新型冠状病毒信息简报

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上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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1. 2020 年 7 月 23 日疫情

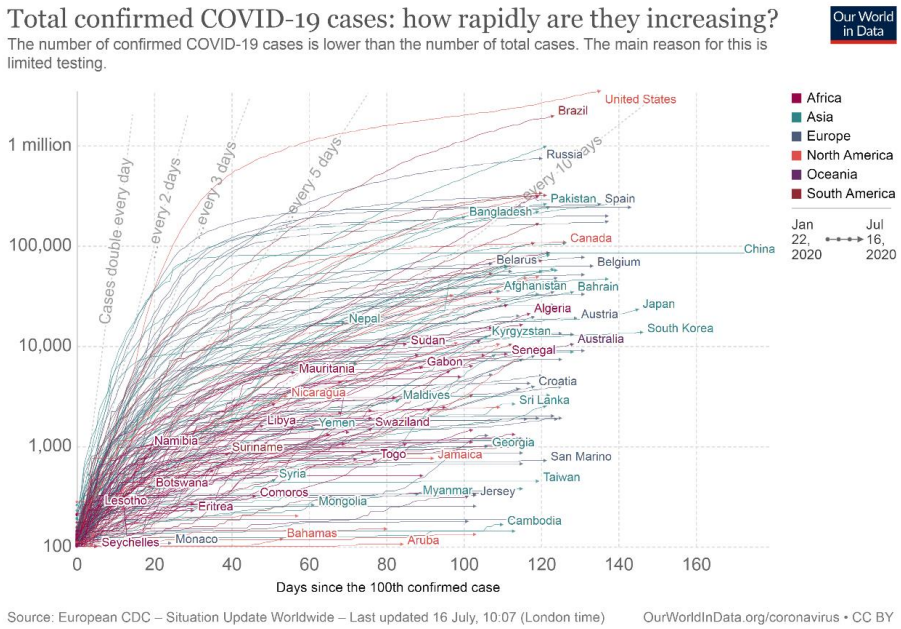
数据来源：WHO

发布时间：2020 年 7 月 23 日北京时间下午 4 点

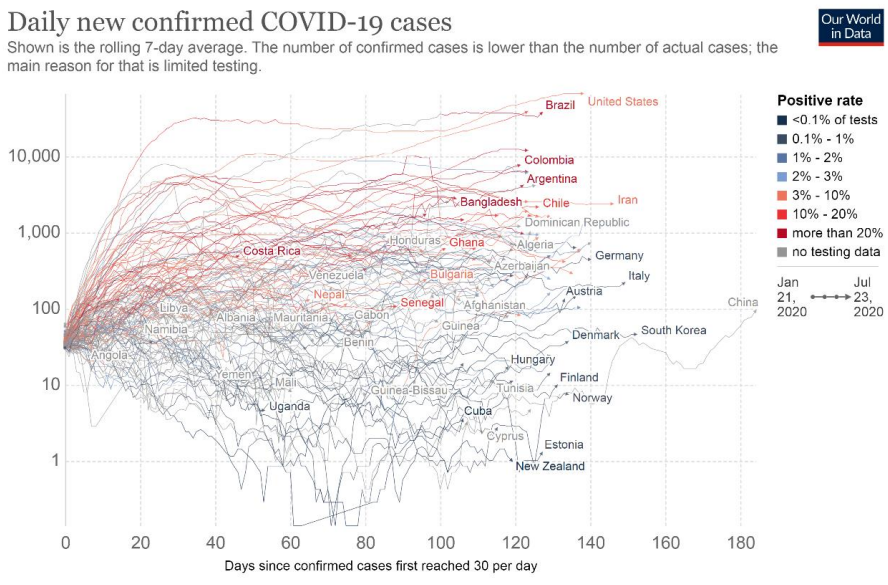
链接：https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

根据 WHO 提供的数据，2020 年 7 月 16 日全球累计确诊新型冠状病毒病人 **15012731** 例，当日新增确诊 **247225** 例，累计死亡 **619150** 例，当日新增死亡 **7097**。

中国累计确诊 86361 例，累计死亡 4655 例，当日新增确诊 135 例，新增死亡 0 例。



重点国家确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）



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（7 月 23 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 抗体对 SARS-CoV-2 的反应短暂

Antibody responses to SARS-CoV-2 short-lived

来源：Nature Reviews Immunology

发布时间：2020-07-20

链接：https://www.nature.com/articles/s41577-020-0405-3

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通讯作者单位：美国纽约州西奈山伊坎医学院

DOI 或 PUBMED ID：https://doi.org/10.1038/s41577-020-0405-3

编译者：张丽双

中文摘要：

在没有确诊的 SARS-CoV-2 再感染病例的情况下，最初感染后引起的免疫保护持续时间仍然未知。该预印本（https://www.medrxiv.org/content/10.1101/2020.07.09.20148429v1）描述了 65 位 SARS-CoV-2 感染者的抗体应答的纵向分析。尽管中和抗体（nAb）反应的强度与疾病严重程度相关，但大多数患者在症状发作后 3 个月内 nAb 滴度迅速下降。作者认为，SARS-CoV-2 引起的瞬时 nAb 反应类似于季节性冠状病毒感染后观察到的反应。然而，对继发免疫反应的后果及其预防再感染的能力仍有待确定。

Abstract:

In the absence of confirmed cases of reinfection by SARS-CoV-2, the duration of immune protection elicited after initial infection is still unknown. This preprint describes a longitudinal analysis of antibody responses in 65 SARS-CoV-2-infected individuals. Although the magnitude of neutralizing antibody (nAb) responses correlated with disease severity, there was a rapid decline in nAb titres in most patients within 3 months after onset of symptoms. The authors

argue that the transient nAb responses elicited by SARS-CoV-2 resemble those observed following seasonal coronavirus infections. However, the consequences on secondary immune responses and their ability to prevent reinfection remain to be determined.

3. SARS-CoV-2 感染可诱导强大的、至少能稳定 3 个月的中和抗体反应

SARS-CoV-2 infection induces robust, neutralizing antibody responses that are stable for at least three months

来源：medRxiv

发布时间：2020-07-17

链接：https://www.medrxiv.org/content/10.1101/2020.07.14.20151126v1

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通讯作者单位：美国西奈山伊坎医学院，

DOI 或 PUBMED ID：

编译者：刘焕珍

中文摘要：

一句话总结：自然轻中度 SARS-CoV-2 感染可诱导强大的中和抗体反应，并且至少能稳定 3 个月。

SARS-CoV-2 引起了全球范围内的大流行病，数百万人受到感染，并造成了无数人死亡。关于抗体对病毒反应的稳健性、功能性和寿命的问题仍未得到解答。在此我们报告，根据在纽约市西奈山卫生系统筛查的 19860 人的数据集，绝大多数具有轻度至中度 COVID-19 的感染个体都经历了针对病毒刺突蛋白的强大 IgG 抗体反应。我们还显示效价至少在大约三个月的时间内稳定，并且刺突蛋白的结合滴度与真实 SARS-CoV-2 的中和作用显着相关。我们的数据表明，超过 90％的血清转化器可检测到中和抗体反应，而且这些滴度至少在近期内稳定。

Abstract:

One Sentence Summary: Antibody responses induced by natural mild-to-moderate SARS-CoV-2 infection are robust, neutralizing and are stable for at least 3 months.

SARS-CoV-2 has caused a global pandemic with millions infected and numerous fatalities. Questions regarding the robustness, functionality and longevity of the antibody response to the virus remain unanswered. Here we report that the vast majority of infected individuals with mild-to-moderate COVID-19 experience robust IgG antibody responses against the viral spike protein, based on a dataset of 19,860 individuals screened at Mount Sinai Health System in New York City. We also show that titers are stable for at least a period approximating three months, and that anti-spike binding titers significantly correlate with neutralization of authentic SARS-CoV-2. Our data suggests that more than 90% of seroconverters make detectible neutralizing antibody responses and that these titers are stable for at least the near-term future.

4. 新的冠状病毒检测的激增可能有助于结束大流行

The explosion of new coronavirus tests that could help to end the pandemic

来源：Nature
发布时间：2020-07-17
链接：https://www.nature.com/articles/d41586-020-02140-8
第一作者：-
通讯作者： Giorgia Guglielmi
通讯作者单位：A freelance science journalist in Basel, Switzerland
DOI 或 PUBMED ID：10.1038/d41586-020-02140-8
编译者：宋张悦
中文摘要：

世界各地的研究小组现在正在设计超越 PCR 的检测方法。数十种诊断方法正在开发中，所有这些方法都能以不同的方式检测病毒：有些是对 RT-PCR 进行了优化，使检测更快或更容易使用；其他人使用基因编辑工具 CRISPR 锁定 SARS-CoV-2 的基因片段；有些人利用病毒表面的蛋白质来识别病毒。许多这些测试，如张锋的 CRISPR，正在使用临床样本进行验证，有些已经进入临床。今年 4 月，美国国立卫生研究院拨款 15 亿美元用于开发冠状病毒测试，旨在今年夏末之前达到每周进行数百万次测试的通量，这是恢复正常的关键一步。

THE GOLD STANDARD

目前最为广泛使用的是逆转录聚合酶链式反应（RT-PCR），检测可以达 100%的准确性，但需要 1-4 个小时，需要专门的设备，实现加热和冷却的循环步骤，检测员也需要有一定的专业经验。

LOOP THE LOOP

一些正在开发的测试使用一套病毒特异性引物，既能激活复制过程，又能放大 RNA。称为环介导等温扩增技术（LAMP），不需要重复加热和冷却，快速放大了病毒序列。随着 DNA 的扩增，溶液呈酸性，通过 pH 敏感染料标记变化。这种测试只需要基本的设备，可以在实验室之外进行。

CUT AND DETECT

一些正在开发的测试使用基因编辑技术 CRISPR 的精确性来检测病毒物质。首先，病毒 RNA 被放大，例如使用 LAMP。然后一个与 CRISPR 相关的蛋白质和一些游离的报告 RNA 链一起被加入。如果发现了病毒遗传物质，CRISPR 蛋白就会切断报告基因 RNA，产生荧光信号。荧光信号可以被计算机检测到，或者报告 RNA 可以与特定分子结合，在试纸上产生条带，就像妊娠测试一样。

Surface screening

另一种更快更便宜的诊断测试方法是寻找病毒表面的分子，而不是试图检测病毒的基因组。这种测试将包含一种专门针对特定蛋白质或抗原的抗体，这种抗原与用于家庭验孕的技术类似。这些化验方法生产成本低，操作简单，已经用于检测流感感染。但抗原测试不像病毒测试那样包含扩增步骤，所以它们不那么灵敏。

Abstract

Researchers are scrambling to find other ways to diagnose the coronavirus and churn out millions of tests a week — a key step in returning to normality.

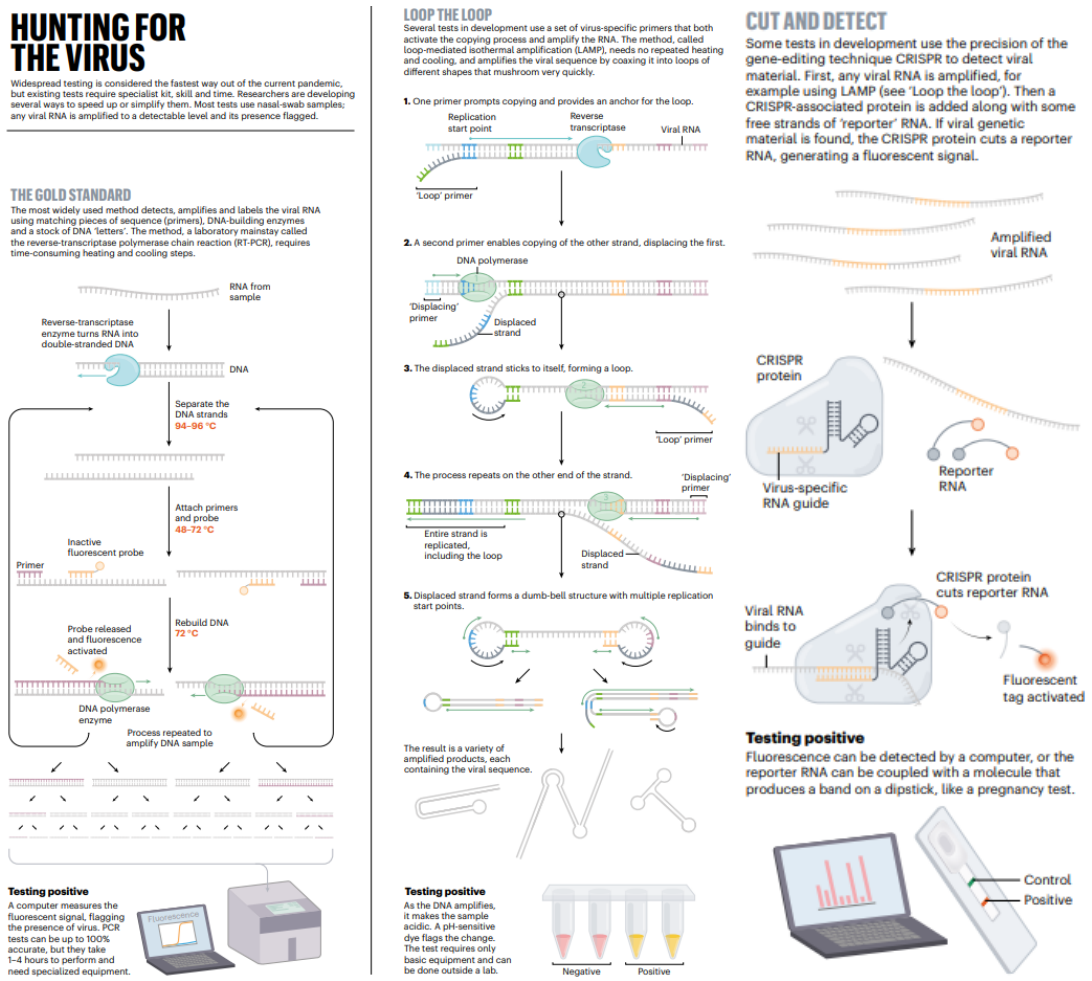

图 1. 常见检测方法的工作流程示意图

5. 美国 Covid-19 诊断测试的快速推广——NIH RADx 计划

Rapid Scaling Up of Covid-19 Diagnostic Testing in the United States — The NIH RADx Initiative

链接：https://www.nejm.org/doi/full/10.1056/NEJMsr2022263?query=featured_home

编译者：宋张悦

中文摘要：

本文综述了当前和预计的测试能力需求，并综述了不同类型的诊断测试。描述了 NIH 的快速加速诊断（Rapid Acceleration of Diagnostics, RADx）计划，RADx 计划有四个组成部分。1.RADx-tech 的目标是最早在 2020 年秋季，确定、加速发展、扩大和部署创新的即时检测技术。2.先进技术平台（RADx-ATP）将支持一些更先进的技术的规模化，可以实现即时、实质性的能力增长。3.RADx-rad（radical 的简写）将专注于真正非传统的测试方法，这些方法的期限稍微长一些。4.服务不足人群（RADx-UP）将建立社区参与的实施项目，以改善服务不足和弱势群体获得检测的机会。

6. SARS-CoV-2 患者中抗体反应的长期评估和抗体水平的下降

Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection

来源：medRxiv
发布时间：2020-07-11
链接：https://www.medrxiv.org/content/10.1101/2020.07.09.20148429v1
第一作者：Jeffrey Seow
通讯作者：Katie J Doores
通讯作者单位：Department of Infectious Diseases, School of Immunology & Microbial Sciences, King's College London, London, UK.
DOI 或 PUBMED ID： preprint
编译者：孔娟
中文摘要：
在 COVID-19 症状出现后的 10-15 天内，大多数患者体内均可检测到抗 SARS-CoV-2 抗体。然而这些抗体的维持时间或者是否能防止再次感染这些尚不清楚。研究者从 65 名经 RT-qPCR 检测阳性的患者采集的连续血清样本，研究显示在症状出现后 94 天内，超过 95%的病例出现血清转化，且在症状出现后 8 天内采集的样本出现中和抗体(nAb)。研究证明疾病的严重程度和 nAb 反应的强弱相关但和 nAb 反应的动力学无关。随访期间观察到 nAb 滴度下降。尽管一些患者 ID50 较高(>10，000)并且在大于 60 天的时间内保持滴度>1000，但一些 ID50 低的个体在随访期内滴度接近基线。在盖伊医院和圣托马斯医院的一组血清反应阳性的医护人员中也检测到了 nAb 滴度的类似下降。我们认为这种短暂的 nAb 反应是引起轻症 SARS-CoV-2 患者与普通感冒相关的季节性冠状病毒的共同特征。这项研究对广泛的血清学检测及抗 SARS-CoV-2 再感染的抗体保护和疫苗保护的持久性研究具有重要的意义。
Abstract:
Antibody (Ab) responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. However, due to the recent emergence of this virus in the human population it is not yet known how long these Ab responses will be maintained or whether they will provide protection from re-infection. Using sequential serum samples collected up to 94 days post onset of symptoms (POS) from 65 RT-qPCR confirmed SARS-CoV-2-infected individuals, we show seroconversion in >95% of cases and neutralizing antibody (nAb) responses when sampled beyond 8 days POS. We demonstrate that the magnitude of the nAb response is dependent upon the disease severity, but this does not affect the kinetics of the nAb response. Declining nAb titres were observed during the follow up period. Whilst some individuals with high peak ID50 (>10,000) maintained titres >1,000 at >60 days POS, some with lower peak ID50 had titres approaching baseline within the follow up period. A similar decline in nAb titres was also observed in a cohort of seropositive healthcare workers from Guy's and St Thomas' Hospitals. We suggest that this transient nAb response is a feature shared by both a SARS-CoV-2 infection that causes low disease severity and the circulating seasonal coronaviruses that are associated with common colds. This study has important implications when considering widespread serological testing, Ab protection against re-infection with SARS-CoV-2 and the durability of vaccine protection.

7. Covid-19：研究揭示了可作为临床预测工具的 6 组症状

Covid-19: Study reveals six clusters of symptoms that could be used as a

clinical prediction tool
来源：BMJ
发布时间：2020-07-20
链接：https://www.bmj.com/content/370/bmj.m2911
第一作者：Jacqui Wise
通讯作者：-
通讯作者单位：London, UK
DOI 或 PUBMED ID：https://doi.org/10.1136/bmj.m2911
编译者：宋张悦
中文摘要：
Covid 症状研究应用程序由伦敦国王学院和健康科技公司 ZOE 共同开发，拥有超过 400 万用户。该应用程序的用户被要求每天记录自己的健康状况和任何新的 covid-19 潜在症状。一种机器学习算法分析显示了六组不同的症状。这六个集群是：

1. 无发热的“流感样”——头痛，嗅觉丧失，肌肉疼痛，咳嗽，咽喉痛，胸痛，无发热
2. 有发热的“流感样”——头痛，嗅觉丧失，咳嗽，咽喉痛，声音嘶哑，发热，食欲不振
3. 胃肠道的症状——头痛，嗅觉丧失，食欲不振，腹泻，咽喉痛，胸痛，无咳嗽
4. 重症一级，疲劳——头痛，嗅觉丧失，咳嗽，发热，声音嘶哑，胸痛，疲劳
5. 重症二级，精神错乱——头痛，嗅觉丧失，食欲不振，咳嗽，发热，声音嘶哑，咽喉痛，胸痛，疲劳，精神错乱，肌肉疼痛
6. 重症三级，腹部和呼吸系统的症状——头痛，嗅觉丧失，食欲不振，咳嗽，发热，声音嘶哑，咽喉痛，胸痛，疲劳，精神错乱，肌肉疼痛，呼吸急促，腹泻，腹痛。

Abstract
The algorithm revealed six distinct groupings of symptoms. This was then tested by running it on a second independent dataset of 1000 users in the UK, US, and Sweden who had logged their symptoms in May. The six clusters are:

1. “Flu-like” with no fever—headache, loss of smell, muscle pains, cough, sore throat, chest pain, no fever
2. “Flu-like” with fever—headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite
3. Gastrointestinal—headache, loss of smell, loss of appetite, diarrhoea, sore throat, chest pain, no cough
4. Severe level one, fatigue—headache, loss of smell, cough, fever, hoarseness, chest pain, fatigue
5. Severe level two, confusion—headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain

Severe level three, abdominal and respiratory—headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, shortness of breath, diarrhoea, abdominal pain.

8. 人 SARS-CoV-2 感染后 S 蛋白反应 IgG 和记忆 B 细胞的产生包含对 S2 亚基的广泛反应性

S protein-reactive IgG and memory B cell production after human SARS-CoV-2 infection includes broad reactivity to the S2 subunit

来源：bioRxiv
发布时间：2020-07-21
链接：https://www.biorxiv.org/content/10.1101/2020.07.20.213298v1
第一作者：Phuong Nguyen-Contant
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DOI 或 PUBMED ID：preprint
编译者：雷颖
中文摘要：
人类对 SARS-CoV-2 感染的高度易感性，是引起 COVID-19 的原因，反映了病毒的新颖性和先前存在的 B 细胞免疫的有限。抗 SARS-CoV-2 刺突(S)蛋白(携带新的受体结合结构域(RBD))的 IgG，在未暴露的个体中缺失或处于低水平。为了更好地了解 B 细胞对 SARS-CoV-2 感染的反应，我们对病毒反应记忆 B 细胞(MBCs)是否存在于未暴露的受试者中，以及 MBC 的产生是否伴随着病毒特异性 IgG 的产生有疑问。我们分析了非 SARS-CoV-2 暴露的健康供体和 COVID-19 恢复期受试者的血清和 PBMCs。SARS-CoV-2 蛋白(S，包括 RBD 和 S2 亚基，核衣壳[N])和非 SARS-CoV-2 蛋白的血清 IgG 水平与循环 IgG 的 MBCs 的测定有关。未暴露受试者无抗 RBD 的 IgG。大多数未暴露的受试者具有抗 S2 的 IgG 和少数有抗 N 的 IgG，但具有这些特异性 IgG 的 MBCs 未被检测到，可能反映了低概率。恢复期受试者对 RBD、S2 和 N 有较高水平的 IgG，以及大量 RBD 和 S2 反应性的 IgG 的 MBC。值得注意的是，恢复期受试者对冠状病毒 OC43 的 S 蛋白的 IgG 滴度高于未暴露的受试者，且与抗 S2 滴度密切相关。我们的发现表明，交叉反应 B 细胞对 S2 亚基的反应，可能增强广泛的冠状病毒保护。重要的是，我们通过 SARS-CoV-2 感染诱导 MBC 的演示表明，即使循环抗体水平下降，B 细胞免疫的持久形式也会保持。

Abstract
The high susceptibility of humans to SARS-CoV-2 infection, the cause of COVID-19, reflects the novelty of the virus and limited preexisting B cell immunity. IgG against the SARS-CoV-2 spike (S) protein, which carries the novel receptor binding domain (RBD), is absent or at low levels in unexposed individuals. To better understand the B cell response to SARS-CoV-2 infection, we asked whether virus-reactive memory B cells (MBCs) were present in unexposed subjects and whether MBC generation accompanied virus-specific IgG production in infected subjects. We analyzed sera and PBMCs from non-SARS-CoV-2-exposed healthy donors and COVID-19 convalescent subjects. Serum IgG levels specific for SARS-CoV-2 proteins (S, including the RBD and S2 subunit, and nucleocapsid [N]) and non-SARS-CoV-2 proteins were related to measurements of circulating IgG MBCs. Anti-RBD IgG was absent in unexposed subjects. Most unexposed subjects had anti-S2 IgG and a minority had anti-N IgG, but IgG MBCs with these specificities were not detected, perhaps reflecting low frequencies. Convalescent subjects had high levels of IgG against the RBD, S2, and N, together with large populations of RBD- and S2-reactive IgG MBCs. Notably, IgG titers against the S protein of the human coronavirus OC43 in convalescent subjects were higher than in unexposed subjects and correlated strongly with anti-S2 titers. Our findings indicate

cross-reactive B cell responses against the S2 subunit that might enhance broad coronavirus protection. Importantly, our demonstration of MBC induction by SARS-CoV-2 infection suggests that a durable form of B cell immunity is maintained even if circulating antibody levels wane.

9. SARS-CoV-2 感染通过 cGASSTING 和 NF-κB 诱导促炎性细胞因子反应

SARS-CoV-2 infection induces a pro-inflammatory cytokine response through cGASSTING and NF-κB

来源：bioRxiv

发布时间：2020-07-21

链接：https://www.biorxiv.org/content/10.1101/2020.07.21.212639v1

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DOI 或 PUBMED ID：https://doi.org/10.1101/2020.07.21.212639

编译者：刘焕珍

中文摘要：

SARS-CoV-2 是一种新型病毒，它迅速传播，引起全球范围的大流行。在大多数受感染的患者中，SARS-CoV-2 会导致轻度疾病；然而，在相当大比例的感染中，个体会出现严重症状，从而导致永久性肺损伤或死亡。这些严重的病例往往与高水平的促炎细胞因子和低抗病毒反应有关，这可能导致全身并发症。我们评估了受感染细胞培养物的转录和细胞因子分泌谱，并检测到炎症细胞因子明显上调,这与从感染患者身上采集的样本相似。基于这些观察结果，我们发现在 SARS-CoV-2 感染细胞中 NF-κB 的特异性激活和 IRF3 核转位的阻断。这种 NF-κB 反应是由 cGAS-STING 激活介导的，并且可以通过靶向药物来减弱。我们的研究结果表明,SARS-CoV-2 在上皮细胞中诱导了一种 cGAS-STING 介导的 NF-κB 驱动的炎症免疫反应，这种反应可能有助于患者的炎症反应，并可能成为抑制严重疾病症状的靶点。

Abstract:

SARS-CoV-2 is a novel virus that has rapidly spread, causing a global pandemic. In the majority of infected patients, SARS-CoV-2 leads to mild disease; however, in a significant proportion of infections, individuals develop severe symptoms that can lead to permanent lung damage or death. These severe cases are often associated with high levels of pro-inflammatory cytokines and low antiviral responses which can lead to systemic complications. We have evaluated transcriptional and cytokine secretion profiles from infected cell cultures and detected a distinct upregulation of inflammatory cytokines that parallels samples taken from infected patients. Building on these observations, we found a specific activation of NF-κB and a block of IRF3 nuclear translocation in SARS-CoV-2 infected cells. This NF-κB response is mediated by cGAS-STING activation and could be attenuated through STING targeting drugs. Our results show that SARS-CoV-2 curates a cGAS-STING mediated NF-κB driven inflammatory immune response in epithelial cells that likely contributes to inflammatory responses seen in patients and might be a target to suppress severe disease symptoms.

10. 对外周血单个核细胞的单细胞测序揭示了 COVID-19 病人和流感病人迥异的免疫反应

谱

Single-cell sequencing of peripheral blood mononuclear cells reveals distinct immune response landscapes of COVID-19 and influenza patients

来源：Immunity

发布日期：2020-07-19

第一作者：Linnan Zhu

通讯作者：William J Liu

通讯作者单位：China CDC

链接：https://www.cell.com/immunity/fulltext/S1074-7613(20)30316-2

中文摘要：

血糖失去控制的糖尿病病人有更高风险发展成 COVID-19 重症。作者们的研究显示血糖升高以及糖酵解作用加强会促进 SARS-CoV-2 的病毒复制以及单个核细胞中细胞因子的产生。这个过程通过线粒体 ROS/HIF-1a 依赖的信号通路发生，导致 T 细胞功能缺失以及上皮细胞死亡。

研究者们建立 COVID-19 病人，流感病人以及健康人的外周血单个核细胞的单细胞表达谱。

在 COVID-19 和流感病人中浆细胞比例显著增加。

COVID-19 病人中特征性地发生 XAF1-, TNF- 和 FAS-诱导的 T 细胞凋亡。

在 COVID-19 和流感病人中信号激活的信号通路迥异。COVID-19 病人中发生 STAT1/IRF3 信号通路激活，而流感病人中发生 STAT3/NFκB 通路激活。

Highlights

We generated a single-cell atlas of PBMCs in both COVID-19 and influenza patients.

Plasma cells increase significantly in both COVID-19 and influenza patients.

COVID-19 is featured with XAF1-, TNF- and FAS-induced T cell apoptosis.

Distinct pathways activate in COVID-19 (STAT1/IRF3) vs. influenza (STAT3/NFκB) patients.

11. 高血糖通过 HIF-1α/糖酵解通路促进了 SARS-CoV-2 的感染以及单核细胞的反应

Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis

来源：Cell Metabolism

发布日期：2020-07-19

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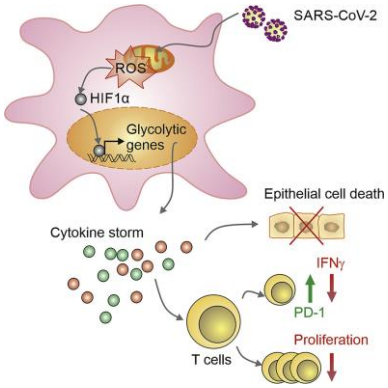
链接：https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30365-X

中文摘要：

血糖失去控制的糖尿病病人有更高风险发展成 COVID-19 重症。作者们的研究显示血糖升高以及糖酵解作用加强会促进 SARS-CoV-2 的病毒复制以及单核细胞中细胞因子的产生。这个过程通过线粒体 ROS/HIF-1a 依赖的信号通路发生，导致 T 细胞功能缺失以及上皮细胞死亡。



Brief:

Diabetic people with uncontrolled blood glucose levels have a greater risk to develop severe COVID-19 disease. Codo et al. show that elevated glucose levels and glycolysis promote SARS-CoV-2 (CoV-2) replication and cytokine production in monocytes through a mitochondrial ROS/hypoxia-inducible factor-1a dependent pathway, resulting in T cell dysfunction and epithelial cell death.

Highlights

Elevated glucose levels regulate viral replication and cytokine production in monocytes

Glycolysis sustains CoV-2-induced monocyte response and viral replication

mtROS/HIF-1α is necessary for CoV-2 replication and monocyte cytokine production

Monocyte-derived cytokines drive T cell dysfunction and epithelial cell death

12. 老化的免疫系统可能加剧 COVID-19

Aging immunity may exacerbate COVID-19

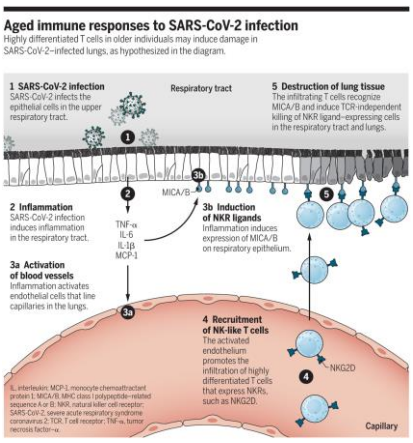
来源：Science

发布日期：2020-07-17

链接：https://science.sciencemag.org/content/369/6501/256

中文摘要：

这篇短综述讨论了老年人的免疫系统为何会加剧 COVID-19。作者推测老年病患中高度分化的 T 细胞可能会在 SARS-CoV-2 感染的肺部诱导损伤的发生，如下图所示。



Highly differentiated T cells in older individuals may induce damage in SARS-CoV-2–infected lungs, as hypothesized in the diagram.

13. 抗 SARS-CoV-2 的 CHADOx1nCoV-19 疫苗的安全性和免疫原性：临床 1/2 期单盲随机对照试验的初步报告

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

来源：Lancet

发布时间：2020-07-20

链接：

https://www.sciencedirect.com/science/article/pii/S0140673620316044?via%3Dihub

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DOI 或 PUBMED ID：https://doi.org/10.1016/S0140-6736(20)31604-4

编译者：雷颖

中文摘要：

背景：SARS-CoV-2 的流行可能可以通过接种疫苗来减少。我们评估了表达 SARS-CoV-2 刺突蛋白的病毒载体冠状病毒疫苗的安全性、反应原性和免疫原性。

方法：我们在英国的五个试验地点对表达 SARS-CoV-2 刺突蛋白的黑猩猩腺病毒疫苗(ChAdOx1nCoV-19)进行了临床 1/2 期、单盲、随机对照试验，并与脑膜炎球菌结合疫苗(MenACWY)进行了对照。无 SARS-CoV-2 确诊感染史或 COVID-19 样症状的 18-55 岁健康成年人被随机分配（1：1）来接受剂量为 5×10^10 病毒颗粒的 ChAdOx1nCoV-19 或 MenACWY 来进行单次肌肉注射。在这五个地点中的两个地点进行了一项流程修订，允许在接种疫苗之前预防性使用扑热息痛。有十名被分配到非随机、非盲的 ChAdOx1nCoV-19 增强组的参与者接受了两次剂量的疗程，在第一次剂量后 28 天注射了增强疫苗。基线和接种后的体液反应采用了标准化的对三聚体 SARS-CoV-2 刺突蛋白的总 IgG 的 ELISA 检测、多联免疫分析、三种活 SARS-CoV-2 中和试验(50%斑块减少中和试验[PRNT50]；微中和试验[MNA50、MNA80 和 MNA90]；和马尔堡病毒中和试验)。细胞反应用体外干扰素-γ 酶联免疫斑点试验进行评估。共同的主要结果是评估疗效，如症状性病毒学证实的 COVID-19 病例，和安全性，如严重不良事件的发生。对接种疫苗的参与者进行分组分配分析。接种疫苗后 28 天以上进行安全性评估。在这里，我们报告了关于安全性、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，并在 ISRCTN，15281137 和临床试验，NCT04324606 注册。

调查结果：在 2020 年 4 月 23 日至 5 月 21 日期间，有 1077 名参与者被登记并分配接受 ChAdOx1nCoV-19(n=543)或男性 ACWY(n=534)，其中 10 人参加了非随机的 ChAdOx1nCoV-19 增强组。局部和全身反应在 ChAdOx1nCoV-19 组中更常见，许多是通过使用预防性扑热息痛来减少的，包括疼痛、发烧、寒战、肌肉疼痛、头痛和不适(所有 p<0.05)。无与 ChAdOx1nCoV-19 相关的严重不良事件。在 ChAdOx1nCoV-19 组中，刺突蛋白特异性 T 细胞反应在第 14 天达到高峰(每百万外周血单个核细胞中位 856 斑点形成细胞，IQR 493-1802；n=43)。抗刺突蛋白 IgG 反应在第 28 天上升(中位 157 个 ELISA 单位[EU]，96-317；n=127)，并在第二次剂量中增强(639 EU，360-792；n=10)。在 MNA80 中 35 名参与者中 32 名（91%）在单次剂量后检测到对 SARS-CoV-2 的中和抗体反应，在 PRNT50 中有 35 名（100%）。在一次增强剂量后，所有参与者都有中和效果(MNA80 第 42 天 9 个人中有 9 个，马尔堡 VN 第 56 天 10 个人中有

10 个)。中和抗体反应与 ELISA 检测的抗体水平密切相关(马尔堡 VN R2=0.67；p<0.001)。解释：ChAdOx1 nCoV-19 显示出可接受的安全性，同源增强抗体反应增加。这些结果，加上体液和细胞免疫反应的诱导，支持在正在进行的临床三期方案中对这种候选疫苗进行大规模评估。

Abstract

Background

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be curtailed by vaccination. We assessed the safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine that expresses the spike protein of SARS-CoV-2.

Methods

We did a phase 1/2, single-blind, randomised controlled trial in five trial sites in the UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control. Healthy adults aged 18–55 years with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5 × 1010 viral particles or MenACWY as a single intramuscular injection. A protocol amendment in two of the five sites allowed prophylactic paracetamol to be administered before vaccination. Ten participants assigned to a non-randomised, unblinded ChAdOx1 nCoV-19 prime-boost group received a two-dose schedule, with the booster vaccine administered 28 days after the first dose. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, a muliplexed immunoassay, three live SARS-CoV-2 neutralisation assays (a 50% plaque reduction neutralisation assay [PRNT50]; a microneutralisation assay [MNA50, MNA80, and MNA90]; and Marburg VN), and a pseudovirus neutralisation assay. Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot assay. The co-primary outcomes are to assess efficacy, as measured by cases of symptomatic virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were done by group allocation in participants who received the vaccine. Safety was assessed over 28 days after vaccination. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. The study is ongoing, and was registered at ISRCTN, 15281137, and ClinicalTrials.gov, NCT04324606.

Findings

Between April 23 and May 21, 2020, 1077 participants were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534), ten of whom were enrolled in the non-randomised ChAdOx1 nCoV-19 prime-boost group. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all p<0.05). There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (median 856 spot-forming cells per

million peripheral blood mononuclear cells, IQR 493–1802; n=43). Anti-spike IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; n=127), and were boosted following a second dose (639 EU, 360–792; n=10). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in MNA80 and in 35 (100%) participants when measured in PRNT50. After a booster dose, all participants had neutralising activity (nine of nine in MNA80 at day 42 and ten of ten in Marburg VN on day 56). Neutralising antibody responses correlated strongly with antibody levels measured by ELISA (R2=0.67 by Marburg VN; p<0.001).

Interpretation

ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses. These results, together with the induction of both humoral and cellular immune responses, support large-scale evaluation of this candidate vaccine in an ongoing phase 3 programme.

14. 鼻内单剂量黑猩猩腺病毒载体疫苗可产生抗 SARS-CoV-2 感染的免疫

A single intranasal dose of chimpanzee adenovirus-vectored vaccine confers sterilizing immunity against SARS-CoV-2 infection

来源：bioRxiv

发布时间：2020-07-17

链接：https://www.biorxiv.org/content/10.1101/2020.07.16.205088v1

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中文摘要：

COVID-19 的大流行使部署有效疫苗成为全球卫生优先事项。我们在严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）和表达人血管紧张素转换酶 2 受体的小鼠的挑战性研究中，评估了一种编码融合前稳定 spike 蛋白(ChAd-SARS-CoV-2-S)的黑猩猩腺病毒载体疫苗的保护活性。肌肉注射 ChAd-SARS-CoV-2-S 可诱导强健的全身体液和细胞介导免疫反应，并可预防肺部感染、炎症和病理学，但不能产生杀菌免疫，如 SARS-CoV-2 攻击后检测病毒 RNA 和诱导抗核蛋白抗体所证明。相比之下，单剂量的 ChAd-SARS-CoV-2-S 可诱导高水平的全身和粘膜 IgA 和 T 细胞反应，完全防止 SARS-CoV-2 在上呼吸道和下呼吸道的感染，并可能在大多数动物中产生杀菌免疫。鼻腔给药是预防 SARS-CoV-2-S 感染和传播，减少大流行传播的一种候选方法。

Abstract:

The Coronavirus Disease 2019 pandemic has made deployment of an effective vaccine a global health priority. We evaluated the protective activity of a chimpanzee adenovirus-vectored vaccine encoding a pre-fusion stabilized spike protein (ChAd-SARS-CoV-2-S) in challenge studies with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and mice expressing the human angiotensin-converting enzyme 2 receptor. Intramuscular dosing of ChAd-SARS-CoV-2-S induces robust systemic humoral and cell-mediated immune responses and protects against lung

infection, inflammation, and pathology but does not confer sterilizing immunity, as evidenced by detection of viral RNA and induction of anti-nucleoprotein antibodies after SARS-CoV-2 challenge. In contrast, a single intranasal dose of ChAd-SARS-CoV-2-S induces high levels of systemic and mucosal IgA and T cell responses, completely prevents SARS-CoV-2 infection in the upper and lower respiratory tracts, and likely confers sterilizing immunity in most animals. Intranasal administration of ChAd-SARS-CoV-2-S is a candidate for preventing SARS-CoV-2 infection and transmission, and curtailing pandemic spread.

15. 用编码 SARS-CoV-2 Spike 蛋白的慢病毒载体进行鼻内免疫可在临床前动物模型中提供有力的保护

Intranasal Immunization with a Lentiviral Vector Coding for SARS-CoV-2 Spike Protein Confers Vigorous Protection in Pre-Clinical Animal Models

来源：bioRxiv

发布时间：2020-07-21

链接：https://www.biorxiv.org/content/10.1101/2020.07.21.214049v1

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中文摘要：

我们开发了一种基于慢病毒载体(LV)的有效疫苗接种策略，能够诱导针对 SARS-CoV-2 Spike 蛋白的中和抗体。在几种编码 S 的不同变体的 LV 中，一个编码全长膜锚定 S (LV::SFL)的 LV 在小鼠体内引发高抗体滴度，中和活性可与从 COVID-19 中恢复的患者相媲美。LV:SFL 全身免疫小鼠，通过腺病毒 5 型（Ad5）载体转导呼吸道细胞诱导 CoV2 受体 hACE2 的表达，尽管具有强烈的血清中和活性，但在 SARS-CoV2 攻击后，仅观察到肺病毒载量减少≈1 log10。因此，我们探索了通过鼻内给药来靶向上呼吸道免疫应答的策略。即使在最初和目标方案后，全身中和活性并未显着增加，但肺病毒载量还是降低了约 5 log10，其中某些动物的载量处于高灵敏度 RT-PCR 分析检测极限之下。所赋予的保护作用也基本上避免了肺部炎症。

我们证实了在金黄仓鼠中使用整合和非整合性 LV 平台的疫苗功效和对肺部炎症的抑制作用，自然允许 SARS-CoV2 复制并恢复人类 COVID-19 生理病理。我们的研究结果为两种临床前动物模型中基于 LV 的疫苗接种策略对 SARS-CoV-2 具有显著的预防作用提供了主要证据，并将基于 LV::SFL 的鼻内免疫作为一种强有力的、有前途的针对 COVID-19 的疫苗方法。

Abstract:

We developed a potent vaccination strategy, based on lentiviral vector (LV), capable of inducing neutralizing antibodies specific to the Spike glycoprotein (S) of SARS-CoV-2, the etiologic agent of CoronaVirus Disease 2019 (COVID-19). Among several LV encoding distinct variants of S, a single one encoding the full-length, membrane anchored S (LV::SFL) triggered high antibody titers in mice, with neutralization activities comparable to patients recovered from COVID-19. LV::SFL systemic vaccination in mice, in which the expression of the CoV2 receptor hACE2 was induced by transduction of the respiratory tract cells by an

adenoviral type 5 (Ad5) vector, despite an intense serum neutralizing activity, only ≈1 log10 reduction of lung viral loads was observed after SARS-CoV2 challenge.

We thus explored the strategy of targeting the immune response to the upper respiratory tract through an intranasal boost administration. Even though, after a prime and target regimen, the systemic neutralizing activity did not increase substantially, ≈5 log10 decrease in lung viral loads was achieved, with the loads in some animals under the limit of detection of a highly sensitive RT-PCR assay. The conferred protection also avoided largely pulmonary inflammation.

We confirmed the vaccine efficacy and inhibition of lung inflammation using both integrative and non-integrative LV platforms in golden hamsters, naturally permissive to SARS-CoV2 replication and restituting human COVID-19 physiopathology. Our results provide the proof-of-principle evidence of marked prophylactic effects of an LV-based vaccination strategy against SARS-CoV-2 in two pre-clinical animal models and designate the intranasal LV::SFL-based immunization as a vigorous and promising vaccine approach against COVID-19.

16. 一个基于甲病毒的 RNA 复制子疫苗可以在小鼠和非人灵长类动物中诱导出 SARS-CoV-2 的中和抗体以及 T 细胞反应

An alphavirus-derived replicon RNA vaccine induces SARS-CoV-2 neutralizing antibody and T cell responses in mice and nonhuman primates

来源：science translational medicine

发布时间：2020-07-20

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链接：https://stm.sciencemag.org/content/early/2020/07/20/scitranslmed.abc9396

我们急需针对 SARS-CoV-2 的有效果疫苗。这个疫苗必须能通过一两次接种就快速产生保护作用，并且其生产设备要适合规模化扩大。作者们开发了一种基于甲病毒的 RNA 复制子候选疫苗，编码 SARS-CoV-2 的刺突蛋白的 repRNA-CoV2S。采用脂类无机纳米微例子对这些 RNA 复制子做成剂型，以增强疫苗的稳定型、改善接种以及免疫原性。他们观察到对小鼠进行一次的鼻内注射就能让能诱导小鼠稳定产生抗 SARS-CoV-2 刺突蛋白的 IgG 抗体，提示一型 T 辅助细胞的反应。初次免疫加上再次免疫的策略可以在小鼠肺和肾中诱导出强的抗原特异性的 T 细胞反应。单独初次免疫 17 个月龄的小鼠诱导出的免疫反应比幼年小鼠更轻，但是再次免疫后这个差异就消失了。重要的是，在非人灵长类中，单独初次免疫的鼻内注射部位或者初次免疫加再次免疫的 5 个鼻内部注射部分诱导出非常轻的 T 细胞反应以及稳定的抗体反应。抗体反应持续了 70 天之久，中和 SARS-CoV-2 的滴度和 COVID-19 康复病人血清中的中和滴度可比。所有这些数据支持进一步开发该疫苗以预防 SARS-CoV-2 感染。

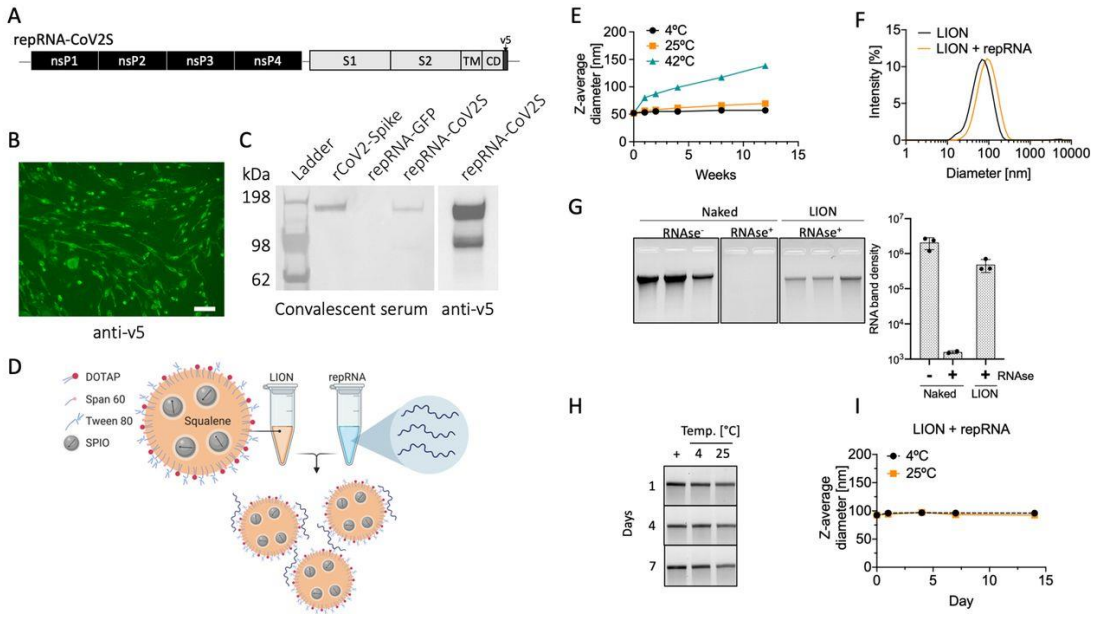

Figure 1: repRNA-CoV2S vaccine design and formulation.

(A) Shown is the codon-optimized full length spike (S) protein open reading frame, including the S1, S2, transmembrane (TM), and cytoplasmic (CD) domains, corresponding to positions 21,536 to 25,384 in the S protein of SARS-CoV-2 isolate Wuhan-Hu-1 (GenBank: MN908947.3). This construct was fused to a C-terminal v5 epitope tag and then was cloned into an alphavirus replicon encoding the 4 nonstructural protein (nsP1-4) genes of Venezuelan equine encephalitis virus, strain TC-83. Following RNA transcription and capping, repRNA-CoV2S was transfected into BHK cells. 24 hours later, the transfected BHK cells were analyzed by (B) anti-v5 immunofluorescence and (C) Western blot using either convalescent human serum or anti-v5 serum for immunodetection. Recombinant SARS-CoV2 spike protein (rCoV2-Spike) and repRNA-GFP were used as positive and negative controls, respectively. (D) Shown is a graphical representation of LION and formation of the vaccine complex after mixing with repRNA. (E) Shown is the evolution of LION particle size over 15 weeks measured by dynamic light scattering during storage at 4° C, 25° C or 42° C. (F) After mixing LION particles and repRNA, complex formation was confirmed by a shift in size distribution. (G) Gel electrophoresis analysis of triplicate preparations of repRNA extracted from LION particles after a concentrated RNase challenge showed substantial protection relative to a triplicate preparation of a dose-matched naked RNA following RNAse challenge. The formulated vaccine was stable for at least one week after mixing and storage at 4° C or 25° C as determined by (H) gel electrophoresis of repRNA extracted by phenol-chloroform treatment and (I) particle size of the complex. Data in B and C are representative of 2 independent experiments. Data in E, H, and I are from a single experiment, whereas data in F and G are representative of 3 independent experiments. Data in E, G, and I are shown as mean ± s.d. of 3 technical replicates. Scale bar in B is 100 μm.

Abstract:
The COVID-19 pandemic, caused by infection with the SARS-CoV-2 coronavirus, is having a deleterious impact on health services and the global economy, highlighting the urgent need for an effective vaccine. Such a vaccine would need to rapidly confer protection after one or two doses and would need to be manufactured using components suitable for scale-up. Here, we developed an alphavirus-derived replicon RNA vaccine candidate, repRNA-CoV2S, encoding the SARS-CoV-2 spike (S) protein. The RNA replicons were formulated with Lipid InOrganic Nanoparticles (LION) that were designed to enhance vaccine stability, delivery, and immunogenicity. We show that a single intramuscular injection of the LION/repRNA-CoV2S vaccine in mice elicited robust production of anti-SARS-CoV-2 S protein IgG antibody isotypes indicative of a Type 1 T helper cell response. A prime/boost regimen induced potent T cell responses in mice including antigen-specific responses in lung and spleen. Prime-only immunization of aged (17-month old) mice induced smaller immune responses compared to young mice, but this difference was abrogated by booster immunization. Importantly, in nonhuman primates, prime-only immunization in one intramuscular injection site or prime/boost immunizations in 5 intramuscular injection sites elicited modest T cell responses and robust antibody responses. The antibody responses persisted for at least 70 days and neutralized SARS-CoV-2 at titers comparable to those in human serum samples collected from individuals convalescing from COVID-19. These data support further development of LION/repRNA-CoV2S as a vaccine candidate for prophylactic protection against SARS-CoV-2 infection.

17. 针对 SARS-CoV-2 刺突的多个表位的有效中和抗体

Potent neutralizing antibodies directed to multiple epitopes on SARS-CoV-2 spike
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DOI：https://doi.org/10.1038/s41586-020-2571-7
编译者：张怡
中文摘要：
SARS-CoV-2 持续肆虐，对人类生命和全球经济造成严重后果。病毒中和单克隆抗体的发现和开发可能是治疗或预防这种新型冠状病毒感染的一种方法。本文报道了从 5 例重症住院患者体内分离出 61 个 SARS-CoV-2 中和单克隆抗体。其中 19 种抗体能在体外有效中和 SARS-CoV-2，其中 9 种抗体表现出良好的效价，50%的病毒抑制浓度为 0.7-9ng /mL。表位作图显示，这 19 个抗体大约平均分配到受体结合区域(RBD)和 N 端区域(NTD)，表明这两个区域位于病毒刺突顶部是免疫原性的。此外，另外两种强有力的中和抗体识别与刺突顶部区域重叠的四元表位。一个抗体靶向 RBD，第二个靶向 NTD，第三个桥接两个单独的 RBD，冷冻电子显微镜重建显示识别封闭的“all RBD-down”的刺突构象。其中一些单克隆抗体有望作为潜

在的治疗和/或预防 SARS-CoV-2 的临床开发候选药物。

Abstract

The SARS-CoV-2 pandemic rages on with devasting consequences on human lives and the global economy. The discovery and development of virus-neutralizing monoclonal antibodies could be one approach to treat or prevent infection by this novel coronavirus. Here we report the isolation of 61 SARS-CoV-2-neutralizing monoclonal antibodies from 5 infected patients hospitalized with severe disease. Among these are 19 antibodies that potently neutralized the authentic SARS-CoV-2 in vitro, 9 of which exhibited exquisite potency, with 50% virus-inhibitory concentrations of 0.7 to 9 ng/mL. Epitope mapping showed this collection of 19 antibodies to be about equally divided between those directed to the receptor-binding domain (RBD) and those to the N-terminal domain (NTD), indicating that both of these regions at the top of the viral spike are immunogenic. In addition, two other powerful neutralizing antibodies recognized quaternary epitopes that overlap with the domains at the top of the spike. Cryo-electron microscopy reconstructions of one antibody targeting RBD, a second targeting NTD, and a third bridging two separate RBDs revealed recognition of the closed, "all RBD-down" conformation of the spike. Several of these monoclonal antibodies are promising candidates for clinical development as potential therapeutic and/or prophylactic agents against SARS-CoV-2.

18. 人源抗体和 COVID-19 RNA 疫苗引起的 TH1 型 T 细胞反应

Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine

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DOI 或 PUBMED ID：Preprint

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中文摘要：

需要一种有效的疫苗来阻止 SARS-CoV-2 大流行的蔓延。最近，研究人员报告了正在进行的安慰剂对照、观察者单盲的 1/2 期 COVID-19 疫苗试验（BNT162b1）的安全性、耐受性和抗体反应数据，BNT162b1 是脂质纳米颗粒（LNP）配制的核苷修饰的 mRNA，编码受体结合域（RBD）的 SARS-CoV-2 刺突蛋白。在这里，研究人员介绍了来自于 18-55 岁的健康成年人的第二次非随机开放标签 1/2 期临床试验，接种 BNT162b1 疫苗后的抗体和 T 细胞应答。 2 剂 1 至 50μgBNT162b1 引起强烈的 CD4 +和 CD8 + T 细胞反应以及强烈的抗体反应，RBD 结合 IgG 的浓度明显高于 COVID-19 恢复期人血清组（HCS）中的浓度。第 43 天 SARS-CoV-2 血清中和平均几何滴度为 HCS 的 0.7 倍（1μg）至 3.5 倍（50μg）。免疫血清广泛地中和了具有多种 SARS-CoV-2 刺突变体的假病毒。大多数参与者产生 TH1 偏向 T 细胞免疫反应，且具有 RBD 特异性 CD8 +和 CD4 + T 细胞扩增。干扰素（IFN）γ由高比例的 RBD 特异性 CD8 +和 CD4 + T 细胞产生。由 BNT162b1 mRNA 疫苗诱导的强大的 RBD 特异性抗体、T 细胞和有利的

细胞因子应答提示了多种有益的机制，具有针对 COVID-19 的保护潜力。

Abstract:
An effective vaccine is needed to halt the spread of the SARS-CoV-2 pandemic. Recently, we reported safety, tolerability and antibody response data from an ongoing placebo-controlled, observer-blinded phase 1/2 COVID-19 vaccine trial with BNT162b1, a lipid nanoparticle (LNP) formulated nucleoside-modified messenger RNA encoding the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. Here we present antibody and T cell responses after BNT162b1 vaccination from a second, non-randomized open-label phase 1/2 trial in healthy adults, 18-55 years of age. Two doses of 1 to 50 μg of BNT162b1 elicited robust CD4+ and CD8+ T cell responses and strong antibody responses, with RBD-binding IgG concentrations clearly above those in a COVID-19 convalescent human serum panel (HCS). Day 43 SARS-CoV-2 serum neutralising geometric mean titers were 0.7-fold (1 μg) to 3.5-fold (50 μg) those of HCS. Immune sera broadly neutralised pseudoviruses with diverse SARS-CoV-2 spike variants. Most participants had TH1 skewed T cell immune responses with RBD-specific CD8+ and CD4+ T cell expansion. Interferon (IFN)γ was produced by a high fraction of RBD-specific CD8+ and CD4+ T cells. The robust RBD-specific antibody, T-cell and favourable cytokine responses induced by the BNT162b1 mRNA vaccine suggest multiple beneficial mechanisms with potential to protect against COVID-19.

19. 重组腺病毒 5 型载体 COVID-19 疫苗在 18 岁及以上健康成人中的免疫原性和安全性：一项随机、双盲、安慰剂对照二期试验

Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebocontrolled, phase 2 trial

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中文摘要：
背景：这是首次评估非复制腺病毒-5 (Ad5)载体的候选 COVID-19 疫苗的免疫原性和安全性的随机对照试验，目的是确定用于疗效研究的候选疫苗的合适剂量。
方法：18 岁及以上的健康成年人，HIV 阴性和未感染过 SARS-CoV-2 都可参与，并被随机分配接受疫苗的剂量为 1×10^11 病毒颗粒每毫升或 5×10^10 病毒颗粒每毫升，或安慰剂。研究者以 2:1:1 的比例分配受试者，在手臂进行一次肌肉注射。随机列表是由独立的统计学家设计的。受试者、调查人员和从事实验室分析的工作人员被分组。免疫原性的主要终点是 28 天特异性 ELISA 抗体对受体结合区域(RBD)反应的几何平均数滴定度 (GMTs)和中和抗体反应。安全性评价的主要终点是 14 天内不良反应的发生率。

结果：在2020年4月11日至16日期间，招募了603名志愿者并对其资格进行了筛选。508名合格受试者（50%为男性；平均年龄39.7岁，SD 12.5）同意参与试验，随机分配接种疫苗(1 × 10^11病毒微粒n=253；5 × 10^10病毒颗粒n=129)或安慰剂（n=126）。在1 × 10^11和5 × 10^10病毒颗粒剂量组中，RBD特异性ELISA抗体在第28天的峰值分别为656.5 (95% CI 575.2－749.2) 和 571.0 (467.6－697.3)，血清转化率分别为96% (95% CI 93-98)和97%(92-99)。两种剂量的疫苗对活的SARS-CoV-2产生了显著的中和抗体反应，在分别接受1 × 10^11和5 × 10^10病毒颗粒的受试者中，GMTs分别为19.5 (95% CI 16.8-22.7)和18.3(14.4-23.3)。特异性干扰素γ酶联免疫斑点试验观察接种后的反应，分别在1 × 10^11和5 × 10^10病毒颗粒剂量组中，227人中 (90%，95% CI 85-93)的253名和113人中(88%，81-92)的129名受试者中观察到。在1 × 10^11和5 × 10^10病毒颗粒剂量组中，253人中有183人(72%)和129人中有96人(74%)报告了征集的不良反应。重度不良反应的受试者有24人(9%)在1 × 10^11病毒颗粒剂量组和1人(1%)在5 × 10^10病毒颗粒剂量组中。无严重不良反应记录。

讨论：本研究是首个评估非复制Ad5载体候选COVID-19疫苗免疫原性和安全性的随机对照试验。在本研究中，单次注射Ad5载体的COVID-19疫苗，剂量为1×10^11病毒颗粒和5×10^10病毒颗粒，在第28天对刺突糖蛋白产生了相似的特异性免疫应答，但两组间无显著差异。在1×10^11病毒颗粒组和5×10^10病毒颗粒组，疫苗分别诱导59%和47%的受试者中和抗体血清转化,96%和97%的受试者结合抗体血清转化。IFNγ-ELISpot检测到90%和88%的受试者分别接受1×10^11病毒颗粒和5×10^10病毒颗粒疫苗。接种疫苗后第28天，95%的 1×10^11 的病毒颗粒组和 91%的 5×10^10 的病毒颗粒组的患者出现细胞或体液免疫应答。已有的对Ad5载体的免疫和年龄的增加可能会部分阻碍免疫接种的特异性免疫反应，特别是体液免疫反应。

Abstract

Background: This is the first randomised controlled trial for assessment of the immunogenicity and safety of a candidate non-replicating adenovirus type-5 (Ad5)-vectored COVID-19 vaccine, aiming to determine an appropriate dose of the candidate vaccine for an efficacy study.

Methods : Healthy adults aged 18 years or older, who were HIV-negative and previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-free, were eligible to participate and were randomly assigned to receive the vaccine at a dose of 1 × 10^{11} viral particles per mL or 5 × 10^{10} viral particles per mL, or placebo. Investigators allocated participants at a ratio of 2:1:1 to receive a single injection intramuscularly in the arm. The randomisation list was generated by an independent statistician. Participants, investigators, and staff undertaking laboratory analyses were masked to group allocation. The primary endpoints for immunogenicity were the geometric mean titres (GMTs) of specific ELISA antibody responses to the receptor binding domain (RBD) and neutralising antibody responses at day 28. The primary endpoint for safety evaluation was the incidence of adverse reactions within 14 days.

Findings: 603 volunteers were recruited and screened for eligibility between April 11 and 16, 2020. 508 eligible participants (50% male; mean age 39.7 years, SD 12.5) consented to participate in the trial and were randomly assigned to receive the vaccine (1 × 10^{11} viral particles n=253; 5 × 10^{10} viral particles n=129) or placebo (n=126). In the 1 × 10^{11} and 5 × 10^{10} viral particles dose

groups, the RBD-specific ELISA antibodies peaked at 656.5 (95% CI 575.2－749.2) and 571.0 (467.6－697.3), with seroconversion rates at 96% (95% CI 93－98) and 97% (92－99), respectively, at day 28. Both doses of the vaccine induced significant neutralising antibody responses to live SARS-CoV-2, with GMTs of 19.5 (95% CI 16.8－22.7) and 18.3 (14.4－23.3) in participants receiving 1 × 10^{11} and 5 × 10^{10} viral particles, respectively. Specific interferon γ enzyme-linked immunospot assay responses post vaccination were observed in 227 (90%, 95% CI 85－93) of 253 and 113 (88%, 81－92) of 129 participants in the 1 × 10^{11} and 5 × 1010 viral particles dose groups, respectively. Solicited adverse reactions were reported by 183 (72%) of 253 and 96 (74%) of 129 participants in the 1 × 10^{11} and 5 × 10^{10} viral particles dose groups, respectively. Severe adverse reactions were reported by 24 (9%) participants in the 1 × 10^{11} viral particles dose group and one (1%) participant in the 5 × 10^{10} viral particles dose group. No serious adverse reactions were documented.

Discussion: This study is the frst randomised controlled trial for evaluation of the immunogenicity and safety of a candidate non-replicating Ad5-vectored COVID-19 vaccine. In this study, a single injection of the Ad5-vectored COVID-19 vaccine at 1 ×10^{11} viral particles and 5×10^{10} viral particles induced comparable specifc immune responses to the spike glycoprotein at day 28, with no signifcant differences noted between the two groups. The vaccine induced seroconversion of the neutralising antibodies in 59% and 47% of participants, and seroconversion of binding antibody in 96% and 97% of participants, in the 1 ×10^{11} and 5 ×10^{10} viral particles dose groups, respectively. Positive specifc T-cell responses measured by IFNγ-ELISpot were found in 90% and 88% of participants receiving the vaccine at 1× 10^{11} and 5 ×10^{10} viral particles, respectively. 95% of participants in the 1×10^{11} viral particles dose group and 91% of the recipients in the 5×10^{10} viral particles dose group showed either cellular or humoral immune responses at day 28 post vaccination (appendix p 12). Preexisting immunity to the Ad5 vector and increasing age could partially hamper the specifc immune responses to vaccination, particularly for the humoral immune responses.

20. SARS-CoV-2 的 Nsp1 蛋白在关闭翻译和逃避免疫方面的结构基础

Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2

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编译者：杨欢

中文简介：

SARS 类冠状病毒的一个主要毒性因子是 Nsp1，它与宿主的核糖体结合，从而抑制宿主基因表达。在这篇文章中，作者首先证实了新冠 SARS-CoV-2 的 Nsp1 与 40S 核糖体亚基结合，并导致体外和细胞中的 mRNA 翻译关闭，发现 Nsp1 的 C 端保守的 KH motif 对结合核糖体和抑制翻译至关重要。在进一步的结构分析中，作者得到了体外重组的 Nsp1-40S 的约 2.6 埃分辨率的冷冻电镜结构，以及细胞内原生的 Nsp1-40S 和-80S 的多种复合物的约 3.0 埃的冷冻电镜结构，结构分析表明，Nsp1 的 C 端的两个 alpha 螺旋与 40S 蛋白上的 mRNA 入口处结合，阻塞了 mRNA 的进入通道。通过关闭翻译，Nsp1 有效地阻断了依赖 RIG-I 的先天免疫反应，逃避了被免疫系统清除。Nsp1 抑制机制的结构表征将有助于基于结构的抗新冠药物设计。

Summary：
SARS-CoV-2 is the causative agent of the current COVID-19 pandemic. A major virulence factor of SARS- CoVs is the nonstructural protein 1 (Nsp1) which suppresses host gene expression by ribosome association. Here, we show that Nsp1 from SARS-CoV-2 binds to the 40S ribosomal subunit, resulting in shutdown of mRNA translation both in vitro and in cells. Structural analysis by cryo-electron microscopy (cryo-EM) of in vitro reconstituted Nsp1-40S and various native Nsp1-40S and -80S complexes revealed that the Nsp1 C terminus binds to and obstructs the mRNA entry tunnel. Thereby, Nsp1 effectively blocks RIG-I-dependent innate immune responses that would otherwise facilitate clearance of the infection. Thus, the structural characterization of the inhibitory mechanism of Nsp1 may aid structure-based drug design against SARS- CoV-2.

21. Covid-19 重症患者血液抗原提呈细胞的单细胞 RNA 测序揭示了抗病毒免疫的多过程的缺陷

Single cell RNA sequencing of blood antigen-presenting cells in severe Covid-19 reveals multi-process defects in antiviral immunity

来源：biorxiv

发布时间：2020-07-21

链接：https://www.biorxiv.org/content/10.1101/2020.07.20.212837v1

第一作者：Melissa Saichi, Maha Zohra Ladjemi, Sarantis Korniotis

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DOI 或 PUBMED ID：

编译者：王玮

中文摘要：
COVID-19 可导致危及生命的急性呼吸衰竭，其特征是炎症介质和病毒载量同时增加。其潜在的细胞和分子机制仍不清楚。该研究利用单细胞 RNA 测序技术，建立了血液抗原呈递细胞（APC）的详尽高分辨率图谱，其中包括 7 例 COVID-19 中度或重度肺炎患者入院后第 1 天和第 4 天以及两名健康献血者的图谱数据。该研究建立了一个包含 31513 个高质量 APC 的独特数据集，包括单核细胞和稀有树突状细胞（DC）亚群。发现重症患者特定 APC 区抗病毒免疫防御的多过程和先前未被认识到的缺陷：i）pDC（Plasmacytoid pre-DC）中的促凋亡基

因增加，而 pDC 是抗病毒免疫的关键效应器；ii）pDC 和 cDC1 的固有感受受体 TLR7 和 DHX9 急剧下降，iii)抗病毒效应分子的下调，包括所有单核细胞亚群中的干扰素刺激基因（ISG），和 iv）MHC II 类相关基因和 cDC2 中 MHC II 类反式激活因子（CIITA）活性的降低，表明病毒抑制了抗原呈递。这些新的机制可以解释病人病情加重，并提出恢复有缺陷的免疫防御的策略。

Abstract:
COVID-19 can lead to life-threatening acute respiratory failure, characterized by simultaneous increase in inflammatory mediators and viral load. The underlying cellular and molecular mechanisms remain unclear. We performed single-cell RNA-sequencing to establish an exhaustive high-resolution map of blood antigen-presenting cells (APC) in 7 COVID-19 patients with moderate or severe pneumonia, at day-1 and day-4 post-admission, and two healthy donors. We generated a unique dataset of 31,513 high quality APC, including monocytes and rare dendritic cell (DC) subsets. We uncovered multiprocess and previously unrecognized defects in anti-viral immune defense in specific APC compartments from severe patients: i) increase of pro-apoptotic genes exclusively in pDC, which are key effectors of antiviral immunity, ii) sharp decrease of innate sensing receptors, TLR7 and DHX9, in pDC and cDC1, respectively, iii) down-regulation of antiviral effector molecules, including Interferon stimulated genes (ISG) in all monocyte subsets, and iv) decrease of MHC class II-related genes, and MHC class II transactivator (CIITA) activity in cDC2, suggesting a viral inhibition of antigen presentation. These novel mechanisms may explain patient aggravation and suggest strategies to restore defective immune defense.

22. SARS-CoV-2 病毒 Spike 蛋白独特的构象状态

Distinct conformational states of SARS-CoV-2 spike protein

来源：Science
发布时间：2020-07-21
链接：https://science.sciencemag.org/content/early/2020/07/20/science.abd4251.full

第一作者：Yongfei Cai, Jun Zhang
通讯作者：Bing Chen
通讯作者单位：Division of Molecular Medicine, Boston Children’s Hospital, Boston, MA 02115, USA.

DOI 或 PUBMED ID：10.1126/science.abd4251

编译者：宋珂

中文摘要：

面对 SARS-CoV-2 病毒造成的疫情，迫切需要人们采取干预策略来控制其继续蔓延。病毒 Spike（S）蛋白三聚体促进了病毒与宿主细胞膜之间的融合，是病毒感染细胞的第一步。本文中，作者报导了其利用 cryo-EM 技术解析的处于两种构象状态下的全长 S 蛋白的结构。其中，处于融合前构象的 S 蛋白结构的分辨率为 2.9Å，处于融合后构象的分辨率为 3.0Å。S 蛋白可以自发地由融合前构象转变为融合后构象，不受宿主细胞的影响。在融合前构象中，S 蛋白三聚体中的三个受体结合结构域受到邻近的融合肽结构片段的挤压。融合后构象的结构中则存在 N-糖基化修饰。说明病毒可能具有对抗宿主免疫反应和恶劣外部环境的保护机

制。现有发现提高了人们对 SARS-CoV-2 病毒侵入宿主机制的认识，并可能对疫苗和治疗药物的研发具有指导意义。

结构数据：RCSB PDB ID：6XR8，6XRA；EMDB number：EMD-22292，EMD-22293

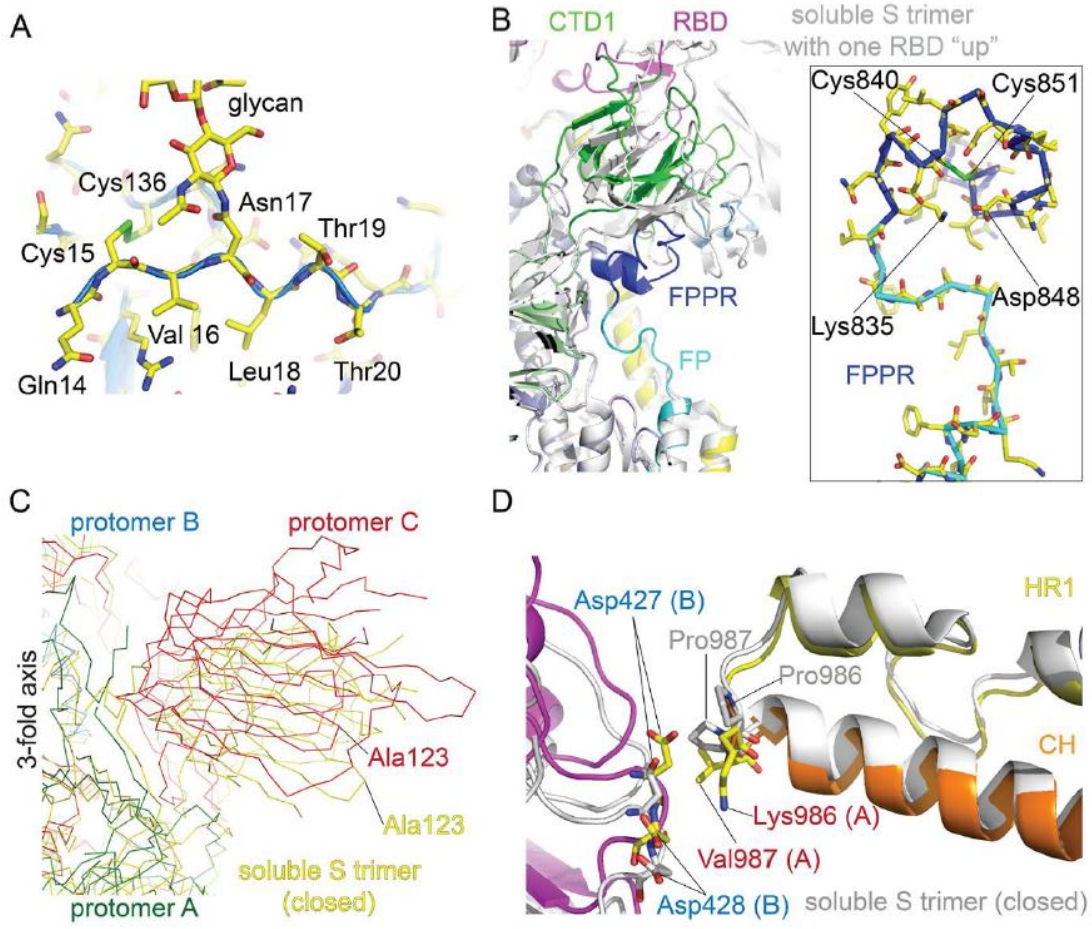

Fig. 3 Selected new features of the SARS-CoV-2 prefusion S trimer.

(**A**) N-terminal segment of S protein. The N terminus is at residue Gln14 after cleavage of the signal peptide. Cys15 forms a disulfide bond with Cys136. We observed good density for the N-linked glycan at Asn17. (**B**) A segment immediately downstream of the fusion peptide, while disordered in the stabilized soluble S ectodomain trimer structure, forms a tightly packed structure, designated FPPR for the fusion peptide proximal region, abutting CTD1. The newly identified FPPR structure would clash with CTD1 in the RBD up conformation. Various domains are shown in the color scheme in Fig. 2B. The structure of the soluble S trimer with one RBD in the up conformation (PDB ID: 6vyb) is shown in gray. In the box, a close-up view of the FPPR with adjacent fusion peptide in both surface representation and stick model. (**C**) The SARS-CoV-2 prefusion S trimer, viewed along the threefold axis, is superposed on the structure of the stabilized soluble S ectodomain trimer in the closed conformation with all three RBDs in the down conformation (PDB ID: 6vxx). While the S2 region is well aligned, there is a significant shift (e.g., ~12Å between two Ala123 residues) in S1. (**D**) Impact of the proline mutations introduced at residues 986 and 987 to stabilize the prefusion conformation. K986P mutation removes a salt bridge between Lys986 of one protomer and either Asp427 or Asp428 of another protomer in the trimer interface.

Abstract:

Intervention strategies are urgently needed to control the SARS-CoV-2 (severe

acute respiratory syndrome coronavirus 2) pandemic. The trimeric viral spike (S) protein catalyzes fusion between viral and target cell membranes to initiate infection. Here we report two cryo-EM structures, derived from a preparation of the full-length S protein, representing its prefusion (2.9Å resolution) and postfusion (3.0Å resolution) conformations, respectively. The spontaneous transition to the postfusion state is independent of target cells. The prefusion trimer has three receptor-binding domains clamped down by a segment adjacent to the fusion peptide. The postfusion structure is strategically decorated by N-linked glycans, suggesting possible protective roles against host immune responses and harsh external conditions. These findings advance our understanding of SARS-CoV-2 entry and may guide development of vaccines and therapeutics.

23. 将 SARS-CoV-2 RNA 基因组中 28-kDa 移码刺激元件作为抗转录靶点的探索，以及冷冻电子显微镜研究

Cryo-electron Microscopy and Exploratory Antisense Targeting of the 28-kDa Frameshift Stimulation Element from the SARS-CoV-2 RNA Genome

来源：bioRxiv

发布时间：2020-07-20

链接：https://www.biorxiv.org/content/10.1101/2020.07.18.209270v1

第一作者：Kaiming Zhang, Ivan N. Zheludev, Rachel J. Hagey

通讯作者：Wah Chiu, Rhiju Das

通讯作者单位：Biophysics Program, Stanford University, Stanford, CA, USA

DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

在研发抵抗 SARS-CoV-2 病毒药物的过程中，病毒 RNA 基因组已开始成为人们关注的靶点。在 SARS-CoV-2 基因组中，移码刺激元件（FSE）对病毒基本蛋白的平衡表达至关重要，而且具有高度的保守性。因此，FSE 也成为小分子和寡核苷酸类抗病毒药物的潜在候选靶点。在全球针对 SARS-CoV-2 移码的研究工作中，本文的作者对锁定核酸（LNA）抗转录寡核苷酸（ASO）进行了移码和细胞复制实验，并报道了探索性的结果。现有的实验结果表明，FSE 可以作为治疗的靶标，但仍然存在显著的难以强效失活的缺点。为了了解目前技术的局限性，作者进一步利用 cryo-EM 技术和 Ribosolve 流程解析出了 SARS-CoV-2 FSE 的三维结构，并通过 RNA 纳米结构标记方法对其进行了验证。这是迄今为止利用单颗粒 cryo-EM 技术解析出来的达到亚纳米分辨率的最小的生物大分子（88 nt；28 kDa）的结构。解析出的三级结构模型的估计精度为 5.9Å，拓扑结构上呈现出复杂的折叠形态，其中 5’端穿过三茎赝结内部形成的环。本文的结果不仅更新了 SARS-CoV-2 移码的模型，也更新了可能作为下一代 ASO 和小分子靶点的结合位点。

结构数据：EMDB code：EMD-22296，EMD-22297。PDB ID：6XRZ

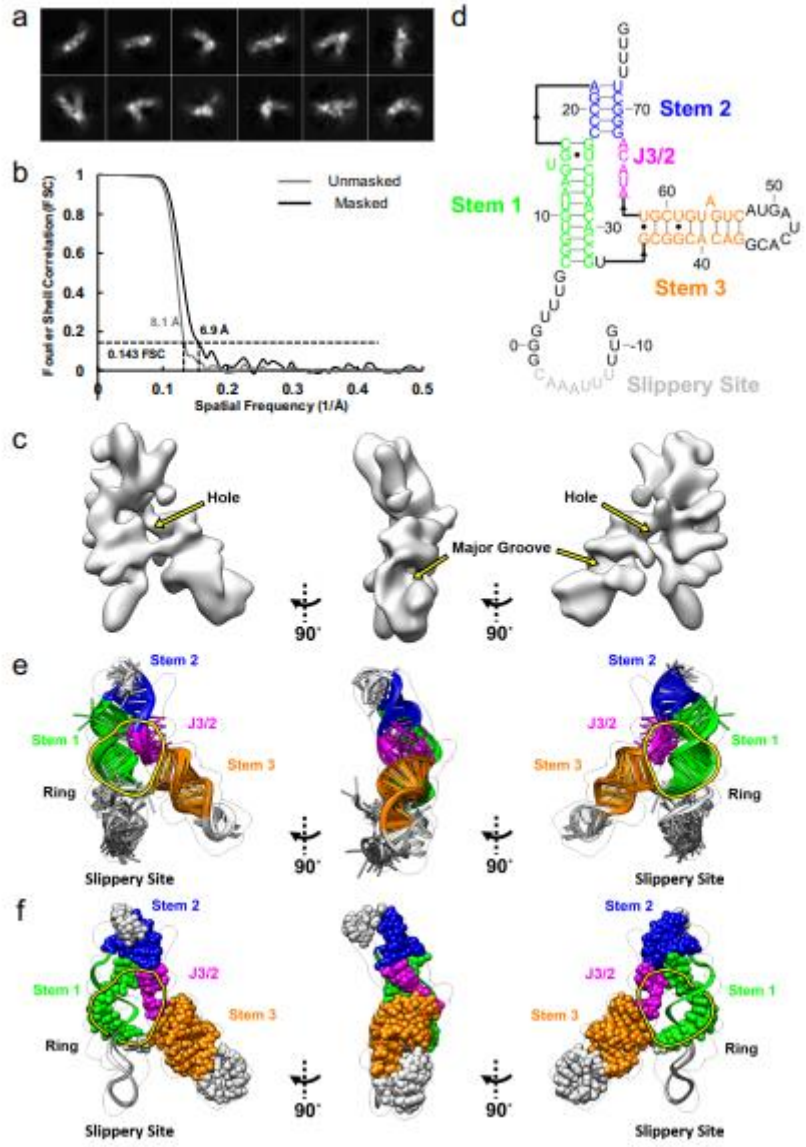

Fig. 2. Single-particle cryo-EM analysis and model building of the FSE. a. Reference-free 2D class averages. **b.** Gold standard FSC plots calculated in Relion. **c.** Reconstructed cryo-EM map in three different views. **d.** Secondary structure of the FSE as determined by 1D SHAPE chemical mapping. **e.** Top 10 tertiary structures of the FSE as determined by autoDRRAFTER using the secondary structure from (c), where equivalent structural elements are indicated. These 10 top scoring models had a mean pairwise root mean squared deviation of 5.68 Å, resulting in an estimated accuracy of 5.9 Å based on the previously determined linear relationship. **f.** A ring formed by the second strand of Stem 1 with Stems 2 and 3 and J3/2, into which the first strand of Stem 1 threads to form a topologically constrained tertiary fold

Abstract:

Drug discovery campaigns against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) are beginning to target the viral RNA genome. The frameshift stimulation element (FSE) of the SARS-CoV-2 genome is required for balanced expression of essential viral proteins and is highly conserved, making it a

potential candidate for antiviral targeting by small molecules and oligonucleotides. To aid global efforts focusing on SARS-CoV-2 frameshifting, we report exploratory results from frameshifting and cellular replication experiments with locked nucleic acid (LNA) antisense oligonucleotides (ASOs), which support the FSE as a therapeutic target but highlight difficulties in achieving strong inactivation. To understand current limitations, we applied cryogenic electron microscopy (cryo-EM) and the Ribosolve pipeline to determine a three-dimensional structure of the SARS-CoV-2 FSE, validated through an RNA nanostructure tagging method. This is the smallest macromolecule (88 nt; 28 kDa) resolved by single-particle cryo-EM at subnanometer resolution to date. The tertiary structure model, defined to an estimated accuracy of 5.9 Å, presents a topologically complex fold in which the 5′ end threads through a ring formed inside a three-stem pseudoknot. Our results suggest an updated model for SARS-CoV-2 frameshifting as well as binding sites that may be targeted by next generation ASOs and small molecules.

24. 基于结构设计稳定的预融合状态 SARS-CoV-2 Spike 蛋白

Structure-based design of prefusion-stabilized SARS-CoV-2 spikes

来源：Science

发布日期：2020-07-22

链接：https://science.sciencemag.org/content/early/2020/07/22/science.abd0826

2020 年 6 月 5 日简报第 23 条报告过该研究的预印本文章。

25. SARS-CoV-2 刺突蛋白突变对病毒感染性和对中和抗体的反应

The impact of mutations in SARS-CoV-2 spike on viral infectivity and antigenicity

来源：CELL 接受，预印

发布日期：2020-07-20

第一作者：

通讯作者：

通讯作者单位：

链接：

https://www.sciencedirect.com/science/article/pii/S0092867420308771?via%3Dihub

Highlights

Over 100 mutations were selected for analyses on their infectivity and antigenicity

•The dominant D614G itself and combined with other mutations are more infectious

•Ablation of both N331 and N343 glycosylation at RBD drastically reduced infectivity

•Ten mutations such as N234Q, L452R, A475V, V483A was markedly resistant to some mAbs

中文微信公众号药时空的解读：https://mp.weixin.qq.com/s/z_Ya7tuCmPjM1ZQHMU7rEg

该解读概述：

作者们采用体外实验研究了包括 SARS-Cov-2 刺突蛋白上包括 D614G 在内的 100 多个突变对病毒感染力和对中和抗体的反应的影响。

D614G 以及同时包含 D614G 和另一个氨基酸变化的几个变体，更具感染性。
D614G 之外的几个突变对中和抗体显示出抗性。

26. SARS-CoV-2 病毒 RNA 修饰图谱

The landscape of SARS-CoV-2 RNA modifications

来源： biorxiv

发布日期： 2020-07-18

第一作者： Milad Miladi

通讯作者：Björn Grüning

通讯作者单位： University of Freiburg, Freiburg, Germany

链接：https://www.biorxiv.org/content/10.1101/2020.07.18.204362v1

中文摘要：

德国和美国的研究团队采用 RNA 直接测序的办法检测了 3 株感染人肺上皮细胞 SARS-CoV-2RNA 的修饰情况。同感染猴肾细胞 SARS-CoV-2 的 RNA 修饰相比，存在非常保守的修饰模式。这些保守的修饰模式对 SARS-CoV-2 的病毒生命周期可能是必需的，这些修饰是潜在的抗病毒药物靶点。

Abstract:

In 2019 the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the first documented cases of severe lung disease COVID-19. Since then, SARS-CoV-2 has been spreading around the globe resulting in a severe pandemic with over 500.000 fatalities and large economical and social disruptions in human societies. Gaining knowledge on how SARS-Cov-2 interacts with its host cells and causes COVID-19 is crucial for the intervention of novel therapeutic strategies. SARS-CoV-2, like other coronaviruses, is a positive-strand RNA virus. The viral RNA is modified by RNA-modifying enzymes provided by the host cell. Direct RNA sequencing (DRS) using nanopores enables unbiased sensing of canonical and modified RNA bases of the viral transcripts. In this work, we used DRS to precisely annotate the open reading frames and the landscape of SARS-CoV-2 RNA modifications. We provide the first DRS data of SARS-CoV-2 in infected human lung epithelial cells. From sequencing three isolates, we derive a robust identification of SARS-CoV-2 modification sites within a physiologically relevant host cell type. A comparison of our data with the DRS data from a previous SARS-CoV-2 isolate, both raised in monkey renal cells, reveals consistent RNA modifications across the viral genome. Conservation of the RNA modification pattern during progression of the current pandemic suggests that this pattern is likely essential for the life cycle of SARS-CoV-2 and represents a possible target for drug interventions.

27. S1/S2 位点间的 PRRA 插入调节了 SARS-CoV-2 的细胞嗜性以及高度相关病毒 raTG13 的 ACE2 利用

The PRRA insert at the S1/S2 site modulates cellular tropism of SARS-CoV-2 and ACE2 usage by the closely related Bat raTG13

来源： biorxiv

发布日期： 2020-07-21

第一作者：Shufeng Liu
通讯作者：Tony T Wang
通讯作者单位:U.S. FDA
链接：https://www.biorxiv.org/content/10.1101/2020.07.20.213280v1
中文摘要：
生化和结构分析提示 SARS-CoV-2 已经高度适应感染人类，而在刺突蛋白的 S1/S2 位点之间的 4 氨基酸 PRRA 可能导致了意外的组织和宿主嗜性。SARS-CoV-2 可以有效的利用 9 个除了小鼠之外的物种的 ACE2 来感染 293T 细胞。类似的,带有和 SARS-CoV-2 高度相关的蝙蝠 raTG13 或者穿山甲 GX 冠状病毒的刺突蛋白的假病毒也可以利用一系列不同物种的 ACE2 进入细胞。删除 SARS-CoV-2 的刺突蛋白中的 PRRA 对假病毒进入不同类型的细胞产生迥异影响。将 PRRA 插入 raTG13 刺突蛋白选择性地让菊头蝠和穿山甲的 ACE2 失去介导病毒进入细胞的能力，但是该插入却能使得小鼠 ACE2 变得能介导病毒进入细胞。
Abstract:
Biochemical and structural analyses suggest that SARS-CoV-2 is well-adapted to infecting human and the presence of four residues (PRRA) at the S1/S2 site within the Spike protein may lead to unexpected tissue or host tropism. Here we report that SARS-CoV-2 efficiently utilized ACE2 of 9 species except mouse to infect 293T cells. Similarly, pseudoviruses bearing spike protein derived from either the bat raTG13 or pangolin GX, two closely related animal coronaviruses, utilized ACE2 of a diverse range of animal species to gain entry. Removal of PRRA from SARS-CoV-2 Spike displayed distinct effects on pseudoviral entry into different cell types. Strikingly, insertion of PRRA into the raTG13 Spike selectively abrogated the usage of horseshoe bat and pangolin ACE2 but conferred usage of mouse ACE2 by the relevant pseudovirus to enter cells. Together, our findings identified a previously unrecognized effect of the PRRA insert on SARS-CoV-2 and raTG13 spike proteins.

28. SARS-CoV-2 感染对 K18 人血管紧张素转换酶 2 转基因小鼠的杀伤作用

Lethality of SARS-CoV-2 infection in K18 human angiotensin converting enzyme 2 transgenic mice
来源：biorxiv
发布时间：2020-07-19
链接：https://www.biorxiv.org/content/10.1101/2020.07.18.210179v1
第一作者：Fatai Oladunni, Jun-Gyu Park, Paula Pino Tamayo, Olga Gonzalez, Anwari Ahkter, Anna Allue Guardia
通讯作者：Joanne Turner, Luis Martinez-Sobrido, Jordi B Torrelles
通讯作者单位：Texas Biomedical Research Institute, San Antonio, TX, 78227, USA
DOI 或 PUBMED ID：
编译者：王玮
中文摘要：
针对 SARS-CoV-2 感染或 COVID-19 疾病的疫苗和抗病毒药物开发目前缺乏一个经过验证的小动物模型。该研究展示了通过人细胞角蛋白 18 启动子（K18 hACE2）表达人血管紧张素转换酶 2（hACE2）的转基因小鼠是一种易感的啮齿动物模型。K18 hACE2 转基因小鼠在第 6 天死于 SARS-CoV-2 感染，在肺气道上皮和大脑中检测到病毒。K18 hACE2 转基因小鼠在肺和

脾脏产生了 TH1/2/17 细胞因子风暴，在第 2 天达到高峰，并且在肺和大脑中检测到一个趋化因子风暴。这种趋化因子风暴在第 4 天也在大脑中被检测到。因此，K18 hACE2 转基因小鼠对 SARS-CoV-2 感染高度敏感，是研究 SARS-CoV-2 病毒致病机理、鉴定疫苗（预防性）和抗病毒药物（治疗）的合适动物模型。

Abstract:
Vaccine and antiviral development against SARS-CoV-2 infection or COVID-19 disease currently lacks a validated small animal model. Here, we show that transgenic mice expressing human angiotensin converting enzyme 2 (hACE2) by the human cytokeratin 18 promoter (K18 hACE2) represent a susceptible rodent model. K18 hACE2-transgenic mice succumbed to SARS-CoV-2 infection by day 6, with virus detected in lung airway epithelium and brain. K18 ACE2-transgenic mice produced a modest TH1/2/17 cytokine storm in the lung and spleen that peaked by day 2, and an extended chemokine storm that was detected in both lungs and brain. This chemokine storm was also detected in the brain at day 4. K18 hACE2-transgenic mice are, therefore, highly susceptible to SARS-CoV-2 infection and represent a suitable animal model for the study of viral pathogenesis, and for identification and characterization of vaccines (prophylactic) and antivirals (therapeutics) for SARS-CoV-2 infection and associated severe COVID-19 disease.

29. JAMA 发表迄今最全面的 COVID-19 教科书式综述

Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19)

来源：JAMA

发布时间：2020-07-10

第一作者：W. Joost Wiersinga

通讯作者：Hallie C.Prescott

通讯作者单位：University of Michigan

链接：https://jamanetwork.com/journals/jama/fullarticle/2768391

Abstract:
Importance
The coronavirus disease 2019 (COVID-19) pandemic, due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a worldwide sudden and substantial increase in hospitalizations for pneumonia with multiorgan disease. This review discusses current evidence regarding the pathophysiology, transmission, diagnosis, and management of COVID-19.
Observations
SARS-CoV-2 is spread primarily via respiratory droplets during close face-to-face contact. Infection can be spread by asymptomatic, presymptomatic, and symptomatic carriers. The average time from exposure to symptom onset is 5 days, and 97.5% of people who develop symptoms do so within 11.5 days. The most common symptoms are fever, dry cough, and shortness of breath. Radiographic and laboratory abnormalities, such as lymphopenia and elevated lactate dehydrogenase, are common, but nonspecific. Diagnosis is made by detection of SARS-CoV-2 via reverse transcription polymerase chain reaction testing, although false-negative

test results may occur in up to 20% to 67% of patients; however, this is dependent on the quality and timing of testing. Manifestations of COVID-19 include asymptomatic carriers and fulminant disease characterized by sepsis and acute respiratory failure. Approximately 5% of patients with COVID-19, and 20% of those hospitalized, experience severe symptoms necessitating intensive care. More than 75% of patients hospitalized with COVID-19 require supplemental oxygen. Treatment for individuals with COVID-19 includes best practices for supportive management of acute hypoxic respiratory failure. Emerging data indicate that dexamethasone therapy reduces 28-day mortality in patients requiring supplemental oxygen compared with usual care (21.6% vs 24.6%; age-adjusted rate ratio, 0.83 [95% CI, 0.74-0.92]) and that remdesivir improves time to recovery (hospital discharge or no supplemental oxygen requirement) from 15 to 11 days. In a randomized trial of 103 patients with COVID-19, convalescent plasma did not shorten time to recovery. Ongoing trials are testing antiviral therapies, immune modulators, and anticoagulants. The case-fatality rate for COVID-19 varies markedly by age, ranging from 0.3 deaths per 1000 cases among patients aged 5 to 17 years to 304.9 deaths per 1000 cases among patients aged 85 years or older in the US. Among patients hospitalized in the intensive care unit, the case fatality is up to 40%. At least 120 SARS-CoV-2 vaccines are under development. Until an effective vaccine is available, the primary methods to reduce spread are face masks, social distancing, and contact tracing. Monoclonal antibodies and hyperimmune globulin may provide additional preventive strategies.

Conclusions and Relevance

As of July 1, 2020, more than 10 million people worldwide had been infected with SARS-CoV-2. Many aspects of transmission, infection, and treatment remain unclear. Advances in prevention and effective management of COVID-19 will require basic and clinical investigation and public health and clinical interventions.

中文解读链接：https://mp.weixin.qq.com/s/JegrlF7o_4s8WBxg2cSY2A

30. 可能和 RNA 代谢相关的 SARS-CoV-2 的可诱导的综合质粒库

Integrative Vectors for Regulated Expression of SARS-CoV-2 Proteins Implicated in RNA Metabolism

爱丁堡大学的研究者们通过分析预测可能参与 RNA 代谢的 12 个 SARS-CoV-2 基因。作者们构建了这些基因 N 端、C 端加表达标签以及不加标签的 TET 诱导调控的表达质粒系统。作者们在 addgene 存放了这些质粒和稳转细胞系，供研究人员共享使用。

来源：biorxiv

发布日期：2020-07-21

链接：https://www.biorxiv.org/content/10.1101/2020.07.20.211623v1

Abstract:

Infection with SARS-CoV-2 is expected to result in substantial reorganization of host cell RNA metabolism. We identified 14 proteins that were predicted to interact with host RNAs or RNA binding proteins, based on published data for SARS-CoV and SARS-CoV-2. Here, we describe a series of affinity-tagged and codon-optimized expression constructs for each of these 14 proteins. Each viral gene

was separately tagged at the N-terminus with Flag-His8, the C-terminus with His8-Flag, or left untagged. The resulting constructs were stably integrated into the HEK293 Flp-In TREx genome. Each viral gene was expressed under the control of an inducible Tet-On promoter, allowing expression levels to be tuned to match physiological conditions during infection. Expression time courses were successfully generated for most of the fusion proteins and quantified by western blot. A few fusion proteins were poorly expressed, whereas others, including Nsp1, Nsp12, and N protein, were toxic unless care was taken to minimize background expression. All plasmids can be obtained from Addgene and cell lines are available. We anticipate that availability of these resources will facilitate a more detailed understanding of coronavirus molecular biology.

31. 《柳叶刀》社论 | COVID-19 与中国：经验与前路

COVID-19 and China: lessons and the way forward

来源：lancet

发布日期：2020-7-25

链接：https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931637-8

柳叶刀中文微信公众号翻译和解读：https://mp.weixin.qq.com/s/HlpLr7DlfBC_P_9IwHKV-g

关于中国经验摘要如下：

第一，中国的应对体现了国内研究和公共卫生能力的重要性

第二个经验是如果没有强有力的高层政治承诺用科学来果断地抗击疫情，那么再坚实的研究基础也无法确保有效控制疫情。

第三，迅速有效地落实 COVID-19 控制措施需要广泛的社区参与。

Highlights:

China’s response shows the importance of domestic research and public health capacity.

A second lesson is that a robust foundation of research cannot guarantee effective control without strong toplevel political commitment to use science to tackle the outbreak decisively.

Third, achieving rapid and effective implementation of control measures for COVID-19 requires broad community engagement.