了 13 例严重不良事件，均未与任何一种研究疫苗相关。在接受了两剂疫苗的参与者中，在三个年龄组中，加强剂量后 28 天抗加标 SARS-CoV-2 IgG 的中位反应相似（标准剂量组：18-55 岁，20 713 任意单位[AU] / mL [IQR 13 898 - 33 550]，n = 39； 56 - 69 岁，16 170 AU / mL [10 233 - 40 353]，n = 26；以及≥70 年 17 561 AU / mL [9705 - 37 796]，n = 47； p = 0.68)。在所有年龄组中，加强剂量后的中和抗体滴度均相似（标准剂量组在第 42 天的 MNA80 中位数：18-55 岁，193 [IQR 113-238]，n = 39； 56-69 岁，144 [119 - 347]，n = 20；≥70 年，161 [73 - 323]，n = 47；p = 0.40)。加强剂量后第 14 天，在 209 名加强参与者中，有 208 名（> 99%）具有中和抗体反应。在单次标准剂量的 ChAdOx1 nCoV-19 后第 14 天，T 细胞反应达到峰值（18-55 岁：每百万外周血单核细胞中位数为 1187 个点形成细胞[SFCs] [IQR 841-2428]，n = 24； 56-69 年：797 个 SFC [383-1817]，n = 29；并且≥70 年：977 个 SFC [458-1914]，n = 48)。

解释：

ChAdOx1 nCoV-19 在老年人中的耐受性似乎好于年轻人，并且在加强剂量后所有年龄组的免疫原性均相似。 在所有年龄段和合并症患者中，都应进一步评估该疫苗的功效。

Abstract:

Background

Older adults (aged ≥70 years) are at increased risk of severe disease and death if they develop COVID-19 and are therefore a priority for immunisation should an efficacious vaccine be developed. Immunogenicity of vaccines is often worse in older adults as a result of immunosenescence. We have reported the immunogenicity of a novel chimpanzee adenovirus-vectored vaccine, ChAdOx1 nCoV-19, in young adults, and now describe the safety and immunogenicity of this vaccine in a wider range of participants, including adults aged 70 years and older.

Methods

In this report of the phase 2 component of a single-blind, randomised, controlled, phase 2/3 trial (COV002), healthy adults aged 18 years and older were enrolled at two UK clinical research facilities, in an age-escalation manner, into 18 - 55 years, 56 - 69 years, and 70 years and older immunogenicity subgroups. Participants were eligible if they did not have severe or uncontrolled medical comorbidities or a high frailty score (if aged ≥65 years). First, participants were recruited to a low-dose cohort, and within each age group, participants were randomly assigned to receive either intramuscular ChAdOx1 nCoV-19 (2.2×10^{10} virus particles) or a control vaccine, MenACWY, using block randomisation

and stratified by age and dose group and study site, using the following ratios: in the 18–55 years group, 1:1 to either two doses of ChAdOx1 nCoV-19 or two doses of MenACWY; in the 56–69 years group, 3:1:3:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY; and in the 70 years and older, 5:1:5:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. Prime-booster regimens were given 28 days apart. Participants were then recruited to the standard-dose cohort ($3.5–6.5 \times 10^{10}$ virus particles of ChAdOx1 nCoV-19) and the same randomisation procedures were followed, except the 18–55 years group was assigned in a 5:1 ratio to two doses of ChAdOx1 nCoV-19 or two doses of MenACWY. Participants and investigators, but not staff administering the vaccine, were masked to vaccine allocation. The specific objectives of this report were to assess the safety and humoral and cellular immunogenicity of a single-dose and two-dose schedule in adults older than 55 years. Humoral responses at baseline and after each vaccination until 1 year after the booster were assessed using an in-house standardised ELISA, a multiplex immunoassay, and a live severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) microneutralisation assay (MNA80). Cellular responses were assessed using an ex-vivo IFN-γ enzyme-linked immunospot assay. The coprimary outcomes of the trial were efficacy, as measured by the number of cases of symptomatic, virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were by group allocation in participants who received the vaccine. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. This study is ongoing and is registered with ClinicalTrials.gov, NCT04400838, and ISRCTN, 15281137.

Findings

Between May 30 and Aug 8, 2020, 560 participants were enrolled: 160 aged 18–55 years (100 assigned to ChAdOx1 nCoV-19, 60 assigned to MenACWY), 160 aged 56–69 years (120 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY), and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY). Seven participants did not receive the boost dose of their assigned two-dose regimen, one participant received the incorrect vaccine, and three were excluded from immunogenicity analyses due to incorrectly labelled samples. 280 (50%) of 552 analysable participants were female. Local and systemic reactions were more common in participants given ChAdOx1 nCoV-19 than in those given the control vaccine, and similar in nature to those previously reported (injection-site pain, feeling feverish, muscle ache, headache), but were less common in older adults (aged ≥56 years) than younger adults. In those receiving two standard doses of ChAdOx1 nCoV-19, after the prime vaccination local reactions were reported in 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 in the 56–69 years group, and 30 (61%) of 49 in the 70 years and older group, and systemic reactions in 42 (86%) participants in the 18–55 years group, 23 (77%) in the 56–69 years group, and 32 (65%) in the 70 years and older group. As of Oct 26, 2020, 13 serious adverse events occurred during the study period, none of which

were considered to be related to either study vaccine. In participants who received two doses of vaccine, median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts (standard-dose groups: 18–55 years, 20 713 arbitrary units [AU]/mL [IQR 13 898–33 550], n=39; 56–69 years, 16 170 AU/mL [10 233–40 353], n=26; and ≥70 years 17 561 AU/mL [9705–37 796], n=47; p=0.68). Neutralising antibody titres after a boost dose were similar across all age groups (median MNA80 at day 42 in the standard-dose groups: 18–55 years, 193 [IQR 113–238], n=39; 56–69 years, 144 [119–347], n=20; and ≥70 years, 161 [73–323], n=47; p=0.40). By 14 days after the boost dose, 208 (>99%) of 209 boosted participants had neutralising antibody responses. T-cell responses peaked at day 14 after a single standard dose of ChAdOx1 nCoV-19 (18–55 years: median 1187 spot-forming cells [SFCs] per million peripheral blood mononuclear cells [IQR 841–2428], n=24; 56–69 years: 797 SFCs [383–1817], n=29; and ≥70 years: 977 SFCs [458–1914], n=48).

Interpretation

ChAdOx1 nCoV-19 appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities.

12. SARS-CoV-2 mRNA 疫苗的初步研究

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

来源：NEJM

发布时间：2020-11-12

链接：

https://www.nejm.org/doi/full/10.1056/NEJMoa2022483?query=recirc_mostViewed_railB_article

第一作者：Graham、Beigel

通讯作者：Lisa A. Jackson

通讯作者单位：华盛顿健康研究院

DOI 或 PUBMED ID：10.1056/NEJMoa2022483

编译者：张丽双

中文摘要：

Moderna 候选 mRNA 疫苗 mRNA-1273 编码稳定的融合前 SARS-CoV-2 刺突蛋白。该疫苗一期临床试验为剂量递增、开放标签试验，包括 45 名 18 至 55 岁的健康成年人，两次疫苗接种，间隔 28 天，分别接种 25μg、100μg 或 250μg 的 mRNA-1273。每个剂量组有 15 名参与者。一期结果：在所有受试者中，mRNA-1273 疫苗诱导了抗 SARS-CoV-2 免疫应答，有报告不良反应，尤其是第二次加强免疫后，和高剂量组不良反应更多，但是安全性方面可以支持进行进一步开发。

Abstract:

BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and spread globally, prompting an international effort to accelerate development of a vaccine. The candidate vaccine mRNA-1273 encodes the stabilized

prefusion SARS-CoV-2 spike protein.
METHODS
We conducted a phase 1, dose-escalation, open-label trial including 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 μg, 100 μg, or 250 μg. There were 15 participants in each dose group.
RESULTS
After the first vaccination, antibody responses were higher with higher dose (day 29 enzyme-linked immunosorbent assay anti-S-2P antibody geometric mean titer [GMT], 40,227 in the 25-μg group, 109,209 in the 100-μg group, and 213,526 in the 250-μg group). After the second vaccination, the titers increased (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively). After the second vaccination, serum-neutralizing activity was detected by two methods in all participants evaluated, with values generally similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-μg dose group reported one or more severe adverse events.
CONCLUSIONS
The mRNA-1273 vaccine induced anti-SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified. These findings support further development of this vaccine. (Funded by the National Institute of Allergy and Infectious Diseases and others; mRNA-1273 ClinicalTrials.gov number, NCT04283461. opens in new tab).

13. 在 SARS-CoV-2 感染和细胞因子休克综合征中，TNF-α 和 IFN-γ 的协同作用触发炎症细胞死亡、组织损伤和死亡

Synergism of TNF-α and IFN-γ triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes
来源：Cell
发布时间：2020-11-18
链接：https://www.cell.com/cell/fulltext/S0092-8674(20)31542-7
第一作者：Rajendra Karki
通讯作者：Thirumala-Devi Kanneganti
通讯作者单位：圣裘德儿童研究医院免疫科
DOI 或 PUBMED ID：https://doi.org/10.1016/j.cell.2020.11.025
编译者：张丽双
中文摘要：
要点：在所检测的几种细胞因子中，只有 TNF-α 和 IFN-γ 的协同作用才能诱发广泛凋亡；TNF-α 和 IFN-γ 介导的广泛凋亡持续细胞因子风暴；TNF-α 和 IFN-γ 休克反映了细胞因子风暴综合征，包括 COVID-19；中和 TNF-α 和 IFN-γ 对小鼠 SARS-CoV-2、HLH 和脓毒症的保护作用。

摘要：COVID-19 的特点是过度产生促炎性细胞因子和与患者死亡率相关的急性肺损伤。在 SARS-CoV-2 感染过程中，先天性免疫细胞产生多种炎性细胞因子，但我们发现只有 TNF-α 和 IFN-γ联合诱导炎性细胞死亡，其特征是自燃、凋亡和广泛凋亡（PANoptosis）。在机制上,TNF-α 和 IFN-γ共同作用激活 JAK/STAT1/IRF1 轴,诱导一氧化氮产生,并驱动 caspase-8/FADD 介导的广泛凋亡。TNF-α 和 IFN-γ在小鼠体内引起了致命的细胞因子休克，这反映了 COVID-19 的组织损伤和炎症反应，抑制广泛凋亡可以保护小鼠免于这种病理和死亡。此外，用抗 TNF-α 和 IFN-γ的中和抗体治疗可保护小鼠在 SARS-CoV-2 感染、败血症、噬血性淋巴组织细胞增多症和细胞因子休克期间的死亡率。总的来说，我们的研究结果表明，阻断细胞因子介导的炎症细胞死亡信号通路可以通过限制组织损伤/炎症而使 COVID-19 或其他感染性和自体炎症性疾病的患者受益。

Abstract: Highlights

•Of several cytokines tested, only synergism of TNF-α and IFN-γ induces PANoptosis

•TNF-α and IFN-γ -mediated PANoptosis perpetuates cytokine storm

•TNF-α and IFN-γ shock mirrors cytokine storm syndromes, including COVID-19

•Neutralizing TNF-α and IFN-γ protects against SARS-CoV-2, HLH, and sepsis in mice

Summary

COVID-19 is characterized by excessive production of pro-inflammatory cytokines and acute lung damage associated with patient mortality. While multiple inflammatory cytokines are produced by innate immune cells during SARS-CoV-2 infection, we found that only the combination of TNF-α and IFN-γ induced inflammatory cell death characterized by pyroptosis, apoptosis, and necroptosis (PANoptosis). Mechanistically, TNF-α and IFN-γ co-treatment activated the JAK/STAT1/IRF1 axis, inducing nitric oxide production and driving caspase-8/FADD-mediated PANoptosis. TNF-α and IFN-γ caused a lethal cytokine shock in mice that mirrors the tissue damage and inflammation of COVID-19, and inhibiting PANoptosis protected mice from this pathology and death. Furthermore, treating with neutralizing antibodies against TNF-α and IFN-γ protected mice from mortality during SARS-CoV-2 infection, sepsis, hemophagocytic lymphohistiocytosis, and cytokine shock. Collectively, our findings suggest that blocking the cytokine-mediated inflammatory cell death signaling pathway identified here may benefit patients with COVID-19 or other infectious and autoinflammatory diseases by limiting tissue damage/inflammation.

14. SARS-CoV-2 表位被多种人类 T 细胞受体所识别

SARS-CoV-2 epitopes are recognized by a public and diverse repertoire of human T cell receptors

来源： Immunity

发布时间：2020-11-13

链接：https://www.cell.com/immunity/fulltext/S1074-7613(20)30469-6

第一作者：Alina S. Shomuradova

通讯作者：Mikhail Shugay

通讯作者单位：Eindhoven University of Technology, Eindhoven, Netherlands

DOI 或 PUBMED ID：https://doi.org/10.1016/j.immuni.2020.11.004
编译者：孔娟
中文摘要：
了解抗 SARS-CoV-2 免疫反应的标志对于遏制 COVID-19 大流行至关重要，文中研究者评估了大流行之前和期间采集的恢复性 COVID-19 患者和健康供体血液的抗体和 T 细胞反应。在大流行期间检查的健康供体显示出 SARS-CoV-2 特异性 T 细胞数量增加，但没有体液反应。它们可能暴露于病毒导致无症状感染而无抗体分泌，或激活预先存在的免疫力。在恢复期患者中，研究人员观察到 SARS-CoV-2 表位被多种 T 细胞所识别，并揭示了具有种系编码特征的 T 细胞受体（TCR）模体。同时发现大量 CD4+和 CD8+T 细胞对 S 糖蛋白的反应是由同源 TCR 组介导的，其中一些在多个供体之间共享。总体而言，这些结果表明，对 SARS-CoV-2 的 T 细胞反应的相关研究（包括鉴定的 TCR 组）为发现抗病毒免疫力相关生物标记提供了一种新的方式。
Abstract：
Understanding the hallmarks of the immune response to SARS-CoV-2 is critical for fighting the COVID-19 pandemic. We assessed antibody and T cell reactivity in convalescent COVID-19 patients and healthy donors sampled both prior to and during the pandemic. Healthy donors examined during the pandemic exhibited increased numbers of SARS-CoV-2-specific T cells, but no humoral response. Their probable exposure to the virus resulted in either asymptomatic infection without antibody secretion, or activation of pre-existing immunity. In convalescent patients, we observed a public and diverse T cell response to SARS-CoV-2 epitopes, revealing T cell receptor (TCR) motifs with germline-encoded features. Bulk CD4+ and CD8+ T cell responses to the spike glycoprotein were mediated by groups of homologous TCRs, some of them shared across multiple donors. Overall, our results demonstrate that the T cell response to SARS-CoV-2, including the identified set of TCRs, can serve as a useful biomarker for surveying antiviral immunity.

15. 慢性炎症失调的新型基因特异性翻译机制揭示了有前景的多方面 COVID-19 治疗手段

Novel gene-specific translation mechanism of dysregulated, chronic inflammation reveals promising, multifaceted COVID-19 therapeutics
来源：bioRxiv
发布时间：2020-11-16
链接：https://www.biorxiv.org/content/10.1101/2020.11.14.382416v1
第一作者：Li Wang
通讯作者：Xian Chen
通讯作者单位：Department of Biochemistry & Biophysics, University of North Carolina at Chapel Hill
DOI 或 PUBMED ID：
编译者：张鹏伟
中文摘要：
SARS-CoV-2 活化的巨噬细胞引起的过度炎症和淋巴细胞减少导致 2019 年冠状病毒病（COVID-19）患者的高死亡率。因此，确定在患者巨噬细胞中异常激活的宿主途径对于开发有效的治疗方法至关重要。我们发现，G9a 是一种在高病毒载量的 COVID-19 患者中过表达的组蛋白甲基转移酶，可激活诱导过度炎症和 T 细胞功能或淋巴细胞减少的特定基因的翻

译。G9a 的这种非规范的促翻译活性与其规范的表观遗传功能相反。在模仿条件使内在的慢性炎症性疾病易患严重症状的内毒素耐受（ET）巨噬细胞中，我们采用生物素化 G9a 抑制剂的化学旋转方法确定了多种 SA9-CoV 上调的与 G9a 相关的翻译调控途径 -2 感染。此外，在严重患者中，用 G9a 抑制剂逐步治疗的 ET 巨噬细胞的定量翻译组分析分析了 G9a 翻译的蛋白，该蛋白将与病毒复制和 SARS-CoV-2 诱导的宿主反应相关的网络结合在一起。因此，抑制 G9a 相关途径产生了多方面的系统性作用，即恢复 T 细胞功能，减轻过度炎症和抑制病毒复制。重要的是，作为一种针对宿主的机制，这种靶向 G9a 的联合治疗药物对劫持宿主反应的 SARS-CoV-2 或任何病毒的新兴抗病毒耐药突变体均具有耐药性。

Abstract:

Hyperinflammation and lymphopenia provoked by SARS-CoV-2-activated macrophages contribute to the high mortality of Coronavirus Disease 2019 (COVID-19) patients. Thus, defining host pathways aberrantly activated in patient macrophages is critical for developing effective therapeutics. We discovered that G9a, a histone methyltransferase that is overexpressed in COVID-19 patients with high viral load, activates translation of specific genes that induce hyperinflammation and impairment of T cell function or lymphopenia. This noncanonical, pro-translation activity of G9a contrasts with its canonical epigenetic function. In endotoxin-tolerant (ET) macrophages that mimic conditions which render patients with pre-existing chronic inflammatory diseases vulnerable to severe symptoms, our chemoproteomic approach with a biotinylated inhibitor of G9a identified multiple G9a-associated translation regulatory pathways that were upregulated by SARS-CoV-2 infection. Further, quantitative translatome analysis of ET macrophages treated progressively with the G9a inhibitor profiled G9a-translated proteins that unite the networks associated with viral replication and the SARS-CoV-2-induced host response in severe patients. Accordingly, inhibition of G9a-associated pathways produced multifaceted, systematic effects, namely, restoration of T cell function, mitigation of hyperinflammation, and suppression of viral replication. Importantly, as a host-directed mechanism, this G9a-targeted, combined therapeutics is refractory to emerging antiviral-resistant mutants of SARS-CoV-2, or any virus, that hijacks host responses.

16. SARS-CoV-2 病毒颗粒上的 Spike 蛋白的实时构象动力学研究

Real-time Conformational Dynamics of SARS-CoV-2 Spikes on Virus Particles

来源：Cell Host & Microbe

发布时间：2020-11-13

链接：https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30618-1?utm_medium=homepage

第一作者：Maolin Lu

通讯作者：Maolin Lu, Walther Mothes

通讯作者单位：

Department of Microbial Pathogenesis, Yale University School of Medicine, New Haven, CT, USA.

DOI 或 PUBMED ID：10.1016/j.chom.2020.11.001

编译者：宋珂

亮点：

- SARS-CoV-2 S 蛋白可在至少 4 种不同的构象状态间动态地转变
- 受到 hACE2 激活，S 蛋白可以从基态构象经历一个中间态转变到活化状态
- S 蛋白的水解过程可以加速其 hACE2 依赖的构象活化
- 抗体可以通过两种不同的中和机制拮抗 S 蛋白

中文摘要：

SARS-CoV-2 spike 蛋白（S）能够介导病毒侵入细胞，因此是开发针对 COVID-19 的疫苗的关键。结构生物学的研究已经揭示了 S 蛋白的不同构象，然而在这些结构间转变的实时信息却仍然缺乏。本文中，作者应用单分子荧光（Förster）共振能量转移（smFRET）成像技术观测了病毒颗粒上的 S 蛋白的构象动力学特性。病毒表面的 S 蛋白可以在至少 4 种不同的构象状态间动态转变。为响应人类受体血管紧张素转换酶 2（hACE2）的激活，S 蛋白经历至少一种过临界点的中间态，从基态构象转变为与 hACE2 结合状态下的打开构象。当暴露于康复患者的血浆或抗体时作者观察到的 S 蛋白的构象偏好，说明存在两种抗体中和机制。分别是与 hACE2 竞争结合受体结合结构域（RBD），或变构干扰病毒侵入所需的构象转变。作者的发现为免疫原设计提供了 S 蛋白的构象和识别的机制。

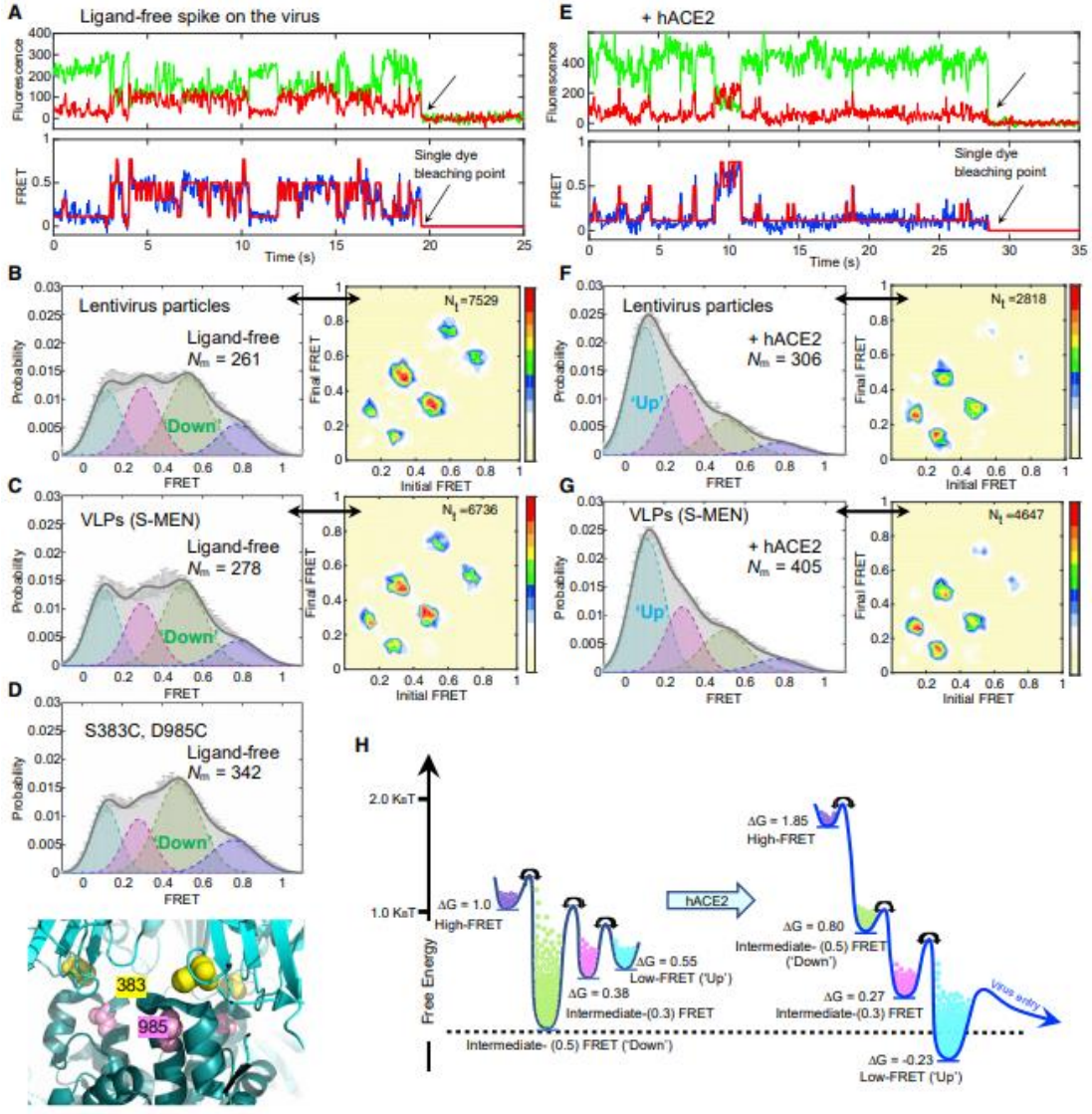


Figure 2. SARS-CoV-2 Spike Protein Is Dynamic, and hACE2 Shifts Conformational Landscape

from the Ground State to the Receptor-Bound State through One Necessary Intermediate

(A–D) The ligand-free S on virus particles primarily resides in "RBD-down" conformation (ground state). **(A)** Example fluorescence trace (Cy3B, green; LD650, red) and resulting quantified FRET traces (FRET efficiency, blue; hidden Markov model initialization, red) of a dually labeled ligand-free spike protein on the surface of HIV-1 lentivirus particle. Arrows point to the single-step photobleaching steps of dyes at the singlemolecule level and define the baseline. **(B and C)** FRET histograms (left) and TDPs (right) of ligand-free spikes on lentivirus particles (B) and S-MEN viral-like particles (C). Also shown is the number (Nm) of individual dynamic molecules/traces compiled into a conformation-population FRET histogram (gray lines) and fitted into a 4-state Gaussian distribution (solid black) centered at 0.1-FRET (dashed cyan), 0.3-FRET (dashed red), 0.5-FRET (dashed green), and 0.8-FRET (dashed magenta). TDPs, displayed as initial FRET versus final FRET with relative frequencies, trace the locations of state-to-state transitions and their relative frequencies (max red scale = 0.01 transitions/second), originated from the idealization of individual FRET traces in FRET histograms. **(D)** A modified spike (S383C and D985C) (Henderson et al., 2020; McCallum et al., 2020) stabilized in RBD-down conformation, observed from the FRET histogram (upper panel). The small increase in the population of the ground state (0.5 FRET) likely reflects the partial nature of the formation of the disulfide in this mutant, which has 40% the infectivity of wild-type (Figure S3C). Modified S383C and D985C depicted in the high-resolution structure of S 6ZOY (lower panel). **(E–G)** Experiments as in (A)–(C), respectively, conducted in the presence of 200 mg/mL monomeric hACE2. The soluble hACE2 activates spike proteins on the virus by shaping the conformational landscape toward stabilizing the RBD-up conformation (activated state). FRET histograms represent mean ± SEM, determined from three randomly assigned populations of all FRET traces under corresponding experimental conditions. N, number of individual FRET traces. Evaluated state occupancies see Table S1. **(H)** Relative free-energy model of conformational landscapes of SARS-CoV-2 spikes in response to the hACE2 binding. The differences in free energies between states were roughly scaled based upon relative state occupancies of each state.

Highlights:

• SARS-CoV-2 S protein dynamically samples at least 4 distinct conformational states

• hACE2 activates S from the ground state to the activated state via an intermediate

• Proteolytic processing of S accelerates hACE2-dependent activation

• Antibodies can antagonize S by two different mechanisms of neutralization

Summary:

SARS-CoV-2 spike (S) mediates viral entry into cells and is critical for vaccine development against COVID-19. Structural studies have revealed distinct conformations of S, but real-time information that connects these structures, is lacking. Here we apply single-molecule Fluorescence (Förster) Resonance Energy Transfer (smFRET) imaging to observe conformational dynamics of S on virus particles. Virus-associated S dynamically samples at least four distinct conformational states. In response to human receptor Angiotensin-Converting Enzyme 2 (hACE2), S opens sequentially into the hACE2-bound S conformation through at least one on-path intermediate. Conformational preferences observed upon expsoure to convalescent plasma or antibodies suggest mechanisms of neutralization involving either competition with hACE2 for binding to the

receptor-binding domain (RBD) or allosteric interference with conformational changes required for entry. Our findings inform on mechanisms of S recognition and conformations for immunogen design.

17. SARS-CoV-2 N 蛋白相分离的磷酸化调控提供了其双重功能的生物物理基础

Phosphoregulation of phase separation by the SARS-CoV-2 N protein suggests a biophysical basis for its dual functions

来源：Molecular Cell

发布时间：2020-11-17

链接：https://www.cell.com/molecular-cell/fulltext/S1097-2765(20)30803-0

第一作者：Christopher R. Carlson

通讯作者：David O. Morgan

通讯作者单位：

Department of Physiology, University of California, San Francisco CA 94143

DOI 或 PUBMED ID：10.1016/j.molcel.2020.11.025

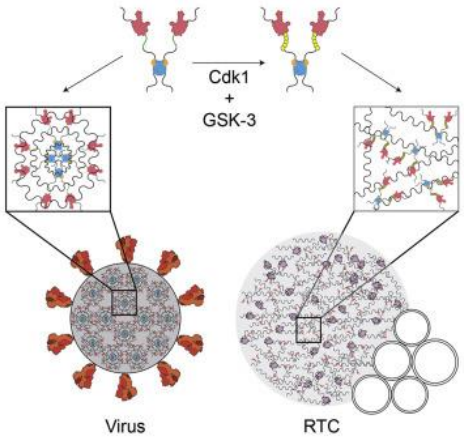
编译者：宋珂

亮点：

- SARS-CoV-2 病毒的核壳蛋白可以与病毒 RNA 形成生物分子团聚物
- 未修饰的 N 蛋白可以形成含有分散 RNP 颗粒的凝胶状团聚物
- 磷酸化的 N 蛋白可以形成动态的液体状团聚物
- 为研究 N 蛋白的两种主要功能，作者详细研究了两种 N 蛋白的团聚物

中文摘要：

冠状病毒的核壳蛋白（N）具有两个主要功能：封装病毒颗粒中的 RNA 基因组，对病毒基因的转录进行调控。目前，对 N 蛋白如何介导这两种不同功能的机制还不明确。N 蛋白包含两个 RNA 结合结构域，被周围的固有无序区域围绕。中央无序区域的磷酸化可以促使 N 蛋白发挥转录功能，但其基础的机制尚不明确。本文中，作者发现 SARS-CoV-2 病毒的 N 蛋白可以与病毒 RNA 一起形成生物分子团聚物。由于存在多价 RNA-蛋白和蛋白-蛋白相互作用，未修饰的 N 蛋白可以形成部分有序的凝胶状团聚物，并分散为 15 nm 的颗粒。磷酸化修饰能够减少这些相互作用，形成了更像液体的液滴。作者提出了独特的寡聚态假设，以解释 N 蛋白的两种功能：未修饰的蛋白形成适合核壳装配的结构化低聚物，而磷酸化修饰的蛋白则形成了类似液体的隔离区域，用于病毒基因组的加工。



Highlights:

• nucleocapsid protein of SARS-CoV-2 forms biomolecular condensates with viral RNA

• unmodified N protein forms gel-like condensates containing discrete RNP particles

• phosphorylated N protein forms dynamic, liquid-like condensates

• the two condensate forms are well suited for the two major functions of N protein

Summary:

The nucleocapsid (N) protein of coronaviruses serves two major functions: compaction of the RNA genome in the virion and regulation of viral gene transcription. It is not clear how the N protein mediates such distinct functions. The N protein contains two RNA-binding domains surrounded by regions of intrinsic disorder. Phosphorylation of the central disordered region promotes the protein's transcriptional function, but the underlying mechanism is not known. Here we show that the N protein of SARS-CoV-2, together with viral RNA, forms biomolecular condensates. Unmodified N protein forms partially ordered gel-like condensates and discrete 15-nm particles based on multivalent RNA-protein and protein-protein interactions. Phosphorylation reduces these interactions, generating a more liquid-like droplet. We propose that distinct oligomeric states support the two functions of the N protein: unmodified protein forms a structured oligomer that is suited for nucleocapsid assembly, and phosphorylated protein forms a liquid-like compartment for viral genome processing.

18. SARS-CoV-2 进入因子在健康人和 COVID-19 患者胰腺中的表达

Expression of SARS-CoV-2 Entry Factors in the Pancreas of Normal Organ Donors and Individuals with COVID-19

来源：Cell Metabolism

发布时间：2020-11-13

链接：https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30600-8#

第一作者：Irina Kusmartseva

通讯作者：Mark A. Atkinson [1, 14]

通讯作者单位：

1 Department of Pathology, Immunology, and Laboratory Medicine, University of Florida Diabetes Institute, College of Medicine, Gainesville,

FL 32610, USA

14 Department of Pediatrics, University of Florida Diabetes Institute, College of Medicine, Gainesville, FL 32610, USA

DOI 或 PUBMED ID：10.1016/j.cmet.2020.11.005

编译者：王玮

中文摘要：

糖尿病与 SARS-CoV-2 的死亡率增加有关。文献表明 SARS-CoV-2 感染与诱导糖尿病之间存在潜在联系，该研究检测了 SARS-CoV-2 感染的关键进入因子血管紧张素转换酶 2（ACE2）的胰腺表达。该研究分析了五个公开的胰腺 scRNA-seq 数据集，并在整个生命周期内对健康

人类胰腺组织以及来自 COVID-19 病例的 ACE2 进行了荧光原位杂交、蛋白质印迹和免疫定位。这些体内外分析显示，ACE2 在胰腺导管上皮和微血管中有显著表达，但内分泌细胞的 mRNA 表达很少。来自 COVID-19 患者的胰腺表现为多发性血栓性病变，SARS-CoV-2 核衣壳蛋白表达主要局限于导管。这些结果表明，SARS-CoV-2 通过 ACE2 感染胰腺内分泌细胞不大可能是 COVID-19 导致糖尿病的原因。

Abstract:
Diabetes is associated with increased mortality from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Given literature suggesting a potential association between SARS-CoV-2 infection and diabetes induction, we examined pancreatic expression of angiotensin-converting enzyme 2 (ACE2), the key entry factor for SARS-CoV-2 infection. Specifically, we analyzed five public scRNA-seq pancreas datasets and performed fluorescence in situ hybridization, western blotting, and immunolocalization for ACE2 with extensive reagent validation on normal human pancreatic tissues across the lifespan, as well as those from coronavirus disease 2019 (COVID-19) cases. These in silico and ex vivo analyses demonstrated prominent expression of ACE2 in pancreatic ductal epithelium and microvasculature, but we found rare endocrine cell expression at the mRNA level. Pancreata from individuals with COVID-19 demonstrated multiple thrombotic lesions with SARS-CoV-2 nucleocapsid protein expression that was primarily limited to ducts. These results suggest SARS-CoV-2 infection of pancreatic endocrine cells, via ACE2, is an unlikely central pathogenic feature of COVID-19-related diabetes.

19. 从水貂分离出的 SARS-CoV-2 基因组中的反复出现的突变指向快速的宿主适应

Recurrent mutations in SARS-CoV-2 genomes isolated from mink point to rapid host-adaptation

来源：bioRxiv
发布时间：2020-11-16
链接：https://www.biorxiv.org/content/10.1101/2020.11.16.384743v1

第一作者：Lucy van Dorp
通讯作者：Lucy van Dorp 和 François Balloux
通讯作者单位：UCL Genetics Institute, University College London, United Kingdom

DOI 或 PUBMED ID：

编译者：宋张悦

中文摘要：

2019 年底， SARS-CoV-2 从一个未知的动物宿主感染人类。与其他冠状病毒一样，SARS-CoV-2 有可能感染广泛的宿主。SARS-CoV-2 基因组现已从猫、狗、狮子、老虎和水貂中分离出来。SARS-CoV-2 似乎在水貂养殖场传播得特别好，西班牙、瑞典、荷兰、意大利、美国和丹麦都有疫情报告。从被感染的水貂中分离出的 SARS-CoV-2 的基因组数据为病毒的二次宿主跳跃提供了一个自然的案例研究，在这种情况下，病毒从人类传播到动物，偶尔也会再传播回来。我们筛选了已发表的从水貂中分离出来的 SARS-CoV-2 基因组，发现水貂中常见的周期性突变，但在人类感染的 SARS-CoV-2 基因组中并不常见。我们确定了 23 个反复出现的突变，包括在 SARS-CoV-2 刺突蛋白受体结合区域的 3 个非同义突变，这些突变至少独立出现了 4 次，但在人类循环的毒株中很少观察到。从水貂身上分离出来的病毒在不同的系统遗传学谱系中重复出现突变，这表明 SARS-CoV-2 正在适应新的宿主。水貂 SARS-CoV-2 突变的

迅速获得和传播表明，如果宿主适应的类似现象发生在人类身上，那么这些人类特有的突变很可能在第一个 SARS-CoV-2 基因组产生之前就已经固定了。

Abstract:
Severe acute respiratory coronavirus 2 (SARS-CoV-2), the agent of the ongoing COVID-19 pandemic, jumped into humans from an unknown animal reservoir in late 2019. In line with other coronaviruses, SARS-CoV-2 has the potential to infect a broad range of hosts. SARS-CoV-2 genomes have now been isolated from cats, dogs, lions, tigers and minks. SARS-CoV-2 seems to transmit particularly well in mink farms with outbreaks reported in Spain, Sweden, the Netherlands, Italy, the USA and Denmark. Genomic data from SARS-CoV-2 isolated from infected minks provides a natural case study of a secondary host jump of the virus, in this case from humans to animals, and occasionally back again. We screened published SARS-CoV-2 genomes isolated from minks for the presence of recurrent mutations common in mink but infrequent in SARS-CoV-2 genomes from human infections. We identify 23 recurrent mutations including three nonsynonymous mutations in the Receptor Binding Domain of the SARS-CoV-2 spike protein that independently emerged at least four times but are only very rarely observed in strains circulating in humans. The repeat emergence of mutations across phylogenetically distinct lineages of the virus isolated from minks points to ongoing adaptation of SARS-CoV-2 to a new host. The rapid acquisition and spread of SARS-CoV-2 mutations in minks suggests that if a similar phenomenon of host adaptation had occurred upon its jump into humans, those human-specific mutations would likely have reached fixation already before the first SARS-CoV-2 genomes were generated.

20. Roborovski 矮仓鼠—一种 SARS-CoV-2 感染后快速致死的模型

The Roborovski dwarf hamster – a highly susceptible model for a rapid and fatal course of SARS-CoV-2 infection

来源：Cell Reports
发布时间：2020-11-18
链接：https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31477-7

第一作者：Jakob Trimpert
通讯作者：Jakob Trimpert
通讯作者单位：Institut für Virologie, Freie Universität Berlin, Berlin, Germany

DOI 或 PUBMED ID：10.1016/j.celrep.2020.108488

编译者：王玮

中文摘要：

由 SARS-CoV-2 引起的 COVID-19 大流行在世界范围内引发了一场前所未有的尚未解决的卫生危机。有不同种类的哺乳动物对 SARS-CoV-2 很敏感；然而，迄今为止被检测的物种很少能发展出强有力的临床病症，这些病症能够反映出严重的人类病症，或者允许在重症条件下测试疫苗和药物。该研究比较了三种矮仓鼠（*Phodopus* spp.）对 SARS-CoV-2 的敏感性，并介绍了 Roborovski 侏儒仓鼠（*P. roborovskii*）作为一种高度敏感的 COVID-19 模型，具有一致和强烈的临床症状。特别的是，只有这一物种显示了 SARS-CoV-2 引起的严重急性弥漫性肺泡损伤和肺透明微血栓，人类患者会这些症状，但在任何实验感染的其他动物中都没有出现。该研究建议 Roborovski 矮仓鼠作为一个有价值的模型来检验候选疫苗和治疗方

法的有效性和安全性，特别是用于高度易感人群。

Abstract:
The COVID-19 pandemic caused by SARS-CoV-2 has precipitated an unprecedented and yet unresolved health crisis worldwide. Different mammals are susceptible to SARS-CoV-2; however, few species examined so far develop robust clinical disease that mirrors severe human cases or allows testing of vaccines and drugs under conditions of severe disease. Here, we compare the susceptibilities of three dwarf hamster species (*Phodopus* spp.) to SARS-CoV-2 and introduce the Roborovski dwarf hamster (*P. roborovskii*) as a highly susceptible COVID-19 model with consistent and fulminant clinical signs. Particularly, only this species shows SARS-CoV-2-induced severe acute diffuse alveolar damage and hyaline microthrombi in the lungs, changes described in patients who succumbed to the infection, but not reproduced in any experimentally infected animal. Based on our findings, we propose the Roborovski dwarf hamster as a valuable model to examine the efficacy and safety of vaccine candidates and therapeutics, particularly for use in highly susceptible individuals.

21. SARS-CoV-2 在家猫中的传播存在狭窄的瓶颈

Transmission of SARS-CoV-2 in domestic cats imposes a narrow bottleneck
来源：bioRxiv
发布时间：2020-11-17
链接：https://www.biorxiv.org/content/10.1101/2020.11.16.384917v1
第一作者：Katarina M. Braun, Gage K. Moreno
通讯作者：Thomas C. Friedrich
通讯作者单位：Department of Pathobiological Sciences, University of Wisconsin-Madison, Madison, WI, United States of America
DOI 或 PUBMED ID：Preprint
编译者：宋张悦
中文摘要：

SARS-CoV-2 病毒适应哺乳动物宿主并可能逃脱人类免疫的进化机制取决于个体宿主内部和之间产生和选择遗传变异的方式。以家猫为模型，我们发现 SARS-CoV-2 的共有序列在宿主体内随时间基本保持不变，但动态亚-共有序列的多样性揭示了遗传漂变和弱纯化选择的过程。这个系统中的传播瓶颈似乎很窄，新感染的被发现少于 10 种病毒。我们在 Spike 的第 655 号氨基酸位置上(H655Y)发现了一个显著的变异，该变异在带有编号的猫中迅速出现，并在三对传播后的两对中固定下来，表明该位点可能在猫宿主中处于正选择状态。我们推测，狭窄的传播瓶颈和缺乏普遍的正向选择两个因素一起，限制了哺乳动物宿主中正在进行的 SARS-CoV-2 适应性进化的步伐。

Abstract:
The evolutionary mechanisms by which SARS-CoV-2 viruses adapt to mammalian hosts and, potentially, escape human immunity depend on the ways genetic variation is generated and selected within and between individual hosts. Using domestic cats as a model, we show that SARS-CoV-2 consensus sequences remain largely unchanged over time within hosts, but dynamic sub-consensus diversity reveals processes of

genetic drift and weak purifying selection. Transmission bottlenecks in this system appear narrow, with new infections being founded by fewer than ten viruses. We identify a notable variant at amino acid position 655 in Spike (H655Y) which arises rapidly in index cats and becomes fixed following transmission in two of three pairs, suggesting this site may be under positive selection in feline hosts. We speculate that narrow transmission bottlenecks and the lack of pervasive positive selection combine to constrain the pace of ongoing SARS-CoV-2 adaptive evolution in mammalian hosts.