新型冠状病毒信息简报

第 68 期（2020 年 8 月 15-8 月 21 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 8 月 20 日疫情
流行病学	2. 大流行对深海的危害：海洋哺乳动物从废水中感染 SARS-CoV-2 的风险 3. 在一起渔船上爆发的高发病率 SARS-CoV-2 感染中，中和抗体与人体预防 SARS-CoV-2 感染能力的关系
疾病检测	4. 评估使用可穿戴设备测量的 COVID-19 相关的生理体征 5. CovidNudge，一种新型的非实验室即时的 SARS-CoV-2 的诊断准确性 6. 快速高效的病毒基因组测序 V-seq 7. SARS-CoV-2 特异性的 CD8+ T 细胞的体外检测：快速诱导，延长的收缩和功能记忆的形成 8. 鼻内单剂量腺病毒载体疫苗可在大猩猩中抵抗 SARS-CoV-2 的呼吸道感染
疾病病理	9. 未暴露的人群中 SARS-CoV-2 选择性和交叉反应的 T 细胞表位 10. SARS-CoV-2 病毒在非洲绿猴肺部的感染动力学 11. COVID-19 尸检的多器官蛋白质组学研究 12. 区分 COVID-19 与 A 型流感（H1N1）的临床和免疫学特征
疫苗研发	13. NVX-CoV2373 疫苗保护食蟹猴上下呼吸道免受 SARS-CoV-2 攻击 14. 经一次注射多靶点的 COVID-19 疫苗可诱导组织驻留记忆 CD8 T 细胞应答 15. 高热稳定性、高免疫原性 SARS-CoV-2 刺突片段的设计 16. 国药新冠疫苗预计 12 月底上市！价格公布！ 17. COVID-19 RNA 疫苗 BNT162b1 在成年人中的临床 1/2 期研究 18. 无症状感染者以及中轻度 COVID-19 康复者中都存在 T 细胞免疫
药物研发	19. 羟氯喹抑制 SARS-CoV2 进入的作用机制
临床试验	20. 基于 RNA 的 COVID-19 疫苗 BNT162b2 用于关键功效研究
基础研究	21. SARS-CoV-2 spike 蛋白在完整病毒颗粒上的结构和分布 22. 单细胞 RNA 测序显示外周和肺对 COVID-19 的免疫应答差异 23. SARS-CoV-2 基因组一个重要缺失对感染严重程度和炎症反应的影响：一项观察性队列研究 24. SARS-CoV-2 外显子(nsp14-nsp10)复合体的特征:其在病毒基因组稳定性和抑制剂鉴定中的作用 25. COVID-19 患者中 Bcl-6+ T 滤泡辅助细胞的降低和生发中心的缺失相关研究 26. 设计的重组 ACE2-Fc 变异型，使抗 SARS-CoV-2 的活性与不必要的心血管效应分离

	27. 使用串行晶体学方法解析 SARS-CoV-2 中甲基化的 RNA 帽的结构 28. IFITM 蛋白促进 SARS-CoV-2 病毒感染人体肺细胞 29. 显而易见：α-1-抗胰蛋白酶在 COVID-19 发病机理和治疗中的作用 30. 细菌对宿主粘多糖肝素的修饰可以调节 SARS-CoV-2 的感染性 31. SRSF 蛋白激酶 1 和 2 (SPRK1/2)是对包括 SARS-CoV-2 在内的人冠状病毒感染不可缺少的宿主因子 32. SARS-CoV-2 操纵了 SR-B1 介导的高密度脂蛋白吸收通路帮助自己进入细胞 33. SARS-CoV-2 刺突蛋白的原位结构分析揭示了其由三个铰链导致的灵活性
疾病模型	34. 猪细胞和家猪对 SARS-CoV-2 的敏感性 35. 一个用于研究 COVID-19 的人类免疫系统的小鼠模型(DRAGA mouse: HLA-A2.HLA-DR4.Rag1KO.IL-2Rγc KO.NOD)
其他	36. 对冠状病毒的免疫反应说明疫苗的前景 37. Moderna 提出了“低于价值格”的 COVID-19 疫苗定价计划的理由

免责申明：

本简报仅作为科研参考之用，不构成医疗建议，如您怀疑自己感染新型冠状病毒，请去正规医院或者咨询医生。

1. 2020 年 8 月 20 日疫情

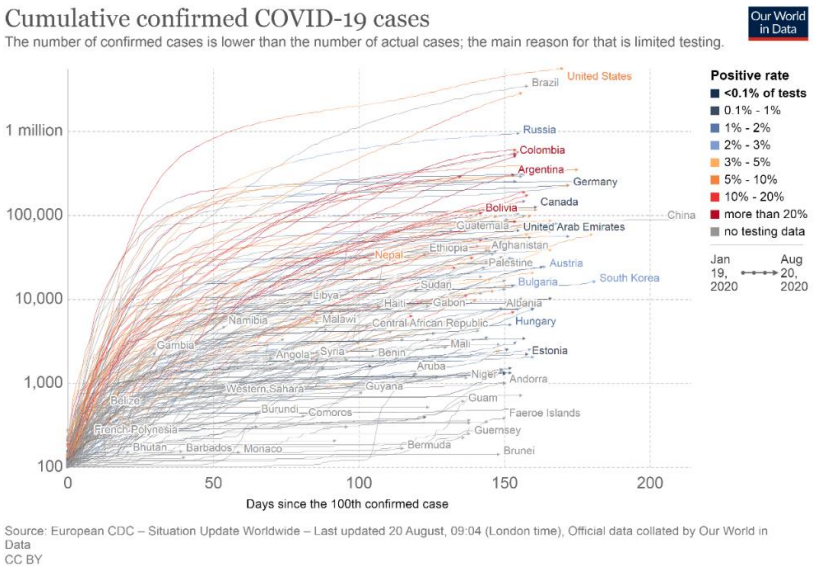
数据来源：WHO

发布时间：2020 年 8 月 20 日北京时间下午 4 点

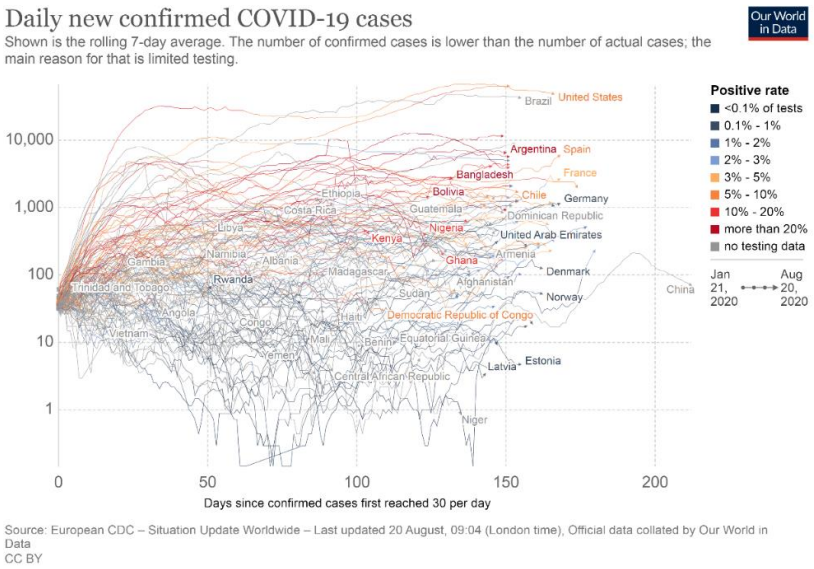
链接：https://covid19.who.int/

根据 WHO 提供的数据，2020 年 8 月 20 日全球累计确诊新型冠状病毒病人 **22256220** 例，当日新增确诊 **263601** 例，累计死亡 **782456** 例，当日新增死亡 **6554**。

中国累计确诊 90013 例，累计死亡 4713 例，当日新增确诊 33 例，新增死亡 1 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 8 月 20 日）



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 8 月 20 日）

全国新型冠状病毒肺炎新增确诊病例分布图（8 月 20 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 大流行对深海的危害：海洋哺乳动物从废水中感染 SARS-CoV-2 的风险

Rapid Pandemic danger to the deep: the risk of marine mammals contracting SARS-CoV-2 from wastewater

链接：https://www.biorxiv.org/content/10.1101/2020.08.13.249904v1

编译者：王玮

来自加拿大的研究者讨论了 COVID-19 大流行时期废水处理和管理的重要作用。他们预测了海洋哺乳动物物种的易感性。许多种类的鲸鱼、海豚、海豹以及水獭都很容易感染 SARS-CoV-2 病毒。

3. 在一起渔船上爆发的高发病率 SARS-CoV-2 感染中，中和抗体与人体预防 SARS-CoV-2 感染能力的关系

Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with high attack rate

来源：medRxiv

发布时间：2020-08-14

链接：https://www.medrxiv.org/content/10.1101/2020.08.13.20173161v1

第一作者：Amin Addetia

通讯作者：Alexander L. Greninger

通讯作者单位：

Department of Laboratory Medicine and Pathology, University of Washington School of Medicine, Seattle, WA

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

鉴别人体预防 SARS-CoV-2 感染能力的免疫学相关因素，将大大促进针对 SARS-CoV-2 疫苗的开发。然而，迄今为止，仅在动物模型中进行了有关保护性免疫的研究，而尚未在人类中建立保护能力的相关性。本文中，作者研究了一起在渔船上暴发的高发病率 SARS-CoV-2 感染。研究者在出发前对船上 122 名船员中的 120 人进行了血清学和病毒 RT-PCR 检测，并在船员返回后进行了重复检测，中位随访时间为 32.5 天（范围为 18.8 至 50.5 天）。在随访期间，共有 104 人存在血清转化，或病毒 RT-PCR 检测为阳性，其 Ct<35。船员整体发病率为 85.2%（104/122 个人）。对 39 个病毒基因组进行的元基因组测序表明，暴发的病毒主要源于单个病毒进化枝。只有三名船员在出发前的血清检测中呈血清阳性，并且在后续的检测中，仍具有中和性和 spike 反应性抗体。这些具有中和抗体滴度的船员中没有一个显示出真正的病毒感染迹象或在病毒爆发期间出现任何症状。因此，存在先前感染后产生的中和抗体与防止再次感染具有显着的相关性（Fisher 精确检验，p = 0.002）

Abstract:

The development of vaccines against SARS-CoV-2 would be greatly facilitated by the identification of immunological correlates of protection in humans. However, to date, studies on protective immunity have only been performed in animal models and correlates of protection have not been established in humans. Here, we describe an outbreak of SARS-CoV-2 on a fishing vessel associated with a high attack rate. Predeparture serological and viral RT-PCR testing along with repeat testing after return to shore was available for 120 of the 122 persons on board over a median follow-up of 32.5 days (range 18.8 to 50.5 days). A total of 104 individuals had an RT-PCR positive viral test with Ct <35 or seroconverted during the follow-up period, yielding an attack rate on board of 85.2% (104/122 individuals). Metagenomic sequencing of 39 viral genomes suggested the outbreak originated largely from a single viral clade. Only three crewmembers tested seropositive prior to the boat's departure in initial serological screening and also had neutralizing and spike-reactive antibodies in follow-up assays. None of these crewmembers with neutralizing antibody titers showed evidence of bona fide viral infection or experienced any symptoms during the viral outbreak. Therefore, the presence of neutralizing antibodies from prior infection was significantly associated with protection against re-infection (Fisher's exact test, p=0.002).

4. 评估使用可穿戴设备测量的 COVID-19 相关的生理体征

Assessment of physiological signs associated with COVID-19 measured using wearable devices

链接：https://www.medrxiv.org/content/10.1101/2020.08.14.20175265v1.full.pdf

作者单位：Fitbit Inc.

编译者：雷颖

可穿戴设备随附的移动应用程序可用于收集相关的自我报告症状和人口统计数据。这使得此类设备成为对抗 COVID-19 大流行的重要工具。我们考虑了两种评估 COVID-19 的方法-一种基于症状的方法和一种基于生理征兆的技术。仅根据自我报告的症状，我们就可以得出 0.77 +/- 0.05 的 AUC 来预测住院需求。基于生理征兆，我们获得了 0.77 +/- 0.03 的 AUC，可用于预测具有过去 4 天病史的特定日期的疾病。这些指标可以帮助早期诊断和监测疾病

的进展。

5. CovidNudge，一种新型的非实验室即时的 SARS-CoV-2 的诊断准确性

CovidNudge :diagnostic accuracy of a novel lab-free point-of-care diagnostic for SARS-CoV-2

来源：medRiv

发布时间：2020-08-15

文章链接：https://www.medrxiv.org/content/10.1101/2020.08.13.20174193v1

第一作者：Malick M Gibani, Christofer Toumazou

通讯作者：Graham S Cooke

通讯作者单位：伦敦帝国理工学院传染病学系

DOI：10.1101/2020.08.13.20174193

编译者：张怡

中文摘要：

背景：快速诊断是控制 SARS-CoV-2 的关键。逆转录酶-聚合酶链反应(RT-PCR)检测通常需要一个集中的实验室和重要的基础设施。作者描述了一种新型、快速的 RT-PCR 检测，即 DnaNudge®平台 CovidNudge 检测的开发和诊断准确性评估，该检测不需要实验室处理或样品预处理。

方法：将鼻咽拭子直接插入包含 RT-PCR 反应所需所有试剂和成分的管中，包括 7 个 SARS-CoV-2 靶基因(rdrp1, rdrp2, e-gene, n-gene, n1, n2 ,n3)的技术复制和人核糖核酸酶 P (RNaseP)的阳性对照。2020 年 4 月至 5 月，拭子样本在病毒转运培养基中使用 CovidNudge 直插式平台和标准实验室 RT-PCR 平行检测。从三组收集样本:自我转诊的疑似 COVID-19 的卫生保健工作者(组 1，n=280/386;73%)；疑似 COVID-19 急诊患者(组 2,n=15/386;4%)和不论是否怀疑 COVID-19 的住院病人(组 3，n=91/386;23%)。

结果：在 386 对样本中，CovidNudge 平台测试出阳性 67 例，标准实验室 RT-PCR 测试出阳性 71 例。检测的灵敏性因组而异(组 1 93%[84-98%]，组 2 100%[48-100%]，组 3 100%[29-100%]，平均灵敏度为 94.4%(95% 置信区间为 86-98%)，总体特异性为 100% (95%CI 99-100%)；组 1 100% [98-100%];组 2 100%[69-100%]和组 3 100%[96-100%])。扩增病毒核衣壳(n1, n2, n3)靶点对 SARS-CoV2 的检测最为敏感，该方法可以在单个拭子中检测出 1x104 个病毒颗粒。

结论：CovidNudge 平台为 SARS CoV-2 的存在提供了一种灵敏、特异性和快速的检测，无需实验室处理或样品预处理。这种设备的实施可以用于临床护理和测试项目的快速决策。

Abstract:

Background Access to rapid diagnosis is key to the control and management of SARS-CoV-2. Reverse Transcriptase- Polymerase Chain Reaction (RT-PCR) testing usually requires a centralised laboratory and significant infrastructure. We describe the development and diagnostic accuracy assessment of a novel, rapid point of-care RT-PCR test, the DnaNudge® platform CovidNudge test, which requires no laboratory handling or sample pre-processing.

Methods Nasopharyngeal swabs are inserted directly into a cartridge which contains all reagents and components required for RT-PCR reactions, including multiple technical replicates of seven SARS-CoV-2 gene targets (rdrp1, rdrp2, e-gene, n-gene, n1, n2 and n3) and human ribonuclease P (RNaseP) as positive

control. Between April and May 2020, swab samples were tested in parallel using the CovidNudge direct-to-cartridge platform and standard laboratory RT-PCR using swabs in viral transport medium. Samples were collected from three groups: self-referred healthcare workers with suspected COVID-19 (Group 1, n=280/386; 73%); patients attending the emergency department with suspected COVID-19 (Group 2, n=15/386; 4%) and hospital inpatient admissions with or without suspected COVID-19 (Group 3, n=91/386; 23%).

Results Of 386 paired samples tested across all groups, 67 tested positive on the CovidNudge platform and 71 with standard laboratory RT-PCR. The sensitivity of the test varied by group (Group 1 93% [84-98%], Group 2 100% [48-100%] and Group 3 100% [29-100%], giving an average sensitivity of 94.4% (95% confidence interval 86-98%) and an overall specificity of 100% (95%CI 99-100%; Group 1 100% [98-100%]; Group 2 100% [69-100%] and Group 3 100% [96-100%]). Amplification of the viral nucleocapsid (n1, n2, n3) targets were most sensitive for detection of SARS-CoV2, with the assay able to detect 1x104 viral particles in a single swab.

Conclusions The CovidNudge platform offers a sensitive, specific and rapid point of care test for the presence of SARS CoV-2 without laboratory handling or sample pre-processing. The implementation of such a device could be used to enable rapid decisions for clinical care and testing programs.

6. 快速高效的病毒基因组测序 V-seq

Rapid cost-effective viral genome sequencing by V-seq

来源：bioRxiv

发布时间：2020-08-15

链接：https://www.biorxiv.org/content/10.1101/2020.08.15.252510v1

第一作者：Longhua Guo

通讯作者：Joshua S. Bloom, Leonid Kruglyak, Yi Yin

通讯作者单位：

Department of Human Genetics, David Geffen School of Medicine, UCLA

DOI 或 PUBMED ID：

编译者：宋张悦

中文摘要：

传统的病毒基因组测序方法主要使用宏转录方法（metatranscriptomic），或者通过病毒特异性 PCR 或基于杂交捕获的扩增子测序来富集病毒基因组。这些现有的方法是昂贵的，需要大量的样品处理时间，并有有限的通量。在这里，我们描述 **V-seq，一种廉价、快速、可扩展的方法，在 cDNA 合成阶段通过多重引物对病毒基因组进行靶向测序。**我们设计了覆盖 SARS-CoV-2 基因组的密集平铺的反转录(RT)引物，在 3 ’端有一个六聚体（hexamers）子集，可以最小化针对大量人类 rRNA 重复序列和人类 RNA PolII 转录组的错配引物。我们发现重叠的 RT 引物并不会相互干扰，而是协同作用以提高低病毒载量样本的病毒基因组覆盖率。我们以 SARS-CoV-2 为例提供了优化 V-seq 的途径。我们预期 V-seq 可以应用于研究基因组进化和追踪 RNA 病毒的爆发，以一种经济有效的方式。更广泛地说，V-seq 的多重 RT 方法可以推广到靶向 RNA 测序的其他应用。

Abstract:

Conventional methods for viral genome sequencing largely use metatranscriptomic approaches or, alternatively, enrich for viral genomes by amplicon sequencing with virus-specific PCR or hybridization-based capture. These existing methods are costly, require extensive sample handling time, and have limited throughput. Here, we describe V-seq, an inexpensive, fast, and scalable method that performs targeted viral genome sequencing by multiplexing virus-specific primers at the cDNA synthesis step. We designed densely tiled reverse transcription (RT) primers across the SARS-CoV-2 genome, with a subset of hexamers at the 3' end to minimize mis-priming from the abundant human rRNA repeats and human RNA PolII transcriptome. We found that overlapping RT primers do not interfere, but rather act in concert to improve viral genome coverage in samples with low viral load. We provide a path to optimize V-seq with SARS-CoV-2 as an example. We anticipate that V-seq can be applied to investigate genome evolution and track outbreaks of RNA viruses in a cost-effective manner. More broadly, the multiplexed RT approach by V-seq can be generalized to other applications of targeted RNA sequencing.

7. SARS-CoV-2 特异性的 CD8+ T 细胞的体外检测：快速诱导，延长的收缩和功能记忆的形成

Ex vivo detection of SARS-CoV-2-specific CD8+ T cells: rapid induction, prolonged contraction, and formation of functional memory

来源：bioRxiv

发布时间：2020-08-14

链接：https://www.biorxiv.org/content/10.1101/2020.08.13.249433v1

第一作者：Isabel Schulien, Janine Kemming, Valerie Oberhardt, Katharina Wild, Lea M. Seidel, Saskia Killmer

通讯作者：Robert Thimme, Maike Hofmann, Christoph Neumann-Haefelin

通讯作者单位：

Department of Medicine II (Gastroenterology, Hepatology, Endocrinology and Infectious Diseases), Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

在轻度的 SARS-CoV-2 感染中，已存在的和新诱导的 SARS-CoV-2 特异性 CD8+ T 细胞响应都是潜在的免疫保护的重要决定因素。作者的结果可特别归纳如下：首先，SARS-CoV-2 特异性 CD8+ T 细胞的免疫显性表位靶向的是从 SARS-CoV-2 感染中恢复的大多数个体。其次，MHC I 类四聚体分析说明，表型多样且功能强大的已存在和新诱导的 SARS-CoV-2 特异性记忆 CD8+ T 细胞的出现，同流感特异性 CD8+ T 细胞相比，具有相似的特征。第三，SARS-CoV-2 特异性 CD8+ T 细胞响应比针对 SARS-CoV-2-spike 蛋白的抗体的可检测性更可靠。在急性自然治愈感染的纵向分析中证实上述发现。该分析表明 SARS-CoV-2 特异性 CD8+ T 细胞在一周内迅速被诱导，随后出现延长的收缩期，并维持逐渐减弱的体液免疫反应。这表明，在康复后，针对 CD8+ T 细胞响应的检测可能比抗体检测更能准确地反应抗病毒免疫的相关性。

总体而言，现有数据为 SARS-CoV-2 特异性记忆 CD8+ T 细胞的优良特异性，异质性和动力学性质提供了新的见解，从而可能为合理开发针对 SARS-CoV-2 的保护性疫苗提供信息。

Abstract:
CD8+ T cells are critical for the elimination and long-lasting protection of many viral infections, but their role in the current SARS-CoV-2 pandemic is unclear. Emerging data indicates that SARS-CoV-2-specific CD8+ T cells are detectable in the majority of individuals recovering from SARS-CoV-2 infection. However, optimal virus-specific epitopes, the role of pre-existing heterologous immunity as well as their kinetics and differentiation program during disease control have not been defined in detail. Here, we show that both pre-existing and newly induced SARS-CoV-2-specific CD8+ T-cell responses are potentially important determinants of immune protection in mild SARS-CoV-2 infection. In particular, our results can be summarized as follows: First, immunodominant SARS-CoV-2-specific CD8+ T-cell epitopes are targeted in the majority of individuals with convalescent SARS-CoV-2 infection. Second, MHC class I tetramer analyses revealed the emergence of phenotypically diverse and functionally competent pre-existing and newly induced SARS-CoV-2-specific memory CD8+ T cells that showed similar characteristics compared to influenza-specific CD8+ T cells. Third, SARS-CoV-2-specific CD8+ T-cell responses are more robustly detectable than antibodies against the SARS-CoV-2-spike protein. This was confirmed in a longitudinal analysis of acute-resolving infection that demonstrated rapid induction of the SARS-CoV-2-specific CD8+ T cells within a week followed by a prolonged contraction phase that outlasted the waning humoral immune response indicating that CD8+ T-cell responses might serve as a more precise correlate of antiviral immunity than antibody measurements after convalescence. Collectively, these data provide new insights into the fine specificity, heterogeneity, and dynamics of SARS-CoV-2-specific memory CD8+ T cells, potentially informing the rational development of a protective vaccine against SARS-CoV-2.

8. 鼻内单剂量腺病毒载体疫苗可在大猩猩中抵抗 SARS-CoV-2 的呼吸道感染

A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2
链接：https://www.cell.com/cell/fulltext/S0092-8674(20)31068-0
简报 7 月 24 日 14 条介绍过该文章的预印本。

9. 未暴露的人群中 SARS-CoV-2 选择性和交叉反应的 T 细胞表位

Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans
来源：Science
发布时间：2020-08-04
链接：https://science.sciencemag.org/content/early/2020/08/04/science.abd3871
第一作者：Jose Mateus
通讯作者：Alessandro Sette, Daniela Weiskopf

通讯作者单位：
Center for Infectious Disease and Vaccine Research, La Jolla Institute for Immunology, La Jolla, CA 92037, USA.
Department of Medicine, Division of Infectious Diseases and Global Public Health, University of California, San Diego, La Jolla, CA 92037, USA.
DOI：10.1126/science.abd3871
编译者：雷颖
中文摘要：

人类对 SARS-CoV-2 病毒的免疫反应存在许多未知因素。SARS-CoV-2 反应性 CD4 T 细胞在未暴露的个体中已被报道，表明 20-50%的人预先存在交叉反应性 T 细胞记忆。然而，这些 T 细胞的来源是推测性的。利用 2019 年 SARS-CoV-2 病毒发现前的人类血液样本，我们在 SARS-CoV-2 基因组上绘制了 142 个 T 细胞表位，以方便对 SARS-CoV-2 特异性 CD4T 细胞库的精确询问。我们展示了一系列预先存在的记忆 CD4 T 细胞，它们与 SARS-CoV-2 和常见的感冒冠状病毒 HCOV-OC43、HCOV-229E、HCOV-NL63 或 HCOV-HKU1 具有相当的亲和力。因此，引起普通感冒的多样的冠状病毒 T 细胞记忆可能是在 COVID-19 疾病中观察到的一些普遍异质性的原因。

Abstract:
Many unknowns exist about human immune responses to the SARS-CoV-2 virus. SARS-CoV-2 reactive CD4+ T cells have been reported in unexposed individuals, suggesting pre-existing cross-reactive T cell memory in 20-50% of people. However, the source of those T cells has been speculative. Using human blood samples derived before the SARS-CoV-2 virus was discovered in 2019, we mapped 142 T cell epitopes across the SARS-CoV-2 genome to facilitate precise interrogation of the SARS-CoV-2-specific CD4+ T cell repertoire. We demonstrate a range of pre-existing memory CD4+ T cells that are cross-reactive with comparable affinity to SARS-CoV-2 and the common cold coronaviruses HCoV-OC43, HCoV-229E, HCoV-NL63, or HCoV-HKU1. Thus, variegated T cell memory to coronaviruses that cause the common cold may underlie at least some of the extensive heterogeneity observed in COVID-19 disease.

10. SARS-CoV-2 病毒在非洲绿猴肺部的感染动力学

SARS-CoV-2 infection dynamics in lungs of African green monkeys
来源：bioRxiv
发布时间：2020-08-20
链接：https://www.biorxiv.org/content/10.1101/2020.08.20.258087v1
第一作者：Emily Speranza
通讯作者：Emmie de Wit
通讯作者单位：
Laboratory of Virology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT, United States of America.
DOI 或 PUBMED ID：
编译者：宋珂

中文摘要：

有关 SARS-CoV-2 病毒的感染动力学的详细知识，对于揭示 COVID-19 发病机制中来自于病毒和宿主的影响因素非常重要。旧世界非人灵长类动物可重现轻度至中度的 COVID-19 病例，因此成为重要的发病机制模型。本文中，作者对接种了 SARS-CoV-2 病毒和灭活病毒的非洲绿猴进行了对比，以研究整个呼吸道中病毒复制的动力学特征。对取自肺和纵隔淋巴结中的样本进行单细胞 RNA 测序，可以对病毒复制和宿主反应进行包含时间序列的高分辨率的分析。作者发现病毒在肺泡细胞中复制的证据，推测病毒复制的场所主要集中在下呼吸道。同时还发现了巨噬细胞在肺部引发促炎状态中起的作用，以及与被病毒感染的肺泡细胞也存在相互作用。针对轻度 COVID-19 发病过程，作者的数据集提供了宿主变化和病毒复制动力学的详细图景，并为鉴别治疗靶点提供了宝贵资源。

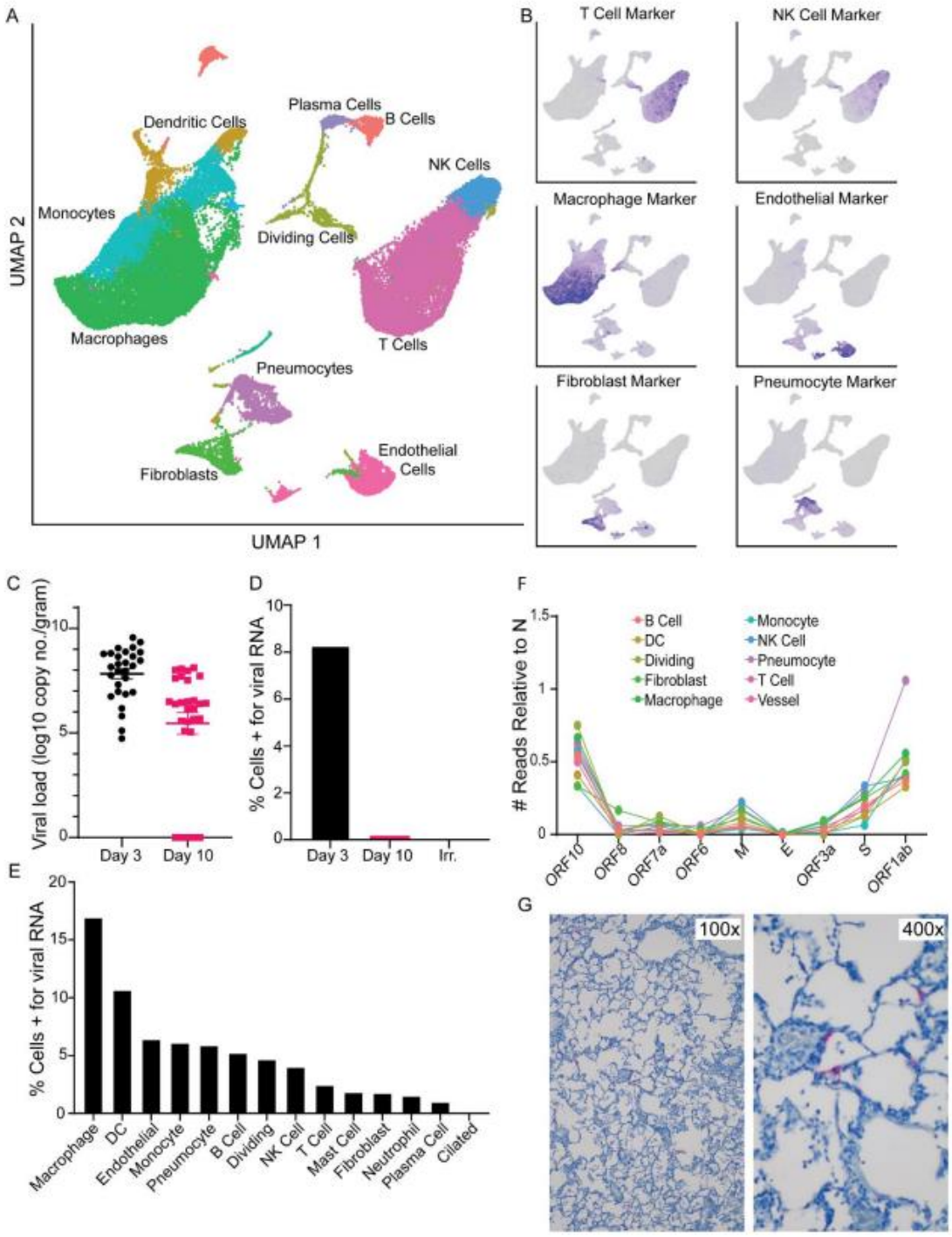


Figure 3. Single cell sequencing and viral dynamics in lung tissue. A. UMAP projection of 3 single-cell RNA sequencing data from whole lung sections from all 10 animals combined. Each point is an individual cell; colors are based on cell type annotation. Cell names are shown next to their largest cluster. **B.** Validation of cell type identities using marker gene sets. The darker the purple in each cell the higher its expression of the marker set. Grey means the cell did not express any genes in the marker set. **C.** Viral load information from the lungs via qRT-PCR for gRNA, grouped for all lobes across all animals. **D.** Percentage of cells identified by single cell RNA-sequencing that are positive for any reads aligning to the viral genome by days post inoculation. **E.** Percentage of cells from the 3 dpi samples positive for any reads aligning to the viral genome grouped by cell type. **F.** The number of cells grouped by cell type

(colored to match the UMAP in A) with reads aligning to various other locations across the viral genome, all normalized to the number of cells expressing N. Genes are ordered from the 3' to 5' end of the SARS-CoV-2 genome. **G.** ISH for viral S RNA in lung tissues at 3 dpi (viral RNA stains red) at 100x magnification and 400x magnification.

Abstract:
Detailed knowledge about the dynamics of SARS-CoV-2 infection is important for unraveling the viral and host factors that contribute to COVID-19 pathogenesis. Old-World nonhuman primates recapitulate mild-moderate COVID-19 cases, thereby serving as important pathogenesis models. We compared African green monkeys inoculated with SARS-CoV-2 or inactivated virus to study the dynamics of virus replication throughout the respiratory tract. RNA sequencing of single cells from the lungs and mediastinal lymph nodes allowed a high-resolution analysis of virus replication and host responses over time. Viral replication was mainly localized to the lower respiratory tract, with evidence of replication in the pneumocytes. Macrophages were found to play a role in initiating a pro-inflammatory state in the lungs, while also interacting with infected pneumocytes. Our dataset provides a detailed view of changes in host and virus replication dynamics over the course of mild COVID-19 and serves as a valuable resource to identify therapeutic targets.

11. COVID-19 尸检的多器官蛋白质组学研究

Multi-organ Proteomic Landscape of COVID-19 Autopsies

来源：medRxiv

发布时间：2020-08-19

链接：https://www.medrxiv.org/content/10.1101/2020.08.16.20176065v2

第一作者：Xiu Nie, Liujia Qian, Rui Sun, Bo Huang, Xiaochuan Dong, Qi Xiao, Qiushi Zhang

通讯作者：Yi Zhu[2, 3], Jiahong Xia[9], Yu Hu[8], Tiannan Guo[2, 3]

通讯作者单位：

2 Zhejiang Provincial Laboratory of Life Sciences and Biomedicine, Key Laboratory of Structural Biology of Zhejiang Province, School of Life Sciences, Westlake University, Hangzhou 310024, China

3 Institute of Basic Medical Sciences, Westlake Institute for Advanced Study, Hangzhou 310024, China

8 Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

9 Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

DOI 或 PUBMED ID：

编译者：王玮

中文摘要：

COVID-19 患者多器官损伤的分子病理学尚不清楚，阻碍了有效治疗方法的发展。该研究报告了 COVID-19 患者尸检样本的多器官蛋白质组学研究。通过对肺、脾、肝、心、肾、甲状腺和睾丸 7 个器官的蛋白质组进行综合分析，共鉴定出 11394 种蛋白质，其中 COVID-19 患者与对照组相比有 5336 个蛋白质受到干扰。数据显示，在 COVID-19 患者的肺组织中，CTSL（而不是 ACE2）显著上调。多脏器存在蛋白质翻译、糖代谢、脂肪酸代谢紊乱。该研究表明，SARS-CoV-2 感染后，可引起炎症反应，进而导致肺内气体交换屏障的损伤，导致肺、肾、脾、肝、心、甲状腺组织缺氧、血管生成、凝血和纤维化。睾丸损伤的证据包括睾丸间质细胞减少，胆固醇生物合成和精子活动受到抑制。综上所述，本研究描绘了 COVID-19 尸检的多器官蛋白质组学图景，揭示了失调的蛋白质和生物学过程，提供了新的治疗线索。

Abstract:
The molecular pathology of multi-organ injuries in COVID-19 patients remains unclear, preventing effective therapeutics development. Here, we report an in-depth multi-organ proteomic landscape of COVID-19 patient autopsy samples. By integrative analysis of proteomes of seven organs, namely lung, spleen, liver, heart, kidney, thyroid and testis, we characterized 11,394 proteins, in which 5336 were perturbed in COVID-19 patients compared to controls. Our data showed that CTSL, rather than ACE2, was significantly upregulated in the lung from COVID-19 patients. Dysregulation of protein translation, glucose metabolism, fatty acid metabolism was detected in multiple organs. Our data suggested upon SARS-CoV-2 infection, hyperinflammation might be triggered which in turn induces damage of gas exchange barrier in the lung, leading to hypoxia, angiogenesis, coagulation and fibrosis in the lung, kidney, spleen, liver, heart and thyroid. Evidence for testicular injuries included reduced Leydig cells, suppressed cholesterol biosynthesis and sperm mobility. In summary, this study depicts the multi-organ proteomic landscape of COVID-19 autopsies, and uncovered dysregulated proteins and biological processes, offering novel therapeutic clues.

12. 区分 COVID-19 与 A 型流感（H1N1）的临床和免疫学特征

Clinical and immunological factors that distinguish COVID-19 from pandemic influenza A(H1N1)

来源：medRxiv

发布时间：2020-08-14

链接：https://www.medrxiv.org/content/10.1101/2020.08.10.20170761v1

第一作者：José Alberto Choreño-Parra

通讯作者：Joaquín Zúñiga

通讯作者单位：

Laboratory of Immunobiology and Genetics, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico.

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

作者比较了 COVID-19 和 A 型流感（H1N1）患者的临床，组织病理学和免疫学特征。发现 A 型流感（H1N1）患者的呼吸道症状的发生频率更高，组织损伤标志物增加，具有肺泡肺炎的组织学模式以及更高水平的 IL-1RA，TNF-α，CCL3，G-CSF，APRIL，sTNF-R1，sTNF-R2，sCD30 和 sCD163。相反，在 COVID-19 患者中，发生干咳，胃肠道症状，间质性肺病变，Th1（IL-12，IFN-γ）和 Th2（IL-4，IL-5，IL-10，IL-13），以及 IL-1β，IL-6，CCL11，VEGF，TWEAK，TSLP，MMP-1 和 MMP-3 细胞因子水平升高。

Abstract:
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), is a global health threat with the potential to cause severe disease manifestations in the lungs. Although clinical descriptions of COVID-19 are currently available, the factors distinguishing SARS-CoV-2 from other respiratory viruses are unknown. Here, we compared the clinical, histopathological, and immunological characteristics of patients with COVID-19 and pandemic influenza A(H1N1). We observed a higher frequency of respiratory symptoms, increased tissue injury markers, a histological pattern of alveolar pneumonia, and higher levels of IL-1RA, TNF-α, CCL3, G-CSF, APRIL, sTNF-R1, sTNF-R2, sCD30, and sCD163 in influenza patients. Conversely, dry cough, gastrointestinal symptoms, interstitial lung pathology, increased Th1 (IL-12, IFN-γ) and Th2 (IL-4, IL-5, IL-10, IL-13) cytokine levels, along with IL-1β, IL-6, CCL11, VEGF, TWEAK, TSLP, MMP-1, and MMP-3, were observed in COVID-19 cases. We demonstrated the diagnostic potential of some clinical and immune factors to differentiate COVID-19 from pandemic influenza A(H1N1). Our data suggest that SARS-CoV-2 induces a dysbalanced polyfunctional inflammatory response that is different from the immune response against influenza. These findings might be relevant for the upcoming 2020-2021 influenza season, which is projected to be historically unique due to its convergence with COVID-19.

13. NVX-CoV2373 疫苗保护食蟹猴上下呼吸道免受 SARS-CoV-2 攻击

NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge

来源：bioRxiv
发布时间：2020-08-19
链接：https://www.biorxiv.org/content/10.1101/2020.08.18.256578v1

第一作者：Mimi Guebre-Xabier
通讯作者：Gale Smith
通讯作者单位：Novavax, Inc. 21 Firstfield Road, Gaithersburg, MD, 20878, USA

DOI 或 PUBMED ID：

编译者：张鹏伟

中文摘要：

在这里，我们报告了 SARS-CoV-2 亚单位疫苗(NVX-CoV2373)的免疫原性和保护效果，该疫苗是由全长 SARS-CoV-2 尖峰(S)糖蛋白稳定在前融合构象中产生的。用 NVX-CoV2373 和

基于皂甙的 Matrix-M 佐剂免疫食蟹猴（macacafcularis）诱导的抗 S 抗体中和并阻断其与人血管紧张素转换酶 2（hACE2）受体的结合。在用 SARS-CoV-2 进行鼻内和气管内激发后，免疫猕猴可免受上下感染和肺部疾病的侵袭。这些结果支持正在进行的 NVX-CoV2327 疫苗（NCT04368988）安全性和免疫原性的临床 1/2 期研究。

Abstract:
There is an urgent need for a safe and protective vaccine to control the global spread of SARS-CoV-2 and prevent COVID-19. Here, we report the immunogenicity and protective efficacy of a SARS-CoV-2 subunit vaccine (NVX-CoV2373) produced from the full-length SARS-CoV-2 spike (S) glycoprotein stabilized in the prefusion conformation. Cynomolgus macaques (Macaca fascicularis) immunized with NVX-CoV2373 and the saponin-based Matrix-M adjuvant induced anti-S antibody that was neutralizing and blocked binding to the human angiotensin-converting enzyme 2 (hACE2) receptor. Following intranasal and intratracheal challenge with SARS-CoV-2, immunized macaques were protected against upper and lower infection and pulmonary disease. These results support ongoing phase 1/2 clinical studies of the safety and immunogenicity of NVX-CoV2327 vaccine (NCT04368988).

14. 经一次注射多靶点的 COVID-19 疫苗可诱导组织驻留记忆 CD8 T 细胞应答

Tissue-resident memory CD8 T-cell responses elicited by a single injection of a multi-target COVID-19 vaccine

来源：bioRxiv
发布时间：2020-08-14
链接：https://www.biorxiv.org/content/10.1101/2020.08.14.240093v1
第一作者：V. Gauttier, A. Morello, I. Girault, C. Mary
通讯作者：N. Poirier
通讯作者单位：1OSE Immunotherapeutics, Nantes, France
DOI 或 PUBMED ID：
编译者：张丽双

中文摘要：

在这里，研究人员介绍了一种针对 SARS-CAV-2 保守区域中几种结构性（S，M，N）和非结构性（NSPs）表位的多靶点 CD8 T 细胞肽 COVID-19 疫苗设计。通过皮下注射这一系列表位可在体内诱导强大的免疫原性，如 IFNγ ELIspot 所测。通过四聚体表征，我们发现该系列表位可诱导很大比例的病毒特异性 CD8 T 细胞表达 CD103，CD44，CXCR3 和 CD49a，即组织驻留记忆 T 淋巴细胞（Trm）的特定表型。最后，对从无症状、中度和重度 COVID-19 康复期患者中分离的血液 T 细胞用结构和非结构蛋白衍生的表位进行再刺激，观察到广泛的细胞反应，以 IFNγ 产生为特征。这些数据为进一步开发第二代 COVID-19 疫苗提供了新见解，该疫苗致力于利用 SARS-CoV-2 感染消退后自然观察到的免疫优势表位来诱导持久的 Th1 偏向记忆 CD8 T 细胞前哨保护。

Abstract:
The COVID-19 pandemic is caused by severe acute respiratory syndrome coronavirus-

2 (SARS-CoV-2) which enters the body principally through the nasal and larynx mucosa and progress to the lungs through the respiratory tract. SARS-CoV-2 replicates efficiently in respiratory epithelial cells motivating the development of alternative and rapidly scalable vaccine inducing mucosal protective and long-lasting immunity. We have previously developed an immunologically optimized multi-neoepitopes-based peptide vaccine platform which has already demonstrated tolerance and efficacy in hundreds of lung cancer patients. Here, we present a multi-target CD8 T cell peptide COVID-19 vaccine design targeting several structural (S, M, N) and non-structural (NSPs) SARS-CoV-2 proteins with selected epitopes in conserved regions of the SARS-CoV-2 genome. We observed that a single subcutaneous injection of a serie of epitopes induces a robust immunogenicity in-vivo as measured by IFNγ ELIspot. Upon tetramer characterization we found that this serie of epitopes induces a strong proportion of virus-specific CD8 T cells expressing CD103, CD44, CXCR3 and CD49a, the specific phenotype of tissue-resident memory T lymphocytes (Trm). Finally, we observed broad cellular responses, as characterized by IFNγ production, upon restimulation with structural and non-structural protein-derived epitopes using blood T cells isolated from convalescent asymptomatic, moderate and severe COVID-19 patients. These data provide insights for further development of a second generation of COVID-19 vaccine focused on inducing lasting Th1-biased memory CD8 T cell sentinels protection using immunodominant epitopes naturally observed after SARS-CoV-2 infection resolution.

15. 高热稳定性、高免疫原性 SARS-CoV-2 刺突片段的设计

Design of a highly thermotolerant, immunogenic SARS-CoV-2 spike fragment

链接：https://www.biorxiv.org/content/10.1101/2020.08.15.252437v1

编译者：张丽双

印度学者描述了一种单体、聚糖工程化的 RBD 蛋白片段，当冻干时可耐受高达 100° C 的温度，并在溶液中高达 70° C。其热稳定性高、产量高、免疫原性强，有希望作为候选疫苗，避免对冷链运输的依赖。

16. 国药新冠疫苗预计 12 月底上市！价格公布！

链接：https://mp.weixin.qq.com/s/MeMR9-ZS42NgI8UNMWmNxg

编者：张丽双

国药集团中国生物武汉生物制品研究所和北京生物制品研究所分别研发的新冠灭活疫苗 6 月份都公布了一二期临床试验阶段性揭盲结果，结果显示疫苗接种后安全性好，无一例严重不良反应，接种者均产生高滴度抗体；6 月 23 日，国药集团在阿拉伯联合酋长国启动国际临床三期试验，国际临床三期试验结束后，灭活疫苗就可以进入审批环节，预计今年 12 月底能够上市。预计北京生物制品研究所的灭活疫苗年产量能达 1.2 亿剂，武汉生物制品研究所的灭活疫苗年产量能达 1 亿剂。“灭活疫苗上市后，价格不会很高，预计几百块钱一针。如果打两针的话，价格应在 1000 块钱以内。另外，基因工程亚单位疫苗预计今年 10 月份能进入临床研究，一旦研发成功后就能快速大规模量产。

17. COVID-19 RNA 疫苗 BNT162b1 在成年人中的临床 1/2 期研究

Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults

来源：Nature
发布时间：2020-08-12
链接：https://www.nature.com/articles/s41586-020-2639-4

第一作者：Mark J. Mulligan, Kirsten E. Lyke, Nicholas Kitchin
通讯作者：Judith Absalon
通讯作者单位：
Vaccine Research and Development, Pfizer Inc, Pearl River, NY, USA

DOI 或 PUBMED ID：10.1038/s41586-020-2639-4

编译者：宋珂

中文摘要：

本文中，作者对一项正在进行的 COVID-19 RNA 疫苗 BNT162b1 的临床试验结果进行了报道。内容包括疫苗的可用安全性，耐受性和免疫原性数据。临床试验采取安慰剂对照，观察者单盲的剂量递增方案。研究对象包括 45 名 18 至 55 岁的健康成年人，随机接受 2 剂，间隔 21 天，每次 10 μg，30 μg 或 100 μg。BNT162b1 是一种采用脂质纳米颗粒配方，经核苷修饰的 mRNA 疫苗，其编码 SARS-CoV-2 spike 糖基化蛋白受体结合结构域（RBD）的三聚体。使用疫苗后，身体的局部反应和全身情况与使用剂量相关，反应通常是轻度至中度和短暂的。与 30 μg 剂量相比，由于一次接种后反应原性增强且免疫原性未发生有意义的增强，因此未进行 100 μg 的第二次疫苗接种。在接种第二剂后，血清中的 RBD 结合 IgG 的浓度和 SARS-CoV-2 中和滴度随剂量水平增加。在 SARS-CoV-2 PCR 阳性后至少 14 天，几何平均中和滴度达到一组 COVID-19 恢复期人血清的 1.9-至 4.6 倍。现有结果支持对该 mRNA 疫苗候选物的进行更进一步的评估。（ClinicalTrials.gov 识别码：NCT04368728）。

Abstract:

In March 2020, the World Health Organization (WHO) declared a pandemic of coronavirus disease 2019 (COVID-19), due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)1. With rapidly accumulating cases and deaths reported globally2, a vaccine is urgently needed. We report the available safety, tolerability, and immunogenicity data from an ongoing placebo-controlled, observer-blinded dose escalation study among 45 healthy adults, 18 to 55 years of age, randomized to receive 2 doses, separated by 21 days, of 10 μg, 30 μg, or 100 μg of BNT162b1, a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD). Local reactions and systemic events were dose-dependent, generally mild to moderate, and transient. A second vaccination with 100 μg was not administered due to increased reactogenicity and a lack of meaningfully increased immunogenicity after a single dose compared to the 30 μg dose. RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers in sera increased with dose level and after a second dose. Geometric mean neutralizing titers reached 1.9- to 4.6-fold that of a panel of COVID-19 convalescent human sera at least 14 days after a positive SARS-CoV-2 PCR. These results support further evaluation of this mRNA vaccine candidate. (ClinicalTrials.gov identifier: NCT04368728).

18. 无症状感染者以及中轻度 COVID-19 康复者中都存在 T 细胞免疫

Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19

链接：https://www.cell.com/cell/fulltext/S0092-8674(20)31008-4

简报 7 月 4 日第 7 条介绍过该文章的预印本。

19. 羟氯喹抑制 SARS-CoV2 进入的作用机制

Hydroxychloroquine: mechanism of action inhibiting SARS-CoV2 entry

来源：bioRxiv

发布时间：2020-08-14

链接：https://www.biorxiv.org/content/10.1101/2020.08.13.250217v1

第一作者：Zixuan Yuan

通讯作者：Scott B. Hansen

通讯作者单位：

Department of Molecular Medicine, The Scripps Research Institute, Jupiter, Florida, 33458, USA

DOI 或 PUBMED ID：

编译者：张鹏伟

中文摘要：

背景：治疗 SARS-CoV-2 感染的潜在药物包括氯喹（CQ）、其衍生物羟基氯喹（HCQ）和麻醉剂异丙酚。它们在 SARS-CoV-2 感染中的作用机制尚不清楚。

方法：在用 50μM 异丙酚、丁卡因、HCQ 和红霉素处理细胞后，使用 SARS-CoV-2 假病毒（SARS2-PV）和病毒表达的荧光素酶报告基因来确定病毒进入。用 dSTORM 监测纳米尺度上单唾液酸四己糖基神经节苷脂 1（GM1）脂筏、磷脂酰肌醇 4,5-二磷酸（PIP2）结构域和 ACE2 受体的 HCQ 破坏。细胞被固定，渗透，然后用荧光霍乱毒素 B（CTxB）或抗体标记，然后在成像前再次固定。dSTORM 图像的聚类分析用于确定大小和数量，交叉对相关分析用于确定内源性表达 ACE2 在脂质结构域内外的转运。

结果：异丙酚、丁卡因和 HCQ 抑制 SARS2-PV 病毒进入。HCQ 直接干扰 GM1 脂质筏和 PIP2 结构域。GM1 的大小和数量增加，类似于麻醉破坏脂质筏；PIP2 结构域的大小和数量减少。HCQ 阻断了 GM1 和 PIP2 结构域对 ACE2 的吸引和聚集能力。

结论：我们的结论是 HCQ 是一种类似麻醉剂的化合物，它能破坏 GM1 脂质筏，类似于异丙酚和其他局部或全身麻醉药。此外，我们得出结论，控制 HCQ 抗病毒特性的是 GM1-raft 功能的破坏，而不是 GM1-raft 分子的浓度。HCQ 破坏膜似乎也破坏了宿主防御肽的产生，因此，抗生素如红霉素可能是一种重要的联合治疗方法。尽管如此，红霉素具有抗 SARS-CoV-2 的活性，并可能与 HCQ 结合以减少感染。

Abstract:

Background SARS-coronavirus 2 (SARS-CoV-2) is currently causing a worldwide pandemic. Potential drugs identified for the treatment of SARS-CoV-2 infection include chloroquine (CQ), its derivative hydroxychloroquine (HCQ), and the anesthetic propofol. Their mechanism of action in SARS-CoV-2 infection is poorly understood. Recently, anesthetics, both general and local, were shown to disrupt ordered lipid domains. These same lipid domains recruit the SARS-CoV-2 surface

receptor angiotensin converting enzyme 2 (ACE2) to an endocytic entry point and their disruption by cholesterol depletion decreases ACE2 recruitment and viral entry.

Methods Viral entry was determined using a SARS-CoV-2 pseudovirus (SARS2-PV) and a luciferase reporter gene expressed by the virus after treatment of the cells with 50 μM propofol, tetracaine, HCQ, and erythromycin. HCQ disruption of monosialotetrahexosylganglioside1 (GM1) lipid rafts, phosphatidylinositol 4,5-bisphosphate (PIP2) domains, and ACE2 receptor at nanoscale distances was monitored by direct stochastic reconstruction microscopy (dSTORM). Cells were fixed, permeabilized, and then labeled with either fluorescent cholera toxin B (CTxB) or antibody and then fixed again prior to imaging. Cluster analysis of dSTORM images was used to determine size and number and cross pair correlation was used to determine trafficking of endogenously expressed ACE2 in and out of lipid domains.

Results Propofol, tetracaine, and HCQ inhibit SARS2-PV viral entry. HCQ directly perturbs both GM1 lipid rafts and PIP2 domains. GM1 rafts increased in size and number similar to anesthetic disruption of lipid rafts; PIP2 domains decreased in size and number. HCQ blocked both GM1 and PIP2 domains ability to attract and cluster ACE2.

Conclusions We conclude HCQ is an anesthetic-like compound that disrupts GM1 lipid rafts similar to propofol and other local or general anesthetics. Furthermore, we conclude disruption of GM1 raft function, and not the concentration of GM1 raft molecules, governs the antiviral properties of HCQ. HCQ disruption of the membrane appears to also disrupt the production of host defense peptide, hence an antimicrobial such as erythromycin could be an important combined treatment. Nonetheless erythromycin has anti-SARS-CoV-2 activity and may combine with HCQ to reduce infection.

20. 基于 RNA 的 COVID-19 疫苗 BNT162b2 用于关键功效研究

RNA-Based COVID-19 Vaccine BNT162b2 Selected for a Pivotal Efficacy Study

来源：medRxiv

发布时间：2020-08-20

链接：https://www.medrxiv.org/content/10.1101/2020.08.17.20176651v1

第一作者：Edward E. Walsh

通讯作者：Judith Absalo

通讯作者单位：美国纽约辉瑞公司

DOI 或 PUBMED ID：10.1101/2020.08.17.2017665

编译者：刘焕珍

中文摘要：

背景：SARS-CoV-2 感染及其引发的 COVID-19 疾病已蔓延到全球数百万人。目前正在开发多种候选疫苗，但目前尚无可用疫苗。

方法：将健康的 18-55 岁和 65-85 岁的成年人随机分为一项正在进行的，安慰剂对照，观察者单盲的剂量递增研究，以安慰剂的 21 天间隔接受 2 剂或两种脂质纳米粒制剂的任一种核

苷修饰的 RNA 疫苗候选物：BNT162b1，其编码分泌的三聚 SARS-CoV-2 受体结合域，或 BNT162b2，其编码融合前稳定的膜锚定 SARS-CoV-2 全长刺突。在 15 名参与者的 13 组中，每组 12 人接受了疫苗，3 人接受了安慰剂。通过候选疫苗、参与者年龄和疫苗剂量水平来分组。以前，美国和德国的试验报告了 BNT162b1 在年轻人中的临时安全性和免疫原性数据。现在，我们提供了来自美国 1 期临床试验的其他安全性和免疫原性数据，这些数据支持选择进行关键 2/3 期安全性和有效性评估的候选疫苗。

结果：在年轻人和老年人中，这两种疫苗候选物均引起相似的剂量依赖性 SARS-CoV-2 中和几何平均滴度（GMT），与一组 SARS-CoV-2 康复期血清的 GMT 相当或更高。BNT162b2 与较低的全身反应原性相关，尤其是在老年人中。

结论：这些结果支持目前正在进行的第 2/3 阶段大规模安全性和有效性评估的 BNT162b2 疫苗候选品的筛选。

Abstract:

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and the resulting disease, coronavirus disease 2019 (COVID-19), have spread to millions of people globally. Multiple vaccine candidates are under development, but no vaccine is currently available.

Methods Healthy adults 18–55 and 65–85 years of age were randomized in an ongoing, placebo-controlled, observer-blinded dose-escalation study to receive 2 doses at 21-day intervals of placebo or either of 2 lipid nanoparticle–formulated, nucleoside-modified RNA vaccine candidates: BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor-binding domain, or BNT162b2, which encodes a prefusion stabilized membrane-anchored SARS-CoV-2 full-length spike. In each of 13 groups of 15 participants, 12 received vaccine and 3 received placebo. Groups were distinguished by vaccine candidate, age of participant, and vaccine dose level. Interim safety and immunogenicity data of BNT162b1 in younger adults have been reported previously from US and German trials. We now present additional safety and immunogenicity data from the US Phase 1 trial that supported selection of the vaccine candidate advanced to a pivotal Phase 2/3 safety and efficacy evaluation.

Results In both younger and older adults, the 2 vaccine candidates elicited similar dosedependent SARS-CoV-2–neutralizing geometric mean titers (GMTs), comparable to or higher than the GMT of a panel of SARS-CoV-2 convalescent sera. BNT162b2 was associated with less systemic reactogenicity, particularly in older adults.

Conclusion These results support selection of the BNT162b2 vaccine candidate for Phase 2/3 large-scale safety and efficacy evaluation, currently underway.

21. SARS-CoV-2 spike 蛋白在完整病毒颗粒上的结构和分布

Structures and distributions of SARS-CoV-2 spike proteins on intact virions

来源：Nature

发布时间：2020-08-17

链接：https://www.nature.com/articles/s41586-020-2665-2

第一作者：Zunlong Ke, Joaquin Oton, Kun Qu

通讯作者：John A. G. Briggs
通讯作者单位：
Structural Studies Division, Medical Research Council Laboratory of Molecular Biology, Cambridge, CB2 0QH, United Kingdom.
DOI 或 PUBMED ID：10.1038/s41586-020-2665-2
编译者：宋珂
中文摘要：

SARS-CoV-2 病毒颗粒表面被双层脂膜包裹，spike（S）蛋白三聚体则从该双层脂膜中伸出。高度糖基化的 S 蛋白三聚体通过与 ACE2 受体结合，介导病毒侵入宿主细胞。S 蛋白表现出很大的构象柔性，因此能够调节构象，暴露其受体结合位点，并随后进行完全的结构重排，以促使病毒膜和细胞膜的融合。科研人员已经使用 cryo-EM 技术详细研究了可溶的，过表达的，以及纯化的 S 蛋白的结构和构象。然而，S 蛋白在病毒颗粒表面上的结构和分布尚未得到表征。本文中，作者利用 cryo-EM 和断层成像技术对完整的 SARS-CoV-2 病毒颗粒进行了成像，在病毒颗粒表面的原位上解析了 S 蛋白三聚体的高分辨率结构，确定了其分布和构象柔性。这些结果揭示了处于病毒颗粒上的 S 蛋白的构象，为理解病毒感染或疫苗接种过程中 S 蛋白与中和抗体之间的相互作用提供了基础。

结构数据：
Electron Microscopy Data Bank (EMDB):
EMD11493 (prefusion consensus structure).
EMD-11494 (3 closed RBDs from subtomogram averaging).
EMD-11495 (1 open RBD).
EMD-11496 (2 open RBDs).
EMD-11497 (3 closed RBDs from cryo-EM.
EMD-11498 (2 open and 1 weak RBDs).
RCSB PDB: **6ZWV** (3 closed RBDs from cryo-EM).

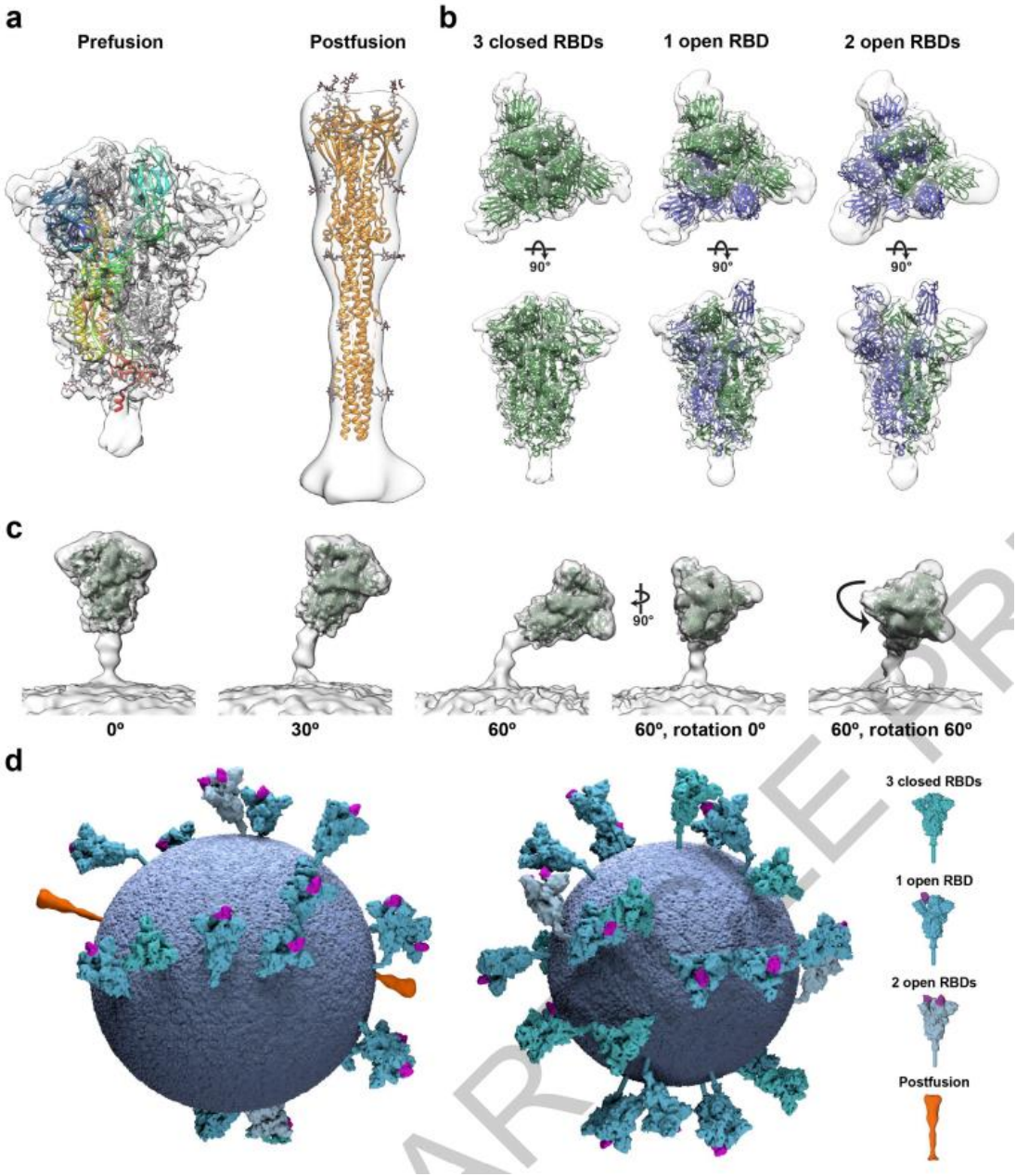


Fig. 2 | Structural analysis of SARS-CoV-2 S trimers on intact virions. (a) Structures of the prefusion (left) and postfusion (right) trimer from intact virions determined by subtomogram averaging. Structures are shown as transparent grey isosurfaces fitted with structures of the closed, prefusion trimer (PDB 6VXX) and the postfusion trimer (PDB 6XRA). One prefusion monomer is colored from blue (N terminus) to red (C terminus). The N-terminal domain is blue, the RBD appears cyan. The NTD does not fully occupy the EM density because some loops are not resolved or built in PDB 6VXX. **(b)** Three conformations of the prefusion trimer observed on intact virions: all RBDs in the closed position (left, fitted with PDB 6VXX); one RBD in the open position (centre, fitted with PDB 6VYB); two RBDs in the open position (right, fitted with PDB 6X2B which lacks modelled glycans). The two-open conformation has only been observed in vitro after inserting multiple stabilizing mutations. S monomers with closed RBDs are green, and with open RBDs are blue. **(c)** Averaging of subsets of trimers grouped according to their orientation relative to the membrane shows flexibility in the stalk region. Examples are shown for pools centred at 0°, 30° and 60° from the perpendicular, and for two rotations of the trimer

relative to the tilt direction. **(d)** 3D models of two individual SARS-CoV-2 virions with a membrane (blue) of the measured radius, and all spike proteins shown in the conformations, positions and orientations determined by subtomogram averaging. Different S conformations are distributed over the virion surface and can be tilted by up to ~90° relative to the membrane (Extended Data Fig. 1c,d).

Abstract:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virions are surrounded by a lipid bilayer from which spike (S) protein trimers protrude1. Heavily glycosylated S trimers bind the ACE2 receptor and mediate entry of virions into target cells2–6. S exhibits extensive conformational flexibility: it modulates exposure of its receptor binding site and later undergoes complete structural rearrangement to drive fusion of viral and cellular membranes2,7,8. The structures and conformations of soluble, overexpressed, purified S proteins have been studied in detail using cryo-electron microscopy2,7,9–12. The structure and distribution of S on the virion surface, however, has not been characterized. Here we applied cryo-electron microscopy and tomography to image intact SARS-CoV-2 virions, determining the high-resolution structure, conformational flexibility and distribution of S trimers in situ on the virion surface. These results reveal the conformations of S present on the virion, and provide a basis from which to understand interactions between S and neutralizing antibodies during infection or vaccination.

22. 单细胞 RNA 测序显示外周和肺对 COVID-19 的免疫应答差异

The differential immune responses to COVID-19 in peripheral and lung revealed by single-cell RNA sequencing

来源：medRxiv
发布时间：2020-08-17
链接：https://www.medrxiv.org/content/10.1101/2020.08.15.20175638v1

第一作者：Gang Xu, Furong Qi, Hanjie Li
通讯作者：Lei Liu[1], Shuye Zhang[5], Zheng Zhang[1]
通讯作者单位：
1 Institute for Hepatology, National Clinical Research Center for Infectious Disease, Shenzhen Third People's Hospital, The Second Affiliated Hospital, School of Medicine, Southern University of Science and Technology, Shenzhen 518112, Guangdong Province, China
5 Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China

DOI 或 PUBMED ID：
编译者：王玮

中文摘要：

了解 SARS-CoV2 病毒引起免疫功能紊乱的机制对于开发 COVID-19 重症患者的治疗方法至关重要。该研究利用单细胞 RNA 测序技术分析了来自未感染对照组和 COVID-19 患者的外

周血单个核细胞（PBMC）和成对的支气管肺泡灌洗液（BALF）中的细胞。该研究发现树突状细胞（DC）减少和类髓源性抑制细胞的单核细胞（MDSC）的增加与重症 COVID-19 患者血液中的淋巴细胞减少和炎症有关。这些 MDSC-like 单核细胞处于免疫麻痹状态。相反，COVID-19 患者 BALFs 中的单核-巨噬细胞产生大量细胞因子和趋化因子，但分泌少量干扰素。与健康对照组相比，重度 COVID-19 患者外周血 T 细胞和 NK 细胞， 尤其是先天性 T 细胞和各种 CD8+T 细胞亚群的频率明显降低。相比之下，重度 COVID-19 患者的各种活化 CD4+T 细胞亚群（包括 Th1、Th2 和 Th17 样细胞）的比例增加，克隆性扩张。患者的外周血 T 细胞没有衰竭或细胞死亡增加的迹象，而 BALFs 中的 T 细胞产生更高水平的 IFNG、TNF、CCL4 和 CCL5 等。配对的 TCR 追踪分析显示外周血 T 细胞向患者肺部大量募集。总之，这项研究全面描述了严重 COVID-19 的免疫细胞格局是如何受到干扰的。

Abstract:
Understanding the mechanism that leads to immune dysfunction induced by SARS-CoV2 virus is crucial to develop treatment for severe COVID-19. Here, using single cell RNA-seq, we characterized the peripheral blood mononuclear cells (PBMC) from uninfected controls and COVID-19 patients, and cells in paired broncho-alveolar lavage fluid (BALF). We found a close association of decreased dendritic cells (DC) and increased monocytes resembling myeloid-derived suppressor cells (MDSC) which correlated with lymphopenia and inflammation in the blood of severe COVID-19 patients. Those MDSC-like monocytes were immune-paralyzed. In contrast, monocyte-macrophages in BALFs of COVID-19 patients produced massive amounts of cytokines and chemokines, but secreted little interferons. The frequencies of peripheral T cells and NK cells were significantly decreased in severe COVID-19 patients, especially for innate-like T and various CD8+ T cell subsets, compared to health controls. In contrast, the proportions of various activated CD4+ T cell subsets, including Th1, Th2 and Th17-like cells were increased and more clonally expanded in severe COVID-19 patients. Patients' peripheral T cells showed no sign of exhaustion or augmented cell death, whereas T cells in BALFs produced higher levels of IFNG, TNF, CCL4 and CCL5 etc. Paired TCR tracking indicated abundant recruitment of peripheral T cells to the patients' lung. Together, this study comprehensively depicts how the immune cell landscape is perturbed in severe COVID-19.

23. SARS-CoV-2 基因组一个重要缺失对感染严重程度和炎症反应的影响：一项观察性队列研究

Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study

来源：The lancet

发布时间：2020-08-18

链接：https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31757-8/fulltext

第一作者：Barnaby E Young, Siew-Wai Fong, Yi-Hao Chan

通讯作者：Gavin J D Smith[1], Lisa F P Ng[2]

通讯作者单位：

1 Duke-NUS Medical School, National University of Singapore, 169857, Singapore
2 Singapore Immunology Network, Agency for Science, Technology, and Research, 138648, Singapore
DOI 或 PUBMED ID：10.1016/S0140-6736(20)31757-8
编译者：宋张悦

中文摘要：
背景：在新加坡等国家已检测到新型冠状病毒(SARS-CoV-2)在基因组开放阅读框 8(ORF8)区域内一个 382-核苷酸的碱基缺失(Δ382)。我们调查了这种缺失对感染临床特征的影响。

方法：我们回顾性地确定了接受Δ382 变异筛选的患者，并招募到新加坡七家公立医院的前瞻性观察队列研究(PROTECT study)。我们从患者的电子病历以及在住院期间和出院后采集的一系列血液和呼吸样本中收集临床、实验室和放射学数据。将Δ382 变异的感染个体与野生型 SARS-CoV-2 的感染个体进行比较。采用精确的 logistic 回归分析感染组与出现缺氧需要补充氧气(COVID-19 严重的指标，主要终点)之间的关系。对研究主要终点的随访已经完成。

发现：2020 年 1 月 22 日至 3 月 21 日，278 名 PCR 确诊的 SARS-CoV-2 患者参与了Δ382 筛选，最终招募了 131 人加入到研究中,其中有 92 例(70%)野生型病毒感染，10 例(8%)是野生型和Δ382 -变异病毒的杂合体，29 例(22%)只有Δ382 变异。**Δ382 变异组(0[0%]/ 29 例)出现缺氧需要补充氧气的几率低于仅野生型组(26[28%]/ 92 例；绝对差 28% [95% CI 14-28])。**在调整了年龄和基础共病后，与仅野生型病毒感染相比，只有Δ382 变异感染的出现缺氧需要补充氧气的几率更低(调整优势比 0·07 [95% CI 0·00-0·48])。

解释：Δ382 变异的 SARS-CoV-2 似乎与较温和的感染有关。观察到的 ORF8 缺失的临床效应可能对治疗和疫苗的开发有影响。
资金：新加坡国家医学研究委员会。

Abstract:
Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with a 382-nucleotide deletion (Δ382) in the open reading frame 8 (ORF8) region of the genome have been detected in Singapore and other countries. We investigated the effect of this deletion on the clinical features of infection.

Methods We retrospectively identified patients who had been screened for the Δ382 variant and recruited to the PROTECT study—a prospective observational cohort study conducted at seven public hospitals in Singapore. We collected clinical, laboratory, and radiological data from patients' electronic medical records and serial blood and respiratory samples taken during hospitalisation and after discharge. Individuals infected with the Δ382 variant were compared with those infected with wild-type SARS-CoV-2. Exact logistic regression was used to examine the association between the infection groups and the development of hypoxia requiring supplemental oxygen (an indicator of severe COVID-19, the primary endpoint). Follow-up for the study's primary endpoint is completed.

Findings Between Jan 22 and March 21, 2020, 278 patients with PCR-confirmed SARS-CoV-2 infection were screened for the Δ382 deletion and 131 were enrolled onto the study, of whom 92 (70%) were infected with the wild-type virus, ten (8%) had a mix of wild-type and Δ382-variant viruses, and 29 (22%) had only the Δ382 variant. Development of hypoxia requiring supplemental oxygen was less frequent

in the Δ382 variant group (0 [0%] of 29 patients) than in the wild-type only group (26 [28%] of 92; absolute difference 28% [95% CI 14－28]). After adjusting for age and presence of comorbidities, infection with the Δ382 variant only was associated with lower odds of developing hypoxia requiring supplemental oxygen (adjusted odds ratio 0·07 [95% CI 0·00－0·48]) compared with infection with wild-type virus only.

Interpretation The Δ382 variant of SARS-CoV-2 seems to be associated with a milder infection. The observed clinical effects of deletions in ORF8 could have implications for the development of treatments and vaccines.

Funding National Medical Research Council Singapore.

24. SARS-CoV-2 外显子(nsp14-nsp10)复合体的特征:其在病毒基因组稳定性和抑制剂鉴定中的作用

Characterisation of the SARS-CoV-2 ExoN (nsp14ExoN-nsp10) complex: implications for its role in viral genome stability and inhibitor identification

来源：bioRxiv
发布时间：2020-08-13
链接：https://www.biorxiv.org/content/10.1101/2020.08.13.248211v1
第一作者：Hannah T. Baddock
通讯作者：Christopher J. Schofield
通讯作者单位：
Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK
DOI 或 PUBMED ID：
编译者：孔娟

中文摘要：

SARS-CoV-2 导致了 COVID-19 的全球流行。SARS-CoV-2 属于病毒目，具有非常大的核糖核酸基因组。有人提出，由非结构蛋白 14 和 10 (nsp14-nsp10)形成的核糖核酸酶复合物有助于 CoV 基因组复制的保真度，非结构蛋白 14 和 10(NSP 14-NSP 10)是抗病毒抑制的一个潜在靶标。在这里，我们确认 SARS-CoV-2 nsp14-nsp10 复合物是一种核糖核酸酶。功能研究表明 nsp14-nsp10 是一种多功能的核酸酶，能够消化各种各样的核糖核酸结构，包括那些被封闭的 3’-末端。我们认为 nsp14-nsp10 在维持复制保真度方面的作用超越了经典的校对，并清除了新生的复制核糖核酸链的一系列潜在的复制终止变异。利用开发的分析方法，研究者鉴定了一系列能有效抑制 nsp14-nsp10 的药物和药物样分子，包括已知的 Sars-Cov-2 主蛋白酶抑制剂 Ebselen 和艾滋病毒整合酶抑制剂 raltegravir，揭示了双功能抑制剂在治疗 COVID-19 中的潜力。

Abstract:

The SARS-CoV-2 coronavirus (CoV) causes COVID-19, a current global pandemic. SARS-CoV-2 belongs to an order of Nidovirales with very large RNA genomes. It is proposed that the fidelity of CoV genome replication is aided by an RNA nuclease complex, formed of non-structural proteins 14 and 10 (nsp14-nsp10), an attractive

target for antiviral inhibition. Here, we confirm that the SARS-CoV-2 nsp14-nsp10 complex is an RNase. Detailed functional characterisation reveals nsp14-nsp10 is a highly versatile nuclease capable of digesting a wide variety of RNA structures, including those with a blocked 3'-terminus. We propose that the role of nsp14-nsp10 in maintaining replication fidelity goes beyond classical proofreading and purges the nascent replicating RNA strand of a range of potentially replication terminating aberrations. Using the developed assays, we identify a series of drug and drug-like molecules that potently inhibit nsp14-nsp10, including the known Sars-Cov-2 major protease (Mpro) inhibitor ebselen and the HIV integrase inhibitor raltegravir, revealing the potential for bifunctional inhibitors in the treatment of COVID-19.

25. COVID-19 患者中 Bcl-6+ T 滤泡辅助细胞的降低和生发中心的缺失相关研究

Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19

来源：cell

发布时间：2020-08-19

链接：https://www.cell.com/cell/fulltext/S0092-8674(20)31067-9

第一作者：Naoki Kaneko

通讯作者：Shiv Pillai

通讯作者单位：Ragon Institute of MGH, MIT and Harvard, Cambridge, MA 02139, USA

DOI 或 PUBMED ID：10.1016/j.cell.2020.08.025

编译者：孔娟

中文摘要：

COVID-19 疾病中的体液反应通常持久性有限，为了研究潜在的病因研究者检查了 SARS-CoV-2 感染的死者胸部淋巴结和脾脏，并观察到生发中心的缺失，Bcl-6+生发中心 B 细胞显著减少，但 AID+ B 细胞保留。生发中心的缺失与 Bcl-6+ TFH 细胞分化的早期特异性阻滞以及 T-bet+ TH1 细胞的增加和滤泡外肿瘤坏死因子-α 的异常积累相关。同时外周血研究显示，在严重疾病中发现移行性和滤泡性 B 细胞缺失，以及 SARS-CoV-2 特异性“疾病相关”B 细胞群的积累。这些数据确定了在 COVID-19 疾病早期有缺陷的 Bcl-6+ TFH 细胞生成和失调的体液免疫诱导，在一定程度上解释了冠状病毒感染中抗体反应的有限持久性，并表明通过自然感染实现群体免疫具有一定的不可行性。

Abstract:

Humoral responses in COVID-19 disease are often of limited durability, as seen with other human coronavirus epidemics. To address the underlying etiology, we examined postmortem thoracic lymph nodes and spleens in acute SARS-CoV-2 infection and observed the absence of germinal centers, a striking reduction in Bcl-6+ germinal center B cells but preservation of AID+ B cells. Absence of germinal centers correlated with an early specific block in Bcl-6+ TFH cell differentiation together with an increase in T-bet+ TH1 cells and aberrant extra-follicular TNF-α accumulation. Parallel peripheral blood studies revealed loss of transitional and follicular B cells in severe disease and accumulation of

SARS-CoV-2-specific “disease-related” B cell populations. These data identify defective Bcl-6+ TFH cell generation and dysregulated humoral immune induction early in COVID-19 disease, providing a mechanistic explanation for the limited durability of antibody responses in coronavirus infections and suggest that achieving herd immunity through natural infection may be difficult.

26. 设计的重组 ACE2-Fc 变异型，使抗 SARS-CoV-2 的活性与不必要的心血管效应分离

Designed Variants of Recombinant ACE2-Fc that Decouple Anti-SARS-CoV-2 Activities from Unwanted Cardiovascular Effects

来源：bioRxiv

发布时间：2020-08-14

链接：https://www.biorxiv.org/content/10.1101/2020.08.13.248351v1

第一作者：Pan Liu

通讯作者：Jing Jin

通讯作者单位：美国芝加哥西北大学范伯格医学院

DOI 或 PUBMED ID：10.1101/2020.08.13.248351

编译者：刘焕珍

中文摘要：

血管紧张素转换酶 2（ACE2）是 SARS-CoV-2 进入细胞的受体，因为重组 ACE2 受体可以作为诱饵能结合这种病毒并阻止细胞感染，因此重组 ACE2 被认为是一种新的抗病毒治疗方法。我们设计并测试了一种 ACE2-Fc 融合蛋白，该蛋白具有较长的药理半衰期和促进病毒免疫清除的潜力。考虑到 ACE2 的内在催化活性可能会无意中改变其激素底物的平衡，并在治疗过程中对心血管产生不利影响，我们对 ACE2 酶进行了突变筛选，目的是筛选出 ACE2 酶失活的突变株。R273A，H378A 和 E402A 这三个突变体完全丧失了对替代底物或生理底物的酶促活性。在细胞培养中，它们都仍然具有结合 SARS-CoV-2 的能力，并且可以抑制假型病毒的转导。这项研究建立了新的 ACE2-Fc 候选药物作为 SARS-CoV-2 的抗病毒治疗剂，而不会因 ACE2 对其血管活性底物的催化作用而产生潜在的有害副作用。

Abstract:

Angiotensin-converting enzyme 2 (ACE2) is the entry receptor for SARS-CoV-2, and recombinant ACE2 decoys are being evaluated as new antiviral therapies. We designed and tested an ACE2-Fc fusion protein, which has the benefits of a long pharmacological half-life and the potential to facilitate immune clearance of the virus. Out of the concern that the intrinsic catalytic activity of ACE2 may unintentionally alter the balance of its hormonal substrates and cause adverse cardiovascular effects in treatment, we performed a mutagenesis screening for inactivating the enzyme. Three mutants, R273A, H378A and E402A, completely lost their enzymatic activity for either surrogate or physiological substrates. All of them remained capable of binding SARS-CoV-2 and could suppress the transduction of a pseudotyped virus in cell culture. This study established new ACE2-Fc candidates as antiviral treatment for SARS-CoV-2 without potentially harmful side effects from ACE2’s catalytic actions toward its vasoactive substrates.

27.使用串行晶体学方法解析 SARS-CoV-2 中甲基化的 RNA 帽的结构

Methylation of RNA Cap in SARS-CoV-2 captured by serial crystallography

来源：bioRxiv

发布时间：2020-08-16

链接：https://www.biorxiv.org/content/10.1101/2020.08.14.251421v2

第一作者：Wilamowski, M.

通讯作者：Andrzej Joachimiak

通讯作者单位：

Structural Biology Center, X-ray Science Division, Argonne National Laboratory, Argonne, Illinois 60439, USA

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

SARS-CoV-2 冠状病毒的基因组包含 29 种蛋白质，其中 15 种是非结构性的。 Nsp10 和 Nsp16 形成的复合物负责 mRNA 的 5’端的加帽反应。在甲基化反应中，S-腺苷-L-甲硫氨酸充当甲基的供体，在第一个转录的核苷酸处，甲基转移至 Cap-0，从而生成 Cap-1。Cap-1 的存在使病毒 RNA 能够模仿宿主的转录物，并防止其降解。为了研究 SARS-CoV-2 Nsp10/16 的 2’-O 甲基转移酶的活性，作者使用固定靶串行同步加速器晶体学（SSX），能够在生理温度下收集数千个晶体的数据。从而显着减少了 X 射线剂量，使样品保持在生物学相关的温度。作者解析了 Nsp10/16 的晶体结构，揭示了体系在甲基化反应之前和之后的状态。这是首次解析的冠状病毒 Nsp10/16 与 m7GpppAm2’-O Cap-1 的复合物结构，其中核糖的 2’OH 发生了甲基化。作者将本文中解析的结构与 297K 和 100K 下收集的 Nsp10/16 的单晶结构进行了比较。本文中的数据，为设计抑制病毒 RNA 成熟的小分子抑制剂，迫使 SARS-CoV-2 对宿主的先天反应敏感，提供了重要的机理信息。

结构数据：RCSB PDB：6XKM，7JHE，7JPE，7JIB

Abstract:

The genome of the SARS-CoV-2 coronavirus contains 29 proteins, of which 15 are nonstructural. Nsp10 and Nsp16 form a complex responsible for the capping of mRNA at the 5′ terminus. In the methylation reaction the S-adenosyl-L-methionine serves as the donor of the methyl group that is transferred to Cap-0 at the first transcribed nucleotide to create Cap-1. The presence of Cap-1 makes viral RNAs mimic the host transcripts and prevents their degradation. To investigate the 2′ -O methyltransferase activity of SARS-CoV-2 Nsp10/16, we applied fixed-target serial synchrotron crystallography (SSX) which allows for physiological temperature data collection from thousands of crystals, significantly reducing the x-ray dose while maintaining a biologically relevant temperature. We determined crystal structures of Nsp10/16 that revealed the states before and after the methylation reaction, for the first time illustrating coronavirus Nsp10/16 complexes with the m7GpppAm2′ -O Cap-1, where 2′ OH of ribose is methylated. We compare these structures with structures of Nsp10/16 at 297 K and 100 K collected from a single crystal. This data provide important mechanistic insight and can be used to design small molecules that inhibit viral RNA maturation making SARS-CoV-2 sensitive to host innate

response.

28. IFITM 蛋白促进 SARS-CoV-2 病毒感染人体肺细胞

IFITM proteins promote SARS-CoV-2 infection of human lung cells

来源：bioRxiv

发布时间：2020-08-18

链接：https://www.biorxiv.org/content/10.1101/2020.08.18.255935v1

第一作者：Caterina Prelli Bozzo

通讯作者：Konstantin M.J. Sparrer， Frank Kirchhoff

通讯作者单位：

Institute for Molecular Virology, Ulm University Medical Centre, 89081 Ulm, Germany

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

干扰素诱导的跨膜蛋白（IFITMs 1、2 和 3）阻碍了许多病毒病原体，并被认为可以预防 SARS-CoVs 的感染。然而，大多数证据来自于单轮假病毒颗粒感染的人工过表达 IFITM 的细胞的。本文中，作者证实了 IFITMs 的过表达可以阻断由 β 冠状病毒（包括 SARS-CoV-2）的 Spike 蛋白介导的假颗粒感染。与之形成鲜明对比的是，无论是否存在干扰素，内源性的 IFITM 表达均可促进真正的 SARS-CoV-2 病毒感染人体肺细胞。IFITM2 对于 SARS-CoV-2 病毒有效侵入宿主，以及促使病毒在 Calu-3 细胞中的产生量提高几个数量级都至关重要。IFITMs 的表达，以及随后被干扰素诱导，可以表明在肺和其他相关组织中发生 SARS-CoV-2 感染的主要位置。作者的发现表明，IFITM 在接近体内情况的条件下会增强 SARS-CoV-2 的感染，这表明 IFITM 可能在 COVID-19 期间促进了病毒侵入。

Abstract:

Interferon-induced transmembrane proteins (IFITMs 1, 2 and 3) restrict numerous viral pathogens and are thought to prevent infection by severe acute respiratory syndrome coronaviruses (SARS-CoVs). However, most evidence comes from single-round pseudoparticle infection of cells artificially overexpressing IFITMs. Here, we confirmed that overexpression of IFITMs blocks pseudoparticle infections mediated by the Spike proteins of β-coronaviruses including pandemic SARS-CoV-2. In striking contrast, however, endogenous IFITM expression promoted genuine SARS-CoV-2 infection in human lung cells both in the presence and absence of interferon. IFITM2 was most critical for efficient entry of SARS-CoV-2 and enhanced virus production from Calu-3 cells by several orders of magnitude. IFITMs are expressed and further induced by interferons in the lung representing the primary site of SARS-CoV-2 infection as well as in other relevant tissues. Our finding that IFITMs enhance SARS-CoV-2 infection under conditions approximating the in vivo situation shows that they may promote viral invasion during COVID-19.

29. 显而易见：α-1-抗胰蛋白酶在 COVID-19 发病机理和治疗中的作用

In plain sight: the role of alpha-1-antitrypsin in COVID-19 pathogenesis and

therapeutics
来源：bioRxiv
发布时间：2020-08-15
链接：https://www.biorxiv.org/content/10.1101/2020.08.14.248880v1
第一作者：Kasopefoluwa Y Oguntuyo, Christian S Stevens
通讯作者：Benhur Lee
通讯作者单位： Icahn School of Medicine at Mount Sinai,
编译者：宋珂
中文摘要：

未被 SARS-CoV-2 感染的血清表现出显著的抑制 SARS-CoV-2 侵入的能力。alpha-1-antitrypsin（AAT）作为主要的血清蛋白酶抑制剂，可以有效地限制蛋白酶介导的 SARS-CoV-2 的侵入。在体外，AAT 能够在浓度远低于在血清和支气管肺泡组织中的条件下抑制蛋白酶介导的 SARS-CoV-2 侵入，这说明 AAT 的作用与生理环境相关。此外，超过 20%的人口受到了 AAT 缺乏症的影响，其症状表现和许多与重症 COVID-19 相关的危险因素相吻合。AAT 除了可能对病毒侵入产生的影响外，作者认为 AAT 的抗炎和凝血调节活性对 COVID-19 的致病性，SARS-CoV-2 组织限制，恢复期血浆疗法，甚至潜在的 AAT 疗法都有影响。

Abstract:
Entry of SARS-CoV-2 is facilitated by endogenous and exogenous proteases. These proteases proteolytically activate the SARS-CoV-2 spike glycoprotein and are key modulators of virus tropism. We show that SARS-CoV-2 naïve serum exhibits significant inhibition of SARS-CoV-2 entry. We identify alpha-1-antitrypsin (AAT) as the major serum protease inhibitor that potently restrict protease-mediated entry of SARS-CoV-2. AAT inhibition of protease-mediated SARS-CoV-2 entry in vitro occurs at concentrations far below what is present in serum and bronchoalveolar tissues, suggesting that AAT effects are physiologically relevant. Moreover, AAT deficiency affects up to 20% of the population and its symptomatic manifestations coincides with many risk factors associated with severe COVID-19 disease. In addition to the effects that AAT may have on viral entry itself, we argue that the anti-inflammatory and coagulation regulatory activity of AAT have implications for coronavirus disease 2019 (COVID-19) pathogenicity, SARS-CoV-2 tissue restriction, convalescent plasma therapies, and even potentially AAT therapy.

30. 细菌对宿主粘多糖肝素的修饰可以调节 SARS-CoV-2 的感染性

Bacterial modification of the host glycosaminoglycan heparan sulfate modulates SARS-CoV-2 infectivity
来源：bioRxiv
发布时间：2020-08-18
链接：https://www.biorxiv.org/content/10.1101/2020.08.17.238444v1
第一作者：Cameron Martino
通讯作者：Rob Knight
通讯作者单位：UCLA
DOI 或 PUBMED ID：10.1101/2020.08.17.238444

编译者：蒋立春

中文摘要：

人体的菌群可以对硫酸乙酰肝素蛋白聚糖在内的多糖进行重建，它们和疾病息息相关。对 SARS-CoV-2 的刺突蛋白受体结合区域的研究表明病毒感染依赖于其对硫酸乙酰肝素蛋白聚糖和 ACE2 相互依赖性的结合。该研究中，作者发现和宿主共生的菌群可以修饰肝素进而调控 SARS-CoV-2 刺突蛋白的结合。这些菌群随着年龄和性别发生变化。作者们鉴定除了包含肝素修饰酶的共生细菌。COVID-19 病人和健康对照组相比，在肺部灌洗液里这些细菌和关键的细菌来源的糖苷酶的表达较低。肝素修饰细菌在两个大的人群中都随着年龄增长而下降，提示了 COVID-19 年龄增加易感性的一个可能机制。在体外实验中，从培养基上清中获得的不经过纯化的细菌糖苷酶可以完全阻断 SARS-CoV-2 刺突蛋白结合到人的 H1299 肺癌细胞上。人的菌群中的肝素修饰细菌可能会调节病毒的结合，失去这些共生菌的人可能会变得对病毒易感。理解菌群的组成以及细菌裂解酶对 SARS-CoV-2 的感染可能会导致发现新的治疗方案以及判断易感性的方法。

Abstract:

The human microbiota has a close relationship with human disease and it remodels components of the glycocalyx including heparan sulfate (HS).

Studies of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) spike protein receptor binding domain suggest that infection requires binding to HS and angiotensin converting enzyme 2 (ACE2) in a codependent manner. Here, we show that commensal host bacterial communities can modify HS and thereby modulate SARS-CoV-2 spike protein binding and that these communities change with host age and sex. Common human-associated commensal bacteria whose genomes encode HS-modifying enzymes were identified. The prevalence of these bacteria and the expression of key microbial glycosidases in bronchoalveolar lavage fluid (BALF) was lower in adult COVID-19 patients than in healthy controls.

The presence of HS-modifying bacteria decreased with age in two large survey datasets, FINRISK 2002 and American Gut, revealing one possible mechanism for the observed increase in COVID-19 susceptibility with age. In vitro, bacterial glycosidases from unpurified culture media supernatants fully blocked SARS-CoV-2 spike binding to human H1299 lung adenocarcinoma cells. HS-modifying bacteria in human microbial communities may regulate viral adhesion, and loss of these commensals could predispose individuals to infection. Understanding the impact of shifts in microbial community composition and bacterial lyases on SARS-CoV-2 infection may lead to new therapeutics and diagnosis of susceptibility.

31. SRSF 蛋白激酶 1 和 2 (SPRK1/2)是对包括 SARS-CoV-2 在内的人冠状病毒感染不可缺少的宿主因子

SRSF protein kinases 1 and 2 are essential host factors for human coronaviruses including SARS-CoV-2

来源：bioRxiv

发布时间：2020-08-15

链接：https://www.biorxiv.org/content/10.1101/2020.08.14.251207v2
第一作者：Brook E. Heaton
通讯作者：Nicholas S. Heaton
通讯作者单位：Duke University
DOI 或 PUBMED ID：
编译者：蒋立春

中文摘要：

靶向对病毒复制的宿主可以抑制病毒传播，同时和少导致病毒发生药物抗性突变。作者们通过在人肺上皮细胞中进行全基因组 CRISPR/Cas9 筛选来鉴定可能的宿主靶点。对筛选的结果进行验证发现激酶 SPRK1 以及和它紧密相关的 SRPK2 两者对 SARS-CoV-2 的复制是必需的。用化学小分子抑制 SRPK1/2 可以在永生化的人肺细胞以及原代细胞中非常显著（高于 10 万倍的）抑制 SARS-CoV-2 的繁殖。接下来的生化分析表明 SPRK1/2 磷酸化病毒的 N 蛋白。磷酸化的位点在人冠状病毒高度保守，因为这个保守行，和 SARS-CoV-2 进化距离相对远的冠状并对也对 SPRK1/2 的抑制剂非常敏感。这些数据表明靶向宿主的 SRPK1/2 可能开发有效的治疗包括 SARS-CoV-2 的冠状病毒感染的手段。
编者注：Duke 大学申请了针对 SRPK1/2 抑制剂的专利。

Abstract:
Antiviral therapeutics against SARS-CoV-2 are needed to treat the pandemic disease COVID-19. Pharmacological targeting of a host factor required for viral replication can suppress viral spread with a low probability of viral mutation leading to resistance. Here, we used a genome-wide loss of function CRISPR/Cas9 screen in human lung epithelial cells to identify potential host therapeutic targets. Validation of our screening hits revealed that the kinase SRPK1, together with the closely related SRPK2, were jointly essential for SARS-CoV-2 replication; inhibition of SRPK1/2 with small molecules led to a dramatic decrease (more than 100,000-fold) in SARS-CoV-2 virus production in immortalized and primary human lung cells. Subsequent biochemical studies revealed that SPRK1/2 phosphorylate the viral nucleocapsid (N) protein at sites highly conserved across human coronaviruses and, due to this conservation, even a distantly related coronavirus was highly sensitive to an SPRK1/2 inhibitor. Together, these data suggest that SRPK1/2-targeted therapies may be an efficacious strategy to prevent or treat COVID-19 and other coronavirus-mediated diseases.

32. SARS-CoV-2 操纵了 SR-B1 介导的高密度脂蛋白吸收通路帮助自己进入细胞

SARS-CoV-2 manipulates the SR-B1-mediated HDL uptake pathway for its entry
来源：bioRxiv
发布时间：2020-08-14
链接：https://www.biorxiv.org/content/10.1101/2020.08.13.248872v1
第一作者：Congwen Wei
通讯作者：Hui Zhong

通讯作者单位：Beijing Institute of Biotechnology
DOI 或 PUBMED ID：
编译者：蒋立春

中文摘要：

作者们发现 SARS-CoV-2 的刺突蛋白的 S1 亚基可以结合到高密度脂蛋白上劫持 SR-B1 介导的高密度脂蛋白的转运信号通路来帮助病毒自己进入细胞。SR-B1 可以通过加强病毒对可侵染细胞的附着而帮助 SARS-CoV-2 更好进去细胞。通过使用 Mab(单克隆抗体)阻断 SARS-CoV-2 的刺突蛋白和高密度脂蛋白的结合，以及 SR-B1 拮抗剂都可以强烈抑制高密度脂蛋白增强的 SARS-CoV-2 感染。SR-B1 和 ACE2 在人肺部以及其他组织中共表达。这些数据提示作者们发现了全新的 SARS-CoV-2 进细胞的机制。

Abstract:

The recently emerged pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly, leading to a global COVID-19 pandemic. Binding of the viral spike protein (SARS-2-S) to cell surface receptor angiotensin-converting enzyme 2 (ACE2) mediates host cell infection. In the present study, we demonstrate that in addition to ACE2, the S1 subunit of SARS-2-S binds to HDL and that SARS-CoV-2 hijacks the SR-B1-mediated HDL uptake pathway to facilitate its entry. SR-B1 facilitates SARS-CoV-2 entry into permissive cells by augmenting virus attachment. MAb (monoclonal antibody)-mediated blocking of SARS-2-S-HDL binding and SR-B1 antagonists strongly inhibit HDL-enhanced SARS-CoV-2 infection. Notably, SR-B1 is co-expressed with ACE2 in human pulmonary and extrapulmonary tissues. These findings revealed a novel mechanism for SARS-CoV-2 entry and could provide a new target to treat SARS-CoV-2 infection.

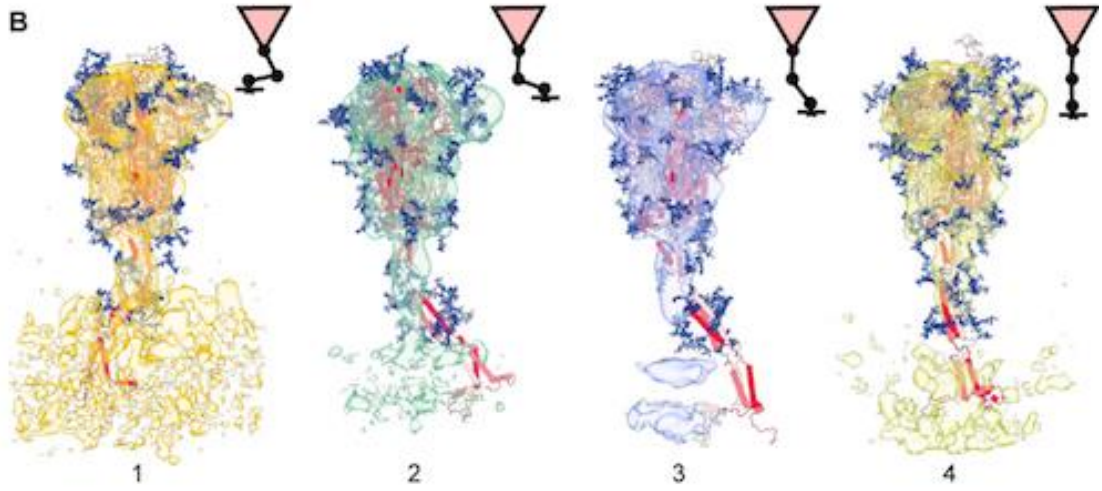
33. SARS-CoV-2 刺突蛋白的原位结构分析揭示了其由三个铰链导致的灵活性

In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges
来源：Science
发布时间：2020-08-22
链接：https://science.sciencemag.org/content/early/2020/08/17/science.abd5223
第一作者：Beata Turonova, Mateusz Sikora, Christoph Schurmann
通讯作者：Gerhard Hummer, Jacomine Krijnse Locker, Martin Beck
通讯作者单位：
European Molecular Biology Laboratory, Germany; Max Planck Institute of Biophysics, Germany
DOI 或 PUBMED ID：10.1126/science.abd5223
编译者：杨欢

中文摘要：

这篇文章中，作者主要分析了新冠病毒的刺突蛋白的原位（in situ）结构。作者将冷冻电镜断层扫描、局部断层平均（subtomogram averaging）和分子动力学模拟相结合，来

分析刺突蛋白的结构。主要观察到下面几点：1）刺突蛋白主要处于融合前构象（pre-fusion conformation），并且在病毒表面随机分布；2）刺突蛋白的头部通过三个灵活的铰链与病毒包膜连接，断层扫描数据与动力学模拟数据都表明这三个铰链的构象非常灵活，使得刺突蛋白的头部可以有很大的位置与朝向变化（如图），这有可能帮助刺突蛋白扫描宿主细胞表面；3）刺突蛋白以及铰链的表面都广泛存在糖基化。



Abstract:
The spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is required for cell entry and is the major focus for vaccine development. Here, we combine cryo electron tomography, subtomogram averaging and molecular dynamics simulations to structurally analyze S in situ. Compared to recombinant S, the viral S was more heavily glycosylated and occurred mostly in the closed pre-fusion conformation. We show that the stalk domain of S contains three hinges, giving the head unexpected orientational freedom. We propose that the hinges allow S to scan the host cell surface, shielded from antibodies by an extensive glycan coat. The structure of native S contributes to our understanding of SARS-CoV-2 infection and the development of safe vaccines.

34. 猪细胞和家猪对 SARS-CoV-2 的敏感性

Susceptibility of swine cells and domestic pigs to SARS-CoV-2

来源：bioRxiv

发布时间：2020-08-16

链接：https://www.biorxiv.org/content/10.1101/2020.08.15.252395v1

第一作者：David A. Meekins

通讯作者：Juergen A. Richt

通讯作者单位：

Center of Excellence for Emerging and Zoonotic Animal Diseases, Department of Diagnostic Medicine/Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

由于种间传播的可能性，以及为开发有效治疗手段而对临床前动物模型的需求，研究不同动物物种对 SARS-CoV-2 病毒的易感性非常值得关注。本文中，作者发现 SARS-CoV-2 病毒具有以下能力：（i）在猪细胞系中复制；（ii）可通过实验性口服/鼻内/气管内接种在家猪中建立感染；（iii）可传播至共同饲养的、未感染过的新猪。SARS-CoV-2 能够在具有细胞病变的两种不同的猪细胞系中复制。有趣的是，接种 SARS-CoV-2 的猪均未显示出临床症状，也未发现病毒复制或 SARS-CoV-2 特异性抗体反应的证据。此外，没有任何新猪表现出 SARS-CoV-2 感染的标志。这些数据表明，尽管 SARS-CoV-2 可感染不同的猪细胞系，但五周龄的猪不易通过口服/鼻内/气管内攻击感染。因此，猪不太可能是 SARS-CoV-2 的重要携带者。也不适合作为临床前动物模型，用于研究 SARS-CoV-2 的发病机理，或研究相应疫苗和药物的功效。

Abstract:

The emergence of SARS-CoV-2 has resulted in an ongoing global pandemic with significant morbidity, mortality, and economic consequences. The susceptibility of different animal species to SARS-CoV-2 is of concern due to the potential for interspecies transmission, and the requirement for pre-clinical animal models to develop effective countermeasures. In the current study, we determined the ability of SARS-CoV-2 to (i) replicate in porcine cell lines, (ii) establish infection in domestic pigs via experimental oral/intranasal/intratracheal inoculation, and (iii) transmit to co-housed naive sentinel pigs. SARS-CoV-2 was able to replicate in two different porcine cell lines with cytopathic effects. Interestingly, none of the SARS-CoV-2-inoculated pigs showed evidence of clinical signs, viral replication or SARS-CoV-2-specific antibody responses. Moreover, none of the sentinel pigs displayed markers of SARS-CoV-2 infection. These data indicate that although different porcine cell lines are permissive to SARS-CoV-2, five-week old pigs are not susceptible to infection via oral/intranasal/intratracheal challenge. Pigs are therefore unlikely to be significant carriers of SARS-CoV-2 and are not a suitable pre-clinical animal model to study SARS-CoV-2 pathogenesis or efficacy of respective vaccines or therapeutics.

35. 一个用于研究 COVID-19 的人类免疫系统的小鼠模型(DRAGA mouse: HLA-A2.HLA-DR4.Rag1KO.IL-2Rγc KO.NOD)

A Human-Immune-System mouse model for COVID-19 research(DRAGA mouse: HLA-A2.HLA-DR4.Rag1KO.IL-2Rγc KO.NOD)

来源：bioRxiv

发布时间：2020-08-20

链接：https://www.biorxiv.org/content/10.1101/2020.08.19.251249v1

第一作者：Teodor-Doru Brumeanu

通讯作者：Sofia A.Casares

通讯作者单位：美国海军医学中心
DOI 或 PUBMED ID：
编译者：蒋立春

中文摘要：

虽然转了人 ACE2 基因的小鼠模型可以感染 SARS-CoV-2，但是这些小鼠不能很好模拟人感染 SARS-CoV-2 后的的免疫病理反应。作者们构建了 DRAGA 即 HLA-A2.HLA-DR4.Rag1.IL-2R. gammac 基因敲除的裸鼠。通过注入人脐带血来源的血液干细胞重建人的免疫系统，移植人的上皮以及内皮细胞，这些小鼠可以持续感染 SARS-CoV-2,并且发展出严重的 COVID-19 症状。这种小鼠是进行对 COVID-19 引发的免疫病理以及免疫反应的好的临床前研究工具。

Abstract:

The current SARS-CoV-2 pandemic is accompanied by high morbidity and mortality rates, and there is a compelling need for effective vaccines and therapeutic agents to lessen the severity of COVID-19 disease. Appropriate animal models are essential for testing of vaccines and therapeutics and for mechanistic studies of infection and the host response. The Spike (S) protein of SARS-COV-2 has a high affinity for the human ACE2 receptor, which is expressed on multiple cell types including alveolar epithelial and vascular endothelial cells. Wild-type mice are not susceptible to developing coronavirus-mediated diseases. Accordingly, several human (h)ACE2 transgenic mouse models have been developed for coronavirus research. However, these mice have failed to closely mimic important aspects of the human immunopathological responses to SARS-CoV-2. We report herein that DRAGA (HLA-A2.HLA-DR4.Rag1KO.IL-2R. gammac KO.NOD) mice infused with human hematopoietic stem cells from cord blood reconstitute a fully functional human immune system, as well as engraft human epithelial and endothelial cells, sustain SARS-CoV-2 infection, and develop severe COVID-19-like symptoms. In pilot experiments, infected mice developed parenchymal and epithelial lung infiltrations with granzyme B+ and perforin+ CD8+ T cells and alveolar CD61+ microthrombi, mimicking human immunopathological responses to SARS-CoV-2. We propose the DRAGA mouse as a novel pre-clinical tool for studying COVID-19 immunopathology and human immune responses to SARS-CoV-2, including events leading to the cytokine storm and coagulopathies, as well as for testing of candidate vaccines and therapeutics.

36. 对冠状病毒的免疫反应说明疫苗的前景

What the immune response to the coronavirus says about the prospects for a vaccine

来源：Nature
发布时间：2020-08-17
链接：https://www.nature.com/articles/d41586-020-02400-7
作者：Heidi Ledford（杂志记者）

编译者：雷颖

中文摘要：

少数 COVID-19 康复病人的复阳引发了人们对免疫力可能短暂的恐惧，并对疫苗的前景提出了令人沮丧的预测。但对于科学家深入研究针对 SARS-CoV-2 的免疫反应的细节而言，目前的复阳数据不足为惧，我们已经看到了出色的免疫反应和奇妙的抗体，只是还不知道这种反应的持续时间。迄今为止，SARS-CoV-2 的研究还是令人鼓舞的。几个研究小组迅速从感染病毒的患者中分离出中和抗体，而大多数患者都可以在确诊后几天内产生这种抗体反应。几种针对 SARS-CoV-2 的候选疫苗都引起了强烈的抗体反应，这是疫苗可能产生免疫力的积极信号。但是一些科学家对初步数据也提出了警告。在感染最严重的人群中，抗体反应往往最高。那些患有轻度感染的人-也就是说大多数患有 COVID-19 的人-有时会产生少量中和抗体。这种模式在病毒中很常见，更长、更严重的感染更有可能产生强烈而持久的反应。这就是普通的冠状病毒有时不能产生持久免疫力的原因之一。即使抗体水平下降到极低的水平，免疫系统通常也有备用计划。记忆 B 细胞能够在从轻度 COVID-19 中恢复的人中产生识别 SARS-CoV-2 的中和抗体。T 细胞可能能够识别被病毒感染的细胞并破坏它们，从而限制了病毒在体内的传播。像记忆 B 细胞一样，T 细胞的探测比抗体要复杂得多，但迄今为止的研究表明，它们在 SARS-CoV-2 感染期间被激活了。总而言之，SARS-CoV-2 对人体的多样且有时具有毁灭性的影响及其易于传播，使它成为非同寻常的敌人。但是到目前为止，免疫系统对这种病毒的反应还没有什么真正独特的。

Abstract:

Sporadic accounts of reinfection — people recovering from COVID-19, only to fall ill and test positive for the disease again — have stoked fears that immunity might be short-lived. Media outlets have latched on to such reports, and have offered gloomy predictions about the prospects for a vaccine. But scientists are more circumspect. For the scientists digging deeply into the details of the immune response to SARS-CoV-2, the data are so far unsurprising — and that bodes well. “We’re seeing great immune responses and fantastic-looking antibodies. We just don’t know the longevity of that response yet,” says Mehul Suthar, a viral immunologist at Emory University in Atlanta, Georgia. “Unfortunately, that will take time.” The signs so far for SARS-CoV-2 are encouraging. Several teams of researchers were quick to isolate neutralizing antibodies from people infected with the virus3; most could mount such an antibody response within days of testing positive. And several vaccine candidates against SARS-CoV-2 provoke a strong antibody response, a positive sign that the vaccines might generate immunity. But some scientists have caveats about the preliminary data. Antibody responses tended to be highest in people with the most severe infection. Those with mild infections — which is to say most people who have had COVID-19 — sometimes produced small amounts of neutralizing antibody. This pattern is often seen with viruses: the longer, more severe infections are more likely to produce strong, durable responses. This is one reason that common-cold coronaviruses sometimes don’t yield long-lasting immunity, says Shane Crotty, a virologist at the La Jolla Institute for Immunology in California. Even if antibody levels dip to vanishingly low levels, the immune system often has a backup plan. One recent study, which has not yet been peer reviewed, found memory B cells capable of producing neutralizing antibodies that recognize SARS-CoV-2 in people who had recovered from mild COVID-196. Furthermore, immunity does not rely entirely on antibodies. T cells might be able to recognize virally infected cells and destroy them, limiting the virus’s spread in the body. Like memory B cells, T cells are more complicated to probe than antibodies, but studies so far

suggest that they are called into action during SARS-CoV-2 infection. Altogether, the diverse and sometimes devastating effects of SARS-CoV-2 on the body and its ease of spread have made it an unusual foe. But the immune system's response to the virus, so far, has held few surprises, says Barreiro. In this case, he adds, 'boring' bodes well for long-lasting immunity. "There are still a lot of things that we don't know, but so far, there's nothing really unique."

37. Moderna 提出了"低于价值"的 COVID-19 疫苗定价计划的理由

Moderna makes case for 'below-value' COVID-19 vaccine pricing plan

来源：biocentury

发布时间：2020-08-06

文章链接：https://www.biocentury.com/article/305868/moderna-makes-case-for-lsquo-below-value-rsquo-covid-19-vaccine-pricing-plan?tag=cov19count&return_feed=%2Fcoronavirus

作者：Paul Bonanos

编译者：张怡

中文摘要：

Moderna 的管理团队周三提出，根据某些供应协议，COVID-19 疫苗的价格为每剂 32- 37 美元，在未来大批量供应协议中，价格可能会降低。

这一价格超过了辉瑞公司和 BioNTech SE 上周确定的 19.50 美元的价格。这些合作伙伴和 Moderna 已经表示，一旦疫情大流行阶段结束，它们的疫苗价格可能会上涨。

Moderna 于 7 月 27 日开始对 mRNA-1273 进行三期 COVE 实验。该公司已收到 9.55 亿美元的 BARDA 开发承诺。

脂质纳米颗粒封装的 mRNA 疫苗编码 SARS-CoV-2 病毒的全长、稳定的预融合 S 蛋白。

Abstract:

Moderna's management team made its case Wednesday for pricing its COVID-19 vaccine at $32-$37 per dose for certain supply agreements, with the potential for lower prices among future higher-volume supply deals.

The price exceeds the $19.50 price set last week by Pfizer Inc. (NYSE:PFE) and BioNTech SE (NASDAQ:BNTX). Those partners, and Moderna, have signaled that the prices of their vaccines -- each of which will likely reach the market in two-dose courses -- would likely rise once the disease's pandemic phase is over.

Moderna began the Phase III COVE trial of mRNA-1273 on July 27. The company has received $955 million in BARDA commitments for its development (see "Pivotal Testing Begins").

The lipid nanoparticle-encapsulated mRNA-based vaccine encodes a full-length, stabilized prefusion spike (S) protein of SARS-CoV-2, the virus that causes COVID-19.