新型冠状病毒信息简报

第 14 期（2020 年 4 月 1 日报）

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

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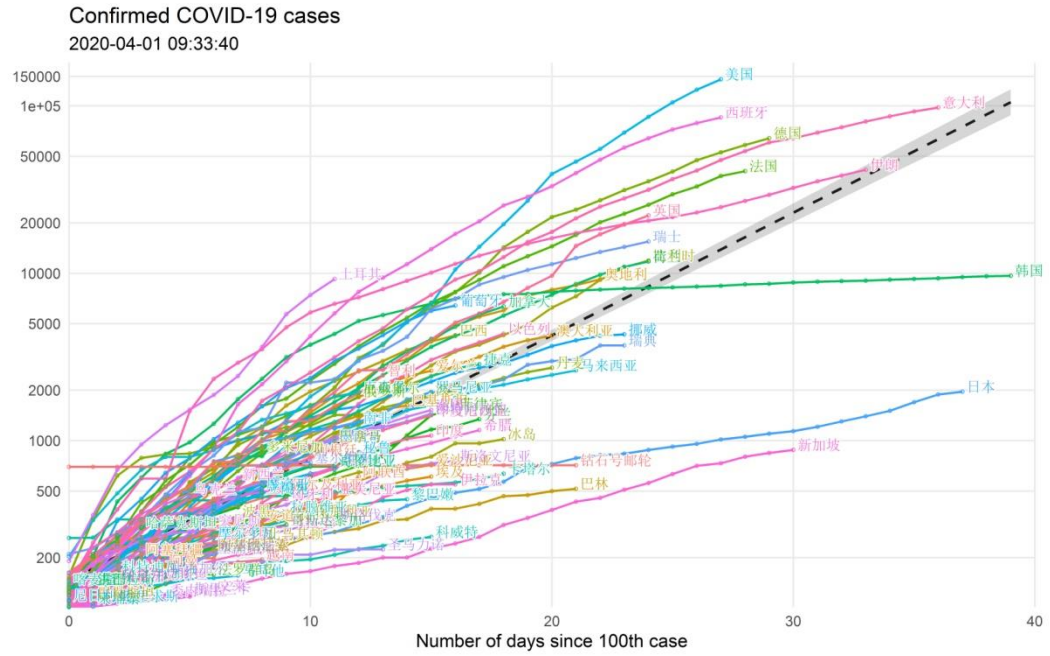
1. 2020 年 3 月 31 日疫情

2020年3月31日疫情
编译：王玮
数据来源：WHO
发布时间：2020年3月31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3月31日全球累计确诊新型冠状病毒病人750890例，当日新增确诊57610例，累计死亡36405例，当日新增死亡3301。
中国累计确诊 82545 例，累计死亡 3314 例，当日新增确诊 98 例，新增死亡 4 例。



国外确诊数量曲线（用 nCoVR 包 https://github.com/GuangchuangYu/nCov2019 作图，数据截止 3 月 31 日北京时间下午 4 点）

2. 雪貂、猫、狗和不同家畜对 SARS-coronavirus-2 的敏感性

Susceptibility of ferrets, cats, dogs, and different domestic animals to SARS-coronavirus-2

来源：biorxiv
发布时间：2020-03-31
来源链接：https://www.biorxiv.org/content/10.1101/2020.03.30.015347v1
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通讯作者：步志高，陈化兰
编译：王玮
内容摘要：
SARS-CoV-2引起的传染性疾病COVID-19于2019年12月在中国武汉首次报道。尽管，为控制这一疾病作出了巨大努力，但COVID-19现已传播到100多个国家，并成为全球流行病。SARS-CoV-2被认为起源于蝙蝠；但目前，病毒的中间宿主仍未找到。该研究调查了与人类密切接触的雪貂等动物对SARS-CoV-2的敏感性。该研究发现SARS-CoV-2在狗、猪、鸡和鸭身上的复制很

差，**但在雪貂和猫身上的复制效率很高**。研究发现病毒通过呼吸道飞沫在猫体内传播。该研究为SARS-CoV-2的动物培养和COVID-19的动物管理提供了重要依据。

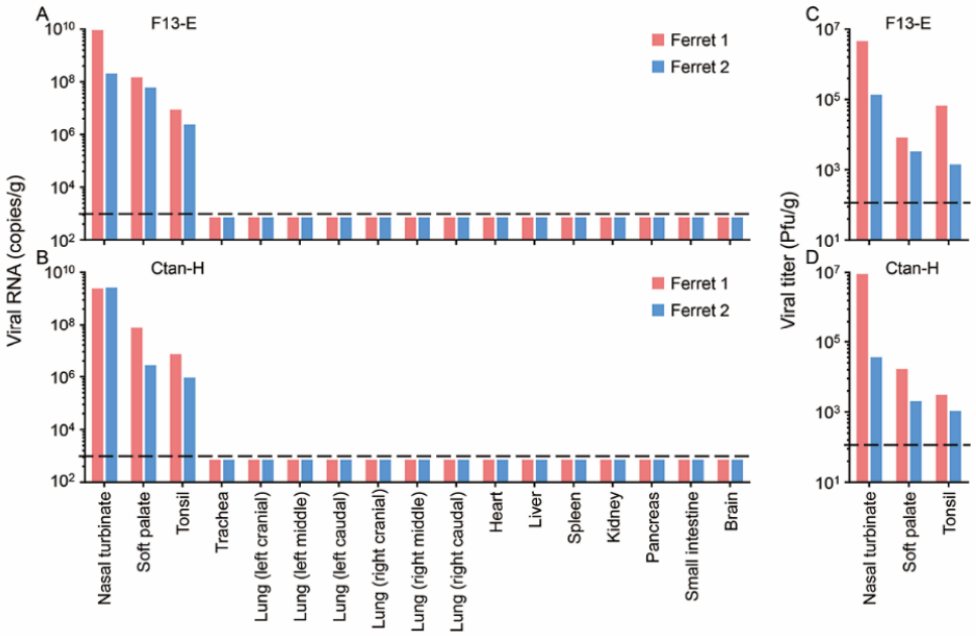


Figure 1. Replication of SARS-CoV-2 viruses in ferrets. Viral RNA in organs or tissues of ferrets inoculated with (**A**) F13-E virus or (**B**) CTan-H virus. Viral titers in organs or tissues of ferrets inoculated with F13-E (**C**) and CTan-H (**D**). Viral RNA in nasal washes of ferrets inoculated with F13-E (**E**) and CTan-H (**F**). Viral titer in nasal washes of ferrets inoculated with F13-E (**G**) and CTan-H (**H**). Antibodies against SARS-CoV-2 tested by an ELISA (**I**, **J**) and neutralization assay (**K, L**) with the sera derived from ferrets inoculated with F13-E (**I, K**) and CTan (**J, L**). Each color bar represents the value from an individual animal. The black bars in the panels **I** to **L** indicate the antibody values of sera collected from each animal before the virus was inoculated. Asterisks indicate animals that were euthanized on day 13 after virus inoculation, the other four animals were euthanized on day 20 p.i. The horizontal dashed lines indicate the lower limit of detection.

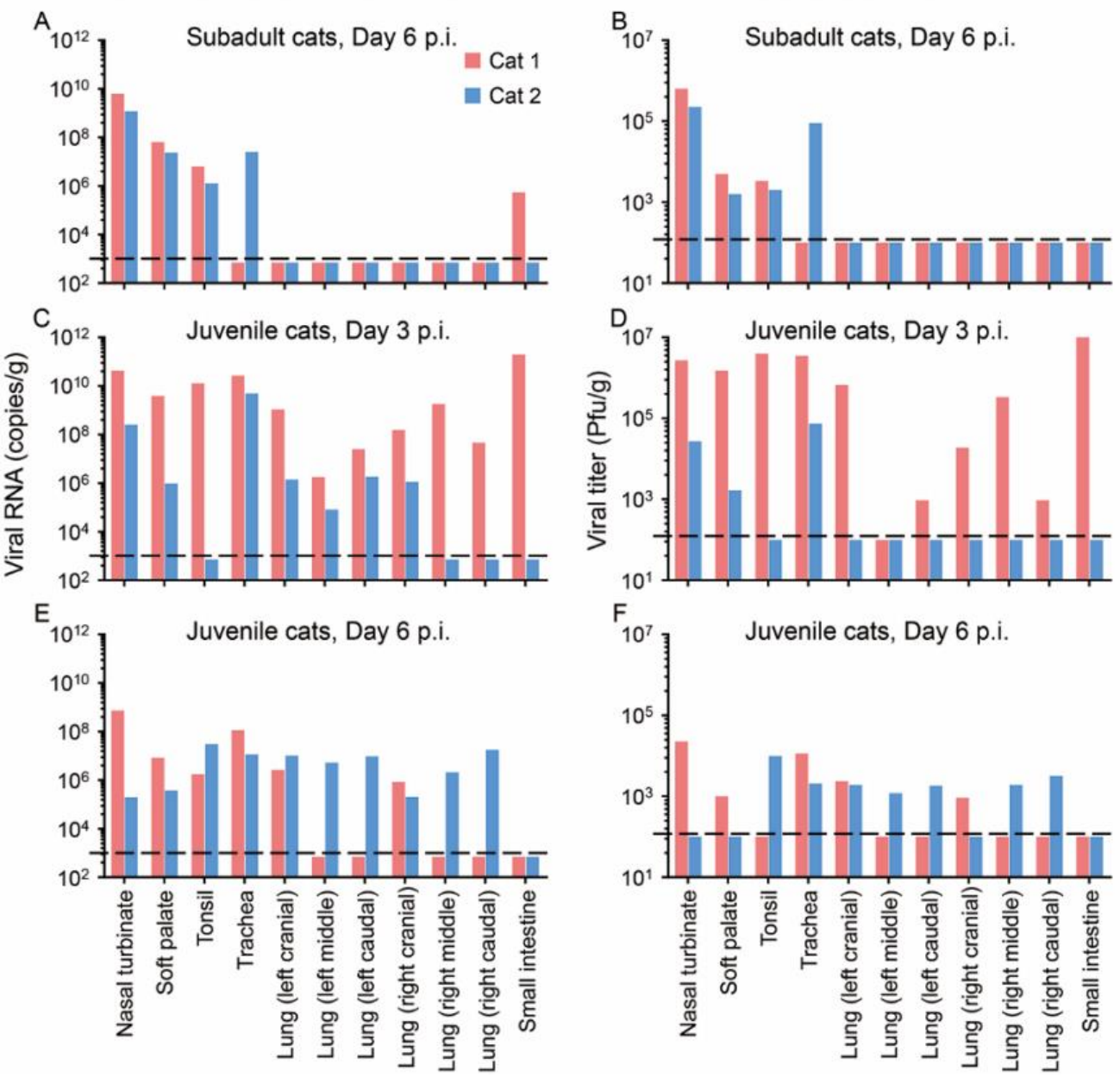


Figure 2. Replication of SARS-CoV-2 in cats. (**A**) Viral RNA and (**B**) viral titers detected in subadult cats that were euthanized on day 6 post-inoculation (p.i.) with CTan-H virus. (**C**) Viral RNA and (**D**) viral titers detected in juvenile cats that were euthanized on day 3 p.i. with CTan-H virus. (**E**) Viral RNA and (**F**) viral titers detected in juvenile cats that were euthanized on day 6 p.i. with CTan-H virus. Each color bar represents the value from an individual animal. The horizontal dashed lines indicate the lower limit of detection.

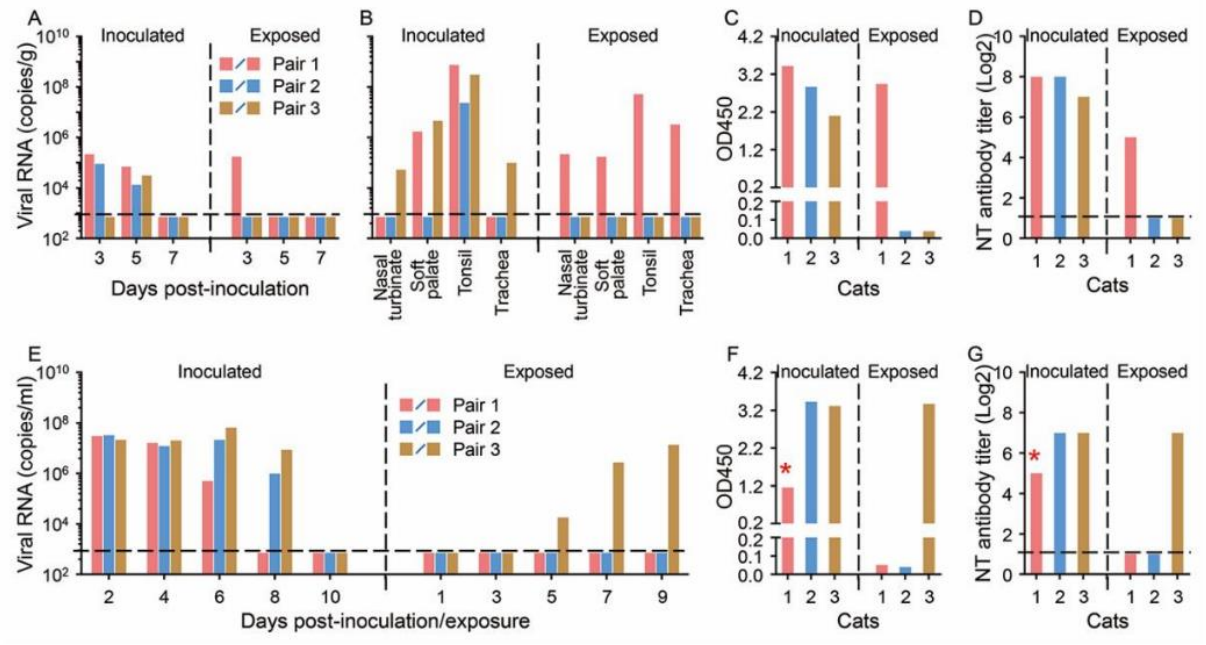


Figure 3. Transmission of SARS-CoV-2 in cats. (**A**) Viral RNA in the feces of subadult cats that were inoculated with or exposed to CTan-H at the indicated timepoints. (**B**) Viral RNA in tissues or organs of subadult cats that were inoculated with or exposed to CTan-H, the pair one cats (red bars) were euthanized on day 11 p.i. and the other two pairs were euthanized on day 12 p.i. Antibodies against SARS-CoV-2 of these euthanized cats were detected by using an ELISA (**C**) and neutralization assay (**D**). (**E**) Viral RNA in nasal washes of juvenile cats that were inoculated with or exposed to CTan-H. Sera of the juvenile cats were collected on day 20 p.i., and their antibodies against SARS-CoV-2 were detected by using an ELISA (**F**) and neutralization assay (**G**). One virus inoculated cat died on day 13 p.i. and the antibody values of this cat (indicated by asterisks) were detected from the sera collected on day 10 p.i. Each color bar represents the value from an individual animal. The horizontal dashed lines indicate the lower limit of detection.

编者注：和昨天简报里面貂的COVID-19动物模型的研究里 https://marlin-prod.literatumonline.com/pb-assets/journals/research/cell-host-microbe/PDFs/chom_2285_preproof.pdf，本文没有探讨貂里面SARS-CoV-2的传播。病毒的检出也有差异—昨天简报里面病毒的浓度最高的部位仍然是上呼吸道，肺部里也检出了病毒核酸和抗原。当然也有可能具体病毒接种方式检测方式等等也可能照成差异，另外动物数目或者遗传背景等等也可能影响在貂里面的相关结果。

这篇文章里重点讲到猫里的病毒的复制和传播，根据图三，不管是半成年猫还是幼猫里面分别安排隔离间的3对猫中，11天后将猫处死时也只有1对中的未接种猫被另一只猫感染（图A和E），一定程度上说明猫之间因为飞沫传染的概率也不是100%（人中密切接触者传染概率约为5%）。

该研究提示COVID-19的人类病患可能将病毒传染给家养宠物猫的风险（可能需要调查病患家养以及疫情高发区流浪猫进行核酸和血清学检测，进一步判断其可能回传给人或者其他动物

的可能性），至于猫在病毒起源中扮演什么角色—编者认为除非对不同地区大量流浪猫进行血清学或者核酸检测拿到更多数据，目前任何推演可能都为时过早。大可不必担心非重点疫区的猫可能携带高致病病毒。这个研究更多的提示猫可以作为SARS-CoV-2的小动物模型。

Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the infectious disease COVID-19, which was first reported in Wuhan, China in December, 2019. Despite the tremendous efforts to control the disease, COVID-19 has now spread to over 100 countries and caused a global pandemic. SARS-CoV-2 is thought to have originated in bats; however, the intermediate animal sources of the virus are completely unknown. Here, we investigated the susceptibility of ferrets and animals in close contact with humans to SARS-CoV-2. We found that SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but efficiently in ferrets and cats. We found that the virus transmits in cats via respiratory droplets. Our study provides important insights into the animal reservoirs of SARS-CoV-2 and animal management for COVID-19 control.

3. COVID-19 产品进展综述：Bodysphere 2 分钟快速抗体检测试剂获得紧急授权批准；其他公司 Qiagen，BD BioMedomics，Rendu，Vaxart，Cobra，GigaGen，Houston Methodist，Anaqua WideTrial 齐发力

COVID-19 roundup: EUA for Bodysphere’s fast antibody test; plus Qiagen, BD-BioMedomics, Rendu, Vaxart, Cobra, GigaGen, Houston Methodist, Anaqua-WideTrial

来源：BioCentury；
发布时间：2020年4月1日
链接：https://www.biocentury.com/article/304780?editionId=ck8gnfqxd2j0j0998zt448ksf&editionType=daily
作者：Sandi Wong，助理编辑
编译：张丽双
摘要：
测试方面进展：Bodysphere公司开发的创新COVID-19血清学检测试剂盒（2分钟出结果，其临床特异性和敏感性分别为91%和99%）和Qiagen的QIAstat-Dx试剂盒（基因检测，将COVID-19与其他20种严重呼吸道感染区分开来，一小时就能产生结果。）周二获得FDA紧急使用授权（EUA）。与此同时，BD和BioMedomics公司发布了一种可以在15分钟内识别的抗体试剂盒，Henry Schein公司将在美国分发该试剂盒。仁度生物科技的SARS-CoV-2核酸试剂盒（基因组提取和核酸扩增在一根试管中进行，90分钟内出结果），获得了中国国家医药产品监督管理局（NMPA）的紧急批准。该公司同时推出了一个与试剂盒兼容的自动化高通量平台AutoSAT。为了缓解美国诊断能力的不足，创新基因研究所（IGI）宣布计划在加州大学伯克利分校建立一个COVID-19自动检测实验室，最多每天可进行3000次检测。12-24小时内提供结果。
疫苗方面进展：Vaxart公司有5种口服COVID-19疫苗候选药物（腺病毒载体）在临床前测试中，预计下半年初进入临床，Emergent BioSolutions 公司负责为其生产符合cGMP的研究用疫苗。CDMO Cobra生物制品公司参与了牛津大学詹纳研究所领导的开发腺病毒疫苗ChAdOx1

的开发，这可能是英国第一个COVID-19疫苗，定于四月开始临床试验。
抗体治疗方面进展：包括GigaGen公布了一项源自COVID-19康复者的多克隆抗体项目，希望在2021年初进入诊所。FDA于3月24日发布指导意见，帮助医生在同情使用的基础上向COVID-19患者提供恢复期血浆，同时承认该方法的安全性和有效性尚未在临床试验中得到证实。FDA于3月28日批准了一项紧急IND，用恢复期血浆治疗一名危重症COVID-19患者。另外，Anaqua公司与WideTrial公司合作，通过医疗事务解决方案ideaPoint产品，为COVID-19治疗开发人员建立了一个基于互联网的平台，使他们的产品在扩展使用计划下（如适用）可用。有关冠状病毒危机的进一步分析，请访问https://www.biocentury.com/coronavirus。

Abstract
FDA’s first emergency use authorization for an antibody-based COVID-19 test, from Bodysphere, has come alongside advancements in therapeutic, vaccine and diagnostic COVID-19 programs, including GigaGen’s unveiling of a polyclonal antibody program derived from convalescent COVID-19 patients.
FDA granted on Tuesday EUAs for the COVID-19 IgG/IgM Rapid Test, a serological test from Bodysphere Inc., and the QIAstat-Dx Respiratory SARS-CoV-2 Panel from Qiagen N.V. (Xetra:QIA; NYSE:QGEN).
Bodysphere’s assay qualitatively detects serum IgM and IgG against SARS-CoV-2 with clinical specificity and sensitivity of 91% and 99%, respectively, in as little as two minutes.
Qiagen’s test, a multiplexed nucleic acid-based diagnostic that differentiates COVID-19 from 20 other serious respiratory infections by detecting two SARS-CoV-2 genes, can produce results in about one hour.
Meanwhile, Becton Dickinson and Co. (NYSE:BDX) and BioMedomics Inc. released a point-of-care test that can identify antibodies against SARS-CoV-2 in 15 minutes. Henry Schein Inc. will distribute the test, which can detect ongoing or resolved COVID-19, in the U.S.
Also passing a regulatory hurdle was a SARS-CoV-2 nucleic acid kit from Rendu Biotechnology, which gained emergency approval from China’s National Medical Products Administration (NMPA). In Rendu’s assay, genome extraction and nucleic acid amplification take place in a single tube, and the test reads out in 90 minutes. The company simultaneously launched AutoSAT, an automated high-throughput platform that’s compatible with the kit.
And to alleviate shortfalls in U.S. diagnostic capabilities, the Innovative Genomics Institute (IGI) announced plans to establish an automated COVID-19 testing lab on the University of California Berkeley campus. The IGI testing lab is starting with FDA-approved RT-PCR tests and will soon conduct 1,000 tests per day, with the ability to run 3,000 tests per day. It will provide results to healthcare workers within 12-24 hours of sample collection. IGI is a San Francisco Bay Area-based research partnership founded by Jennifer Doudna.
VIRAL VACCINES QUEUING UP
Vaxart Inc. (NASDAQ:VXRT) announced it has five oral COVID-19 vaccine candidates in preclinical testing to pick its clinical candidate. Each of Vaxart’s vaccine constructs, from its adenovirus serotype 5 (Ad5)-based VAAST platform, delivers genes encoding a different combination of SARS-CoV-2 antigens. The company

expects to enter the clinic early next half, with partner Emergent BioSolutions Inc. (NYSE:EBS) expected to produce bulk cGMP vaccine for use in the study.
CDMO Cobra Biologics said that it, as part of a consortium led by Oxford University's Jenner Institute to develop adenoviral COVID-19 vaccine candidate ChAdOx1, is planning a rapid set-up phase to enable efficient GMP production of the vaccine. Clinical testing of ChAdOx1, which could be the U.K.'s first COVID-19 vaccine, is slated to begin in April.
FULL ANTIBODY REPERTOIRE
GigaGen Inc. unveiled on Monday its recombinant polyclonal antibody treatment for COVID-19, recombinant anti-coronavirus hyperimmune gammaglobulin (rCIG). The company generates rCIG using its single cell technology for recreating the antibody repertoire of individuals who have recovered from COVID-19, and can therefore circumvent the need to continually acquire convalescent plasma donations. GigaGen is recruiting donors for rCIG production, and hopes to enter the clinic in early 2021.
Houston Methodist said FDA approved on Saturday an emergency IND to treat a critically ill COVID-19 patient with convalescent plasma donated by a recovered COVID-19 patient.
FDA released guidance on March 24 to help physicians provide convalescent plasma to COVID-19 patients on a compassionate use basis while acknowledging that the safety and efficacy of the approach has not been established in clinical trials (see "FDA Facilitating Compassionate Use").
Separately, Anaqua Inc., via its ideaPoint product for medical affairs solutions, and WideTrial partnered Tuesday to set up an internet-based platform for COVID-19 therapeutic developers to make their products available, if applicable, under expanded use programs. Through the online system, healthcare providers can sign up to participate in expanded use program of their choice.
Further analysis of the coronavirus crisis can be found at https://www.biocentury.com/coronavirus.

4. 用于 SARS-CoV-2 的单酶 RT-qPCR 测定法和试剂生产程序

A one-enzyme RT-qPCR assay for SARS-CoV-2, and procedures for reagent production
来源：biorxiv
发表时间：2020-3-31
链接：https://www.biorxiv.org/content/10.1101/2020.03.29.013342v1
通讯作者：Andrew D Ellington
作者单位：University of Texas at Austin
编译：雷颖
摘要：
考虑到正在爆发的COVID-19大流行的规模、对可靠可扩展的测试的需求、以及在资源匮乏的地区试剂短缺的可能性，作者开发了一种RT-qPCR分析法，采用了常规病毒逆转录酶的替代品，一种热稳定的逆转录酶/DNA聚合酶（RTX）1。本文中，作者显示了RTX与其他CDC认可并以试剂盒形式验证的测定法具有可比性。作者验证了两种使用RTX的模式-（i）仅需要RTX聚合酶的基于染料的RT-qPCR分析，以及（ii）使用RTX和Taq DNA聚合酶组合的TaqMan RT-qPCR

分析（因为RTX核酸外切酶不会降解TaqMan探针）。作者还提供了纯化这种替代试剂的简单配方。他们预计，在资源匮乏或高需求的环境中，无论在何种监管框架下，研究人员都可以从Addgene或他们的实验室获得可用的结构，并开发自己的检测方法。

Abstract

Given the scale of the ongoing COVID-19 pandemic, the need for reliable, scalable testing, and the likelihood of reagent shortages, especially in resource-poor settings, we have developed a RT-qPCR assay that relies on an alternative to conventional viral reverse transcriptases, a thermostable reverse transcriptase / DNA polymerase (RTX)1. Here we show that RTX performs comparably to the other assays sanctioned by the CDC and validated in kit format. We demonstrate two modes of RTX use - (i) dye-based RT-qPCR assays that require only RTX polymerase, and (ii) TaqMan RT-qPCR assays that use a combination of RTX and Taq DNA polymerases (as the RTX exonuclease does not degrade a TaqMan probe). We also provide straightforward recipes for the purification of this alternative reagent. We anticipate that in low resource or point-of-need settings researchers could obtain the available constructs from Addgene or our lab and begin to develop their own assays, within whatever regulatory framework exists for them.

5. SARS-CoV-2 识别宿主受体蛋白的结构基础

Structural basis of receptor recognition by SARS-CoV-2

来源：Nature， accelerated article preview

发布时间：2020-03-30

来源链接：https://www.nature.com/articles/s41586-020-2179-y

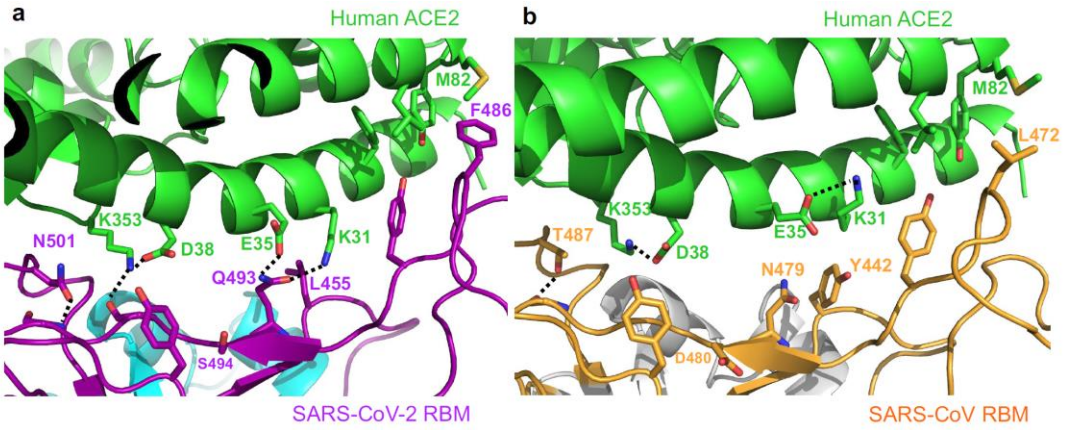
通讯作者：Fang Li

作者单位：美国明尼苏达大学兽医和生物医学系

编译：张智斌，指导老师徐菲

摘要：

理解病毒的受体识别机制是应对疫情的关键，因为病毒与受体的识别调控其传染性、发病机制和宿主范围。SARS-CoV-2和SARS-CoV识别相同的宿主受体——人源ACE2(hACE2)受体。本文解析了SARS-CoV-2受体结合结构域(RBD)和hACE2复合物的晶体结构。和SARS-CoV相比，SARS-CoV-2的RBD上用以结合hACE2的区域具有更致密的构象；此外，SARS-CoV-2 RBD上的几个氨基酸残基变化进一步稳定了RBD/hACE2界面上的两个病毒结合热点。SARS-CoV-2 RBD上的这些结构特点增强了它对hACE2结合的亲和力。此外，本文发现一种与SARS-CoV-2密切相关的蝙蝠冠状病毒——RaTG13,也以hACE2为受体。SARS-CoV-2、SARS-CoV和RaTG13这三种病毒在识别hACE2受体时的结构差异揭示了SARS-CoV-2从动物到人的潜在传播机理。因此，本文的研究结果对SARS-CoV-2受体识别的干预策略提供了一定指导。



SARS-CoV-2(a)和SARS-CoV(b)受体结合基序(RBM)和人ACE2受体相互作用界面的结构细节

Abstract:

A novel SARS-like coronavirus (SARS-CoV-2) recently emerged and is rapidly spreading in humans. A key to tackling this epidemic is to understand the virus' s receptor recognition mechanism, which regulates its infectivity, pathogenesis and host range. SARS-CoV-2 and SARS-CoV recognize the same receptor - human ACE2 (hACE2). Here we determined the crystal structure of the SARS-CoV-2 receptor-binding domain (RBD) (engineered to facilitate crystallization) in complex with hACE2. Compared with the SARS-CoV RBD, a hACE2-binding ridge in SARS-CoV-2 RBD takes a more compact conformation; moreover, several residue changes in SARS-CoV-2 RBD stabilize two virus-binding hotspots at the RBD/hACE2 interface. These structural features of SARS-CoV-2 RBD enhance its hACE2-binding affinity. Additionally, we show that RaTG13, a bat coronavirus closely related to SARS-CoV-2, also uses hACE2 as its receptor. The differences among SARS-CoV-2, SARS-CoV and RaTG13 in hACE2 recognition shed light on potential animal-to-human transmission of SARS-CoV-2. This study provides guidance for intervention strategies targeting receptor recognition by SARS-CoV-2.

6. SARS-CoV-2 直接损坏脾脏和淋巴结

The Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Directly Decimates Human Spleens and Lymph Nodes

来源：medrxiv

发布日期：2020-03-31

通讯作者：Yuzhang Wu

通讯作者单位：第三军医大学

链接：https://www.medrxiv.org/content/10.1101/2020.03.27.20045427v1

编译：蒋立春

通过对6名COVID-19病人的遗体的脾脏和淋巴节的研究，该研究揭示了SARS-CoV-2引起淋巴细胞减少的原因。在病人遗体中发现，SARS-CoV-2可以直接感染外周淋巴器官引起细胞坏死。免疫组化分析证明在脾脏和淋巴结组织定植的CD169+的巨噬细胞表达ACE2蛋白--病毒的潜在的宿主受体蛋白。免疫荧光染色证明病毒的核衣壳蛋白存在于ACE2阳性的细胞胞，CD169+的巨噬细胞中，但病毒的核衣壳蛋白不存在于脾脏和淋巴节的CD3+的T细胞或者B220+的B 细胞中。SARS-CoV-2感染引起严重的组织损伤，包括淋巴结的消失，脾脏节萎缩、组织细胞增

生以及淋巴细胞减少。原位TUNEL染色分析表明病毒感染导致了严重的淋巴细胞坏死，有可能是由于病毒的抗原诱导Fas的上调。更进一步，SARS-CoV-2激发巨噬细胞产生会导致淋巴细胞坏死的炎性细胞因子IL-6。

总结起来（总的来说），这些数据表明SARS-CoV-2通过感染组织定殖的CD169+巨噬细胞直接封阻（neutralize）了人体的脾脏和淋巴结。

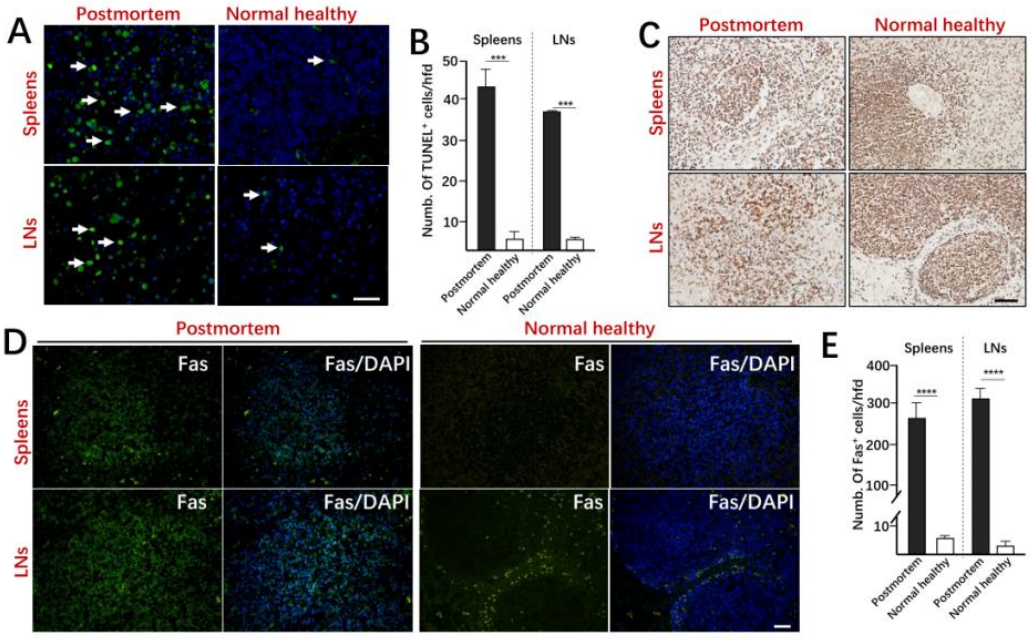


Figure 4 SARS-CoV-2 induces lymphocyte apoptosis *via* enhancing Fas signaling. (A) Cell apoptosis was detected by *in situ* TUNEL staining, **(B)** statistical analysis of apoptotic lymphocytes in sections from postmortem and normal healthy controls. **(C)** Immunohistochemistry detected FasL expression. **(D)** Immunofluorescent staining analyzed Fas expression. **(E)** Statistical analysis of Fas^+ cells in sections from postmortem and normal healthy controls. Scale bar= 100 μM, ***p<0.001, ****p<0.00001.

While lymphocytopenia is a common characteristic of patients infected by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the mechanisms responsible for this depletion are unclear. Through careful inspection of the spleens and lymph nodes (LNs) from six cases with postmortem examinations, we observed that SARS-CoV-2 could directly infect secondary lymphoid organs to induce cell death. Immunohistochemistry demonstrated ACE2 (angiotensin-converting enzyme 2), the potential receptor of SARS-CoV-2, expresses on tissue-resident CD169+ macrophages in spleens and LNs. Immunofluorescent staining confirmed that viral nucleocaspid protein (NP) can be found in ACE2+ cells, CD169+ macrophages, but not in CD3+ T cells or B220+ B cells in spleens and LNs. SARS-CoV-2 infection induces severe tissue damage including lymph follicle depletion, splenic nodule atrophy, histiocyte hyperplasia and lymphocyte reductions. Moreover, in situ TUNEL staining illustrated that viral infection

leads to severe lymphocyte apoptosis, which might be mediated by viral antigens inducing Fas upregulation. Furthermore, SARS-CoV-2 also triggers macrophages to produce IL-6, a proinflammatory cytokine that directly promotes lymphocyte necrosis. Collectively, these results demonstrate that SARS-CoV-2 directly neutralizes human spleens and LNs through infecting tissue- resident CD169+ macrophages.Collectively, these results demonstrate that SARS-CoV-2 directly neutralizes human spleens and LNs through infecting tissue- resident CD169+ macrophages.

7. 康复的 COVID-19 患者血清中的有效中和抗体是针对 SARS-CoV-2 spike 蛋白的保守线性表位

Potent neutralizing antibodies in the sera of convalescent COVID-19 patients are directed against conserved linear epitopes on the SARS-CoV-2 spike

来源：BioRxiv

发布时间：2020.3.30

链接：https://www.biorxiv.org/content/10.1101/2020.03.30.015461v1

通讯作者：Lisa F.P. Ng，明星研究生院执行董事，新加坡免疫网络高级首席研究员。研究专长是关节源性虫媒病毒的免疫学领域，包含对抗病毒感染发展预后和治疗策略，比如SARS and Zika

作者单位：新加坡免疫学网络微生物免疫实验室

编译：张鹏伟

摘要：

目前的SARS-CoV-2大流行需要快速鉴定免疫原性靶点，以设计有效的疫苗和血清学检测工具。在本文中，作者利用重叠的线性肽库和功能测定，在COVID-19康复患者的血清中，提出了两个通过中和抗体高度识别的spike糖蛋白免疫优势区。一种是对SARS-CoV-2高度特异性，另一种是潜在的泛冠状病毒靶点。

作者使用一个线性的B细胞肽库来评估这些血清的抗原靶点，这个B细胞肽库跨越了有五个重叠的混合肽的SARS-CoV或SARS-CoV-2的整个S蛋白。来自SARS-CoV-2s文库的两个不同的肽池，即混合肽S14和S21，被COVID-19患者的血清检测到，而没有被康复的SARS患者检测到。在混合肽S14和S21的单个肽中进一步评估分别缩小了肽的特定区域S14P5和S21P2。

Abstract：

The ongoing SARS-CoV-2 pandemic demands rapid identification of immunogenic targets for the design of efficient vaccines and serological detection tools. In this report, using pools of overlapping linear peptides and functional assays, we present two immunodominant regions on the spike glycoprotein that were highly recognized by neutralizing antibodies in the sera of COVID-19 convalescent patients. One is highly specific to SARS-CoV-2, and the other is a potential pan-coronavirus target.

we assessed the antigenic targets of these sera using a linear B-cell peptide library spanning the entire S protein of either SARS-CoV or SARS-CoV-2 with pools of five overlapping peptides. Two distinct peptide pools from SARS-CoV-2 S library, pools S14 and S21, were strongly detected by sera from COVID-19 patients, and not by recovered SARS patients. Further assessment of individual

peptides within pools S14 and S21 narrowed down the specific region of interest to peptides S14P5 and S21P2, respectively.

8. 针对 SARS-CoV-2（之前名为 2019-nCoV）感染的一种高效泛冠状病毒融合抑制剂，该抑制剂靶向能够高效介导膜融合的刺突蛋白

Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion

来源：Cell Research

发布时间：2020-03-30

来源链接：https://www.nature.com/articles/s41422-020-0305-x

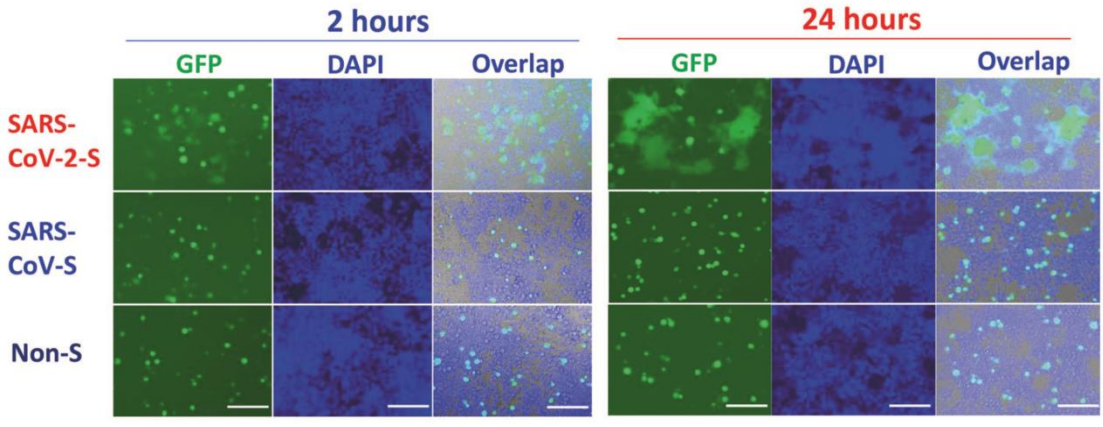
作者：复旦大学基础医学院、上海市公共卫生临床中心陆路和姜世勃团队，中科院生物物理所孙飞和朱赟团队，以及中科院武汉病毒所石正丽团队

编译：王玮

内容摘要：

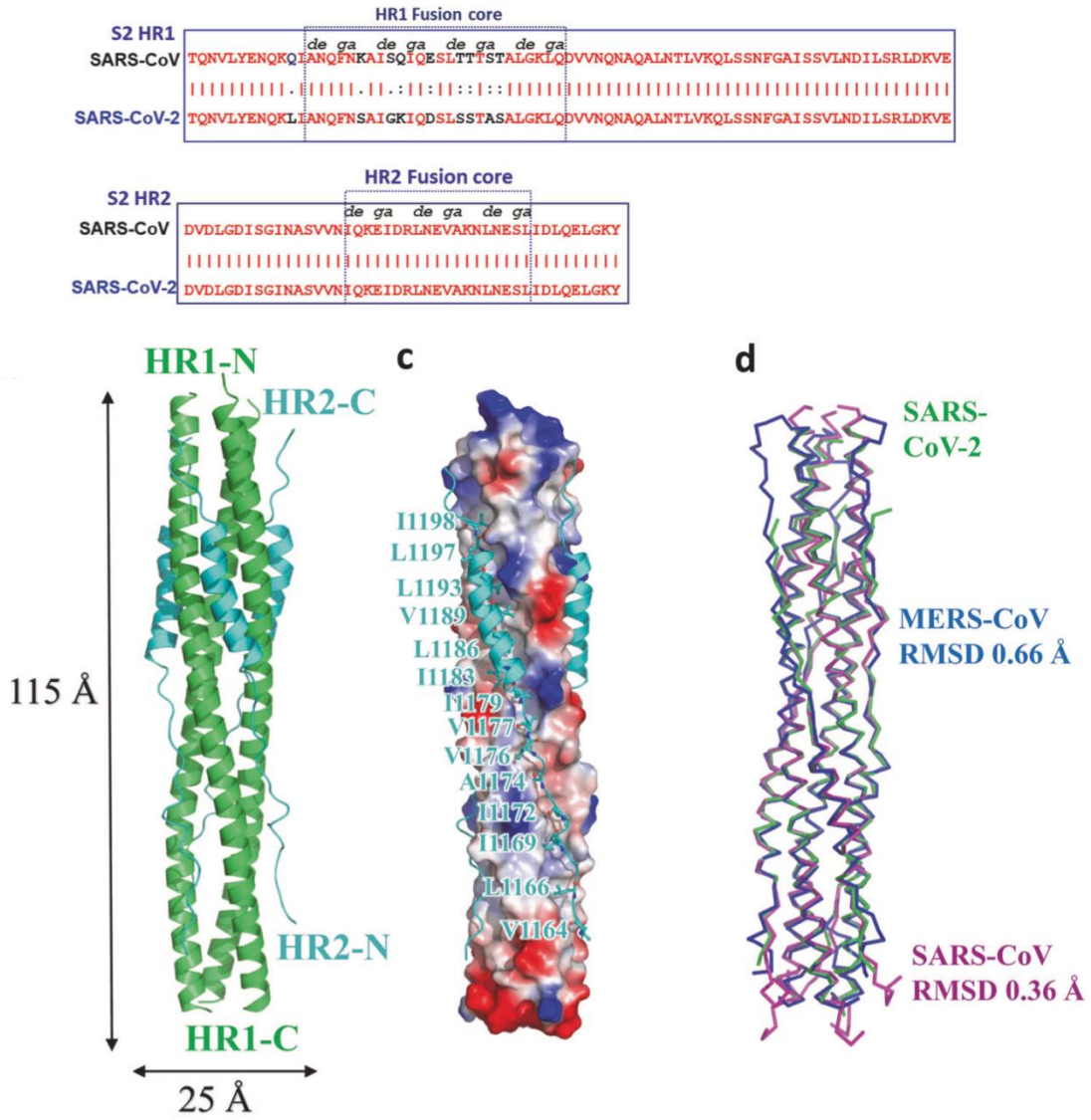
中国武汉市最近爆发的由SARS-CoV-2病毒感染引起的COVID-19已对全球公共卫生构成严重威胁。为了开发特异性针对冠状病毒的治疗和预防性药物，首先必须确定病毒感染的分子机制。

该研究首先建立了一种SARS-CoV-2刺突蛋白介导的细胞-细胞融合实验，发现SARS-CoV-2的细胞膜融合能力优于SARS-CoV。研究人员克隆了冠状病毒的刺突蛋白，并将其整合到细胞株系293T中。携带刺突蛋白的293T细胞，具备了新冠病毒的膜融合能力。将表达刺突蛋白的细胞和表达ACE2的细胞在合适的条件下培育一段时间之后，研究人员发现，如果刺突蛋白是SARS-CoV-2的，就会出现合胞体；如果刺突蛋白是SARS-CoV的，就没有合胞体；没有刺突蛋白或者ACE2，也不会形成合胞体（图一）。与SARS-CoV相比，SARS-CoV-2介导的膜融合能力要更强，进入细胞的效率也会更高。



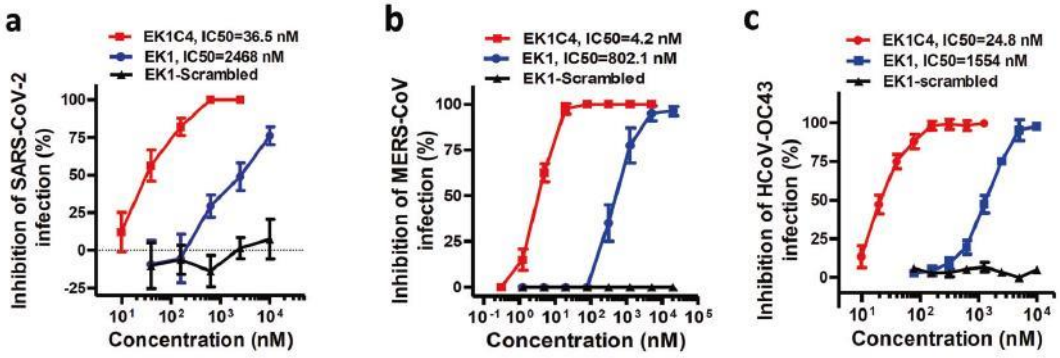
图一 病毒感染介导形成合胞体

SARS-CoV-2刺突蛋白的S2亚基中存在两个重要的保守重复氨基酸序列：HR1和HR2。它俩会纠缠在一起，形成一个叫6-HB的螺旋结构。该研究解析了6-HB的X射线晶体结构，发现HR1结构域中的几个突变氨基酸残基可能与HR2结构域的相互作用增强有关（图二）。HR1和HR2结构域之间的相互作用增强，可以进一步稳定6-HB结构，有可能会导致SARS-CoV-2感染能力增强。



图二 SARS-CoV-2与SARS-CoV HR1和HR2的区别，以及复合体的差异

陆路和姜世勃团队先前开发了一种泛冠状病毒融合抑制剂EK1，它以HR1结构域为靶点，可以抑制不同的人类冠状病毒的感染，包括SARS-CoV和MERS-CoV。该研究从EK1衍生出一系列脂肽，发现EK1C4是最有效的抗SARS-CoV-2刺突蛋白介导的膜融合和假病毒感染的融合抑制剂，其IC50s分别为1.3和15.8 nM，比EK1强241和149倍（图三）。EK1C4对SARS-CoV、MERS-CoV和SARSr-CoV等其他冠状病毒的膜融合和感染也有很强的抑制作用，并能有效抑制SARS-CoV-2等5种冠状病毒的复制。由于没有适合SARS-CoV-2感染的模式小鼠，研究人员用另一种人冠状病毒HCoV-OC43做了相关的研究。在HCoV-OC43感染前后鼻内EK1C4给药，可保护小鼠免受感染，提示EK1C4可能可用于预防和治疗目前流行的SARS-CoV-2和其他新发SARSr-CoV感染。



图三　EK1C4有效抑制冠状病毒感染

部分文字参考https://mp.weixin.qq.com/s/1FOvx5V3FX68nXfaUdCXtg

Abstract

The recent outbreak of coronavirus disease (COVID-19) caused by SARS-CoV-2 infection in Wuhan, China has posed a serious threat to global public health. To develop specific anti-coronavirus therapeutics and prophylactics, the molecular mechanism that underlies viral infection must first be defined. Therefore, we herein established a SARS-CoV-2 spike (S) protein-mediated cell–cell fusion assay and found that SARS-CoV-2 showed a superior plasma membrane fusion capacity compared to that of SARS-CoV. We solved the X-ray crystal structure of six-helical bundle (6-HB) core of the HR1 and HR2 domains in the SARS-CoV-2 S protein S2 subunit, revealing that several mutated amino acid residues in the HR1 domain may be associated with enhanced interactions with the HR2 domain. We previously developed a pan-coronavirus fusion inhibitor, EK1, which targeted the HR1 domain and could inhibit infection by divergent human coronaviruses tested, including SARS-CoV and MERS-CoV. Here we generated a series of lipopeptides derived from EK1 and found that EK1C4 was the most potent fusion inhibitor against SARS-CoV-2 S protein-mediated membrane fusion and pseudovirus infection with IC50s of 1.3 and 15.8 nM, about 241- and 149-fold more potent than the original EK1 peptide, respectively. EK1C4 was also highly effective against membrane fusion and infection of other human coronavirus pseudoviruses tested, including SARS-CoV and MERS-CoV, as well as SARSr-CoVs, and potently inhibited the replication of 5 live human coronaviruses examined, including SARS-CoV-2. Intranasal application of EK1C4 before or after challenge with HCoV-OC43 protected mice from infection, suggesting that EK1C4 could be used for prevention and treatment of infection by the currently circulating SARS-CoV-2 and other em

9. 利用互补的全基因组筛选技术在蝙蝠细胞中鉴定出 MTHFD1 可能是一个广谱抗病毒药的靶点

Orthogonal genome-wide screenings in bat cells identify MTHFD1 as a target of broad antiviral therapy

通讯作者：清华大学 Xu Tan，杜克大学（Duke University）Lin-fa Wang

链接：https://www.biorxiv.org/content/10.1101/2020.03.29.014209v1
编译：蒋立春

蝙蝠被认为是包括SARS,SARS-CoV-2在内几个主要动物来源病毒疫情爆发的源头。虽然蝙蝠的基因组序列研究表明其天然免疫系统有对应对病毒的适应性，仍然需要用功能基因组学研究来揭示蝙蝠可以耐受病毒感染的分子机制。

该研究中，来自清华大学、杜克大学、中国CDC等单位的研究者建立了大蝙蝠模式生物澳洲黑狐蝠的全基因组CRISPR和RNAi文库。研究者们用这两种互补的技术对澳洲黑狐蝠的细胞系进行腮腺炎和甲型流感的感染情况进行了筛选。两种技术都筛选到细胞内吞和蛋白质分泌这两条通路为病毒感染所必须。另外，在两个筛选中，研究者们发现了唯一一个共同的宿主基因MTHFD1。 MTHFD1是一个C-1-4氢叶酸合成酶。实验证明，除了在蝙蝠细胞中，该酶是病毒复制所必须的。该酶对于病毒在人细胞中得复制也一样是必须的。MTHFD1的抑制剂carolacton可以抑制包括SARS-CoV-2在内的多种RNA病毒的复制扩增。该研究提供了一个研究蝙蝠生物学的遗传学平台，找到了一个有潜力开发成为广谱抗病毒药物的药物靶点。

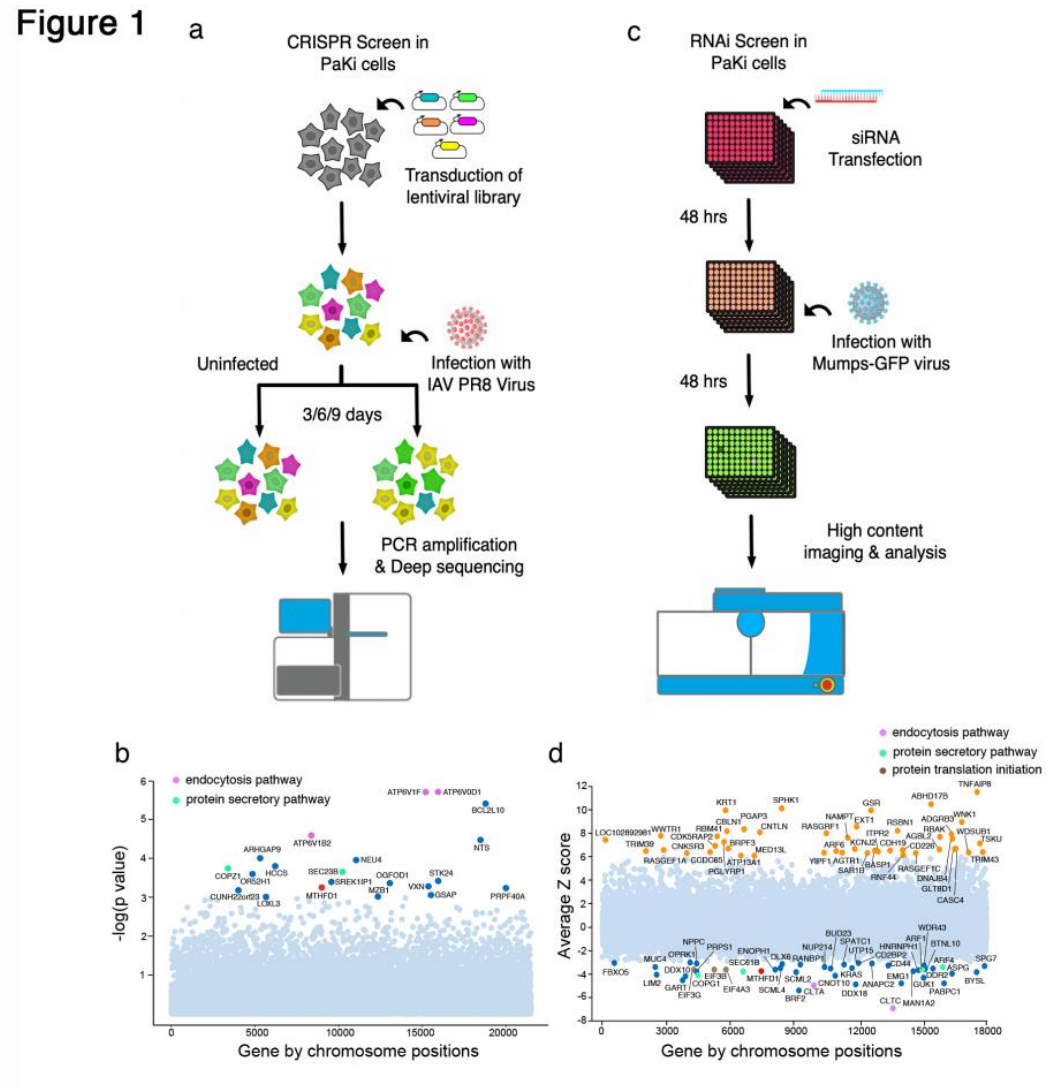


Figure1 Work flows and results of CRISPR and RNAi screens in 1 PaKi cells.

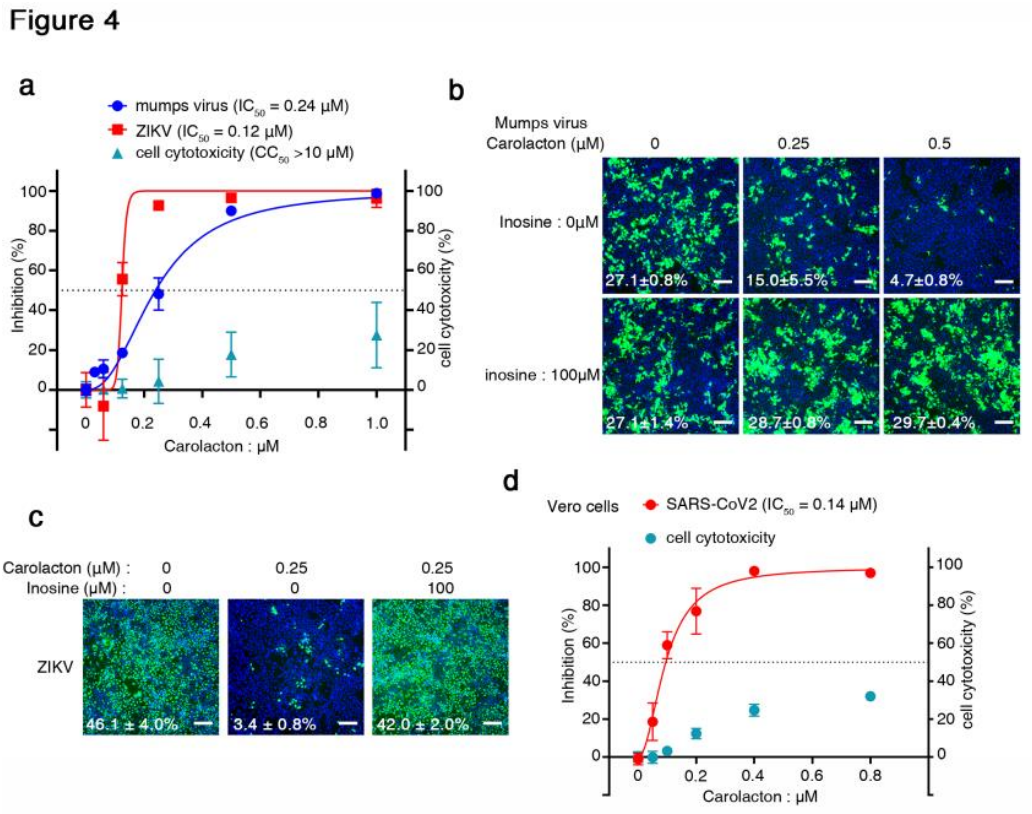


Figure4 MTHFD1 inhibitor carolacton can inhibit a number of RNA viruses including SARS-CoV-2.

Bats are responsible for the zoonotic transmission of several major viral diseases including the 2003 SARS outbreak and the ongoing COVID-19 pandemic. While bat genomic sequencing studies have revealed characteristic adaptations of the innate immune system, functional genomic studies are urgently needed to provide a foundation for the molecular dissection of the tolerance of viral infections in bats. Here we report the establishment and screening of genome-wide RNAi library and CRISPR library for the model megabat, Pteropus Alecto. We used the complementary RNAi and CRISPR libraries to interrogate Pteropus Alecto cells for infection with two different viruses, mumps virus and Influenza A virus, respectively. Screening results converged on the endocytosis pathway and the protein secretory pathway as required for both viral infections. Additionally, we revealed a general dependence of the C-1-tetrahydrofolate synthase gene, MTHFD1, for viral replication in bat cells as well as in human cells. MTHFD1 inhibitor carolacton potently blocked replication of several RNA viruses including SARS-CoV-2. Our studies provide a resource for systematic inquiry into the genetic underpinnings of bat biology and a potential target for developing broad spectrum antiviral therapy.

10. Covid-19 患者的肾素-血管紧张素-醛固酮系统的抑制剂

Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

来源：The newengland journal of medicine
发表时间：2020-3-31
链接：https://www.nejm.org/doi/full/10.1056/NEJMsr2005760?query=featured_home
作者：Muthiah Vaduganathan等
作者单位：Cardiovascular Division, Brigham and Women’s Hospital, and Harvard Medical School, Boston
编译：刘焕珍
摘要：
肾素-血管紧张素-醛固酮系统（RAAS）是一类优雅的血管活性肽，可协调人体生理学的关键过程。严重急性呼吸系统综合症冠状病毒1（SARS-CoV-1）和SARS-CoV-2，分别导致2002年至2004年的SARS流行和最近的2019年冠状病毒病（Covid-19）大流行，通过血管紧张素转换酶2（ACE2）与RAAS结合使用，该酶在生理上抵抗RAAS激活，但同时也是两种SARS病毒的受体。有人提出将SARS病毒与ACE2之间的相互作用作为其感染力的潜在因素，并且人们担心RAAS抑制剂的使用可能会改变ACE2，以及ACE2表达的变化是否可能是部分导致正在进行的Covid-19流行病的疾病毒力。实际上，一些媒体系统和卫生系统最近都要求在预防性和可疑的Covid-19方面停用ACE抑制剂和血管紧张素受体阻滞剂（ARB）。
考虑到ACE抑制剂和ARB在全球范围内的普遍使用，迫切需要在Covid-19患者中使用这些药物的指南。在这里，我们强调指出，在人体的数据太有限，无法支持或驳斥这些假设和担忧。具体而言，我们讨论了RAAS阻滞剂对人类ACE2水平和活性的不确定影响，并提出了另一种假设，即ACE2对肺损伤患者可能有益而不是有害。 我们还明确提出了这样的担忧，即在已知或疑似Covid-19的某些高风险患者中，RAAS抑制剂的停用可能对患者有害。

Abstract
The renin–angiotensin–aldosterone system (RAAS) is an elegant cascade of vasoactive peptides that orchestrate key processes in human physiology. Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2, which have been responsible for the SARS epidemic in 2002 to 2004 and for the more recent coronavirus disease 2019 (Covid-19) pandemic, respectively, interface with the RAAS through angiotensin-converting enzyme 2 (ACE2), an enzyme that physiologically counters RAAS activation but also functions as a receptor for both SARS viruses. The interaction between the SARS viruses and ACE2 has been proposed as a potential factor in their infectivity, and there are concerns about the use of RAAS inhibitors that may alter ACE2 and whether variation in ACE2 expression may be in part responsible for disease virulence in the ongoing Covid-19 pandemic. Indeed, some media sources and health systems have recently called for the discontinuation of ACE inhibitors and angiotensin-receptor blockers (ARBs), both prophylactically and in the context of suspected Covid-19.
Given the common use of ACE inhibitors and ARBs worldwide, guidance on the use of these drugs in patients with Covid-19 is urgently needed. Here, we highlight that the data in humans are too limited to support or refute these hypotheses and concerns. Specifically, we discuss the uncertain effects of RAAS blockers on ACE2 levels and activity in humans, and we propose an alternative hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury. We also explicitly raise the concern that withdrawal of RAAS inhibitors may be harmful in certain high-risk patients with known or suspected Covid-19.