新型冠状病毒信息简报

第 22 期（2020 年 4 月 9 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联合编译制作

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1. 2020年4月8日疫情

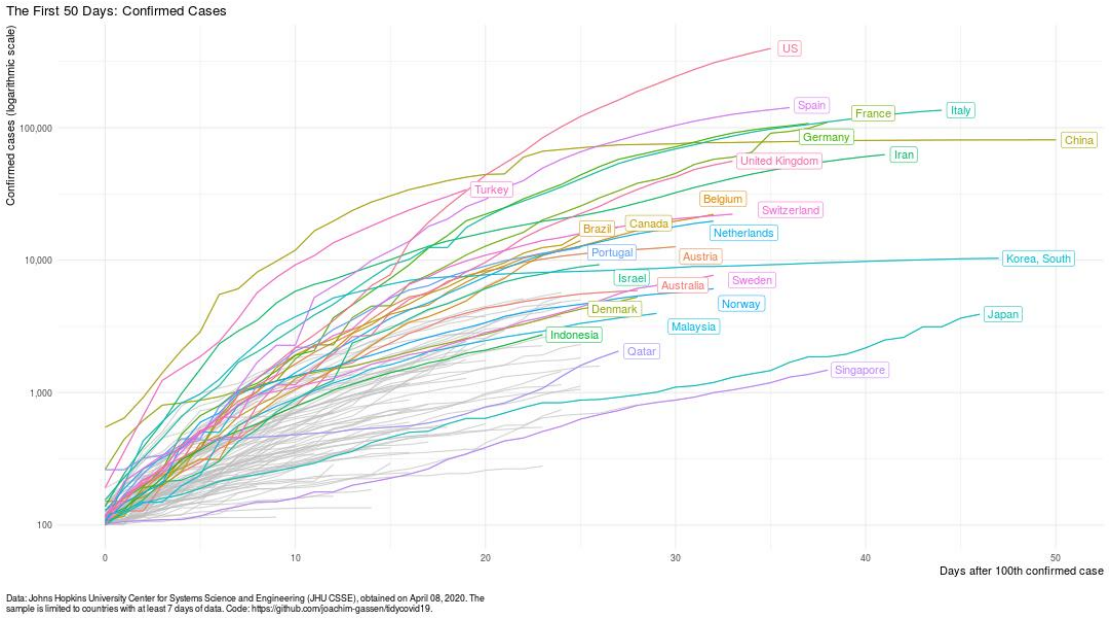
数据来源：WHO

发布时间：2020年4月8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4月8日全球累计确诊新型冠状病毒病人1353361例，当日新增确诊73639例，累计死亡79235例，当日新增死亡6695。

中国累计确诊83157例，累计死亡3342例，当日新增确诊86例，新增死亡2例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止4月8日北京时间下午4点）

全国新型冠状病毒肺炎新增确诊病例分布图（4月8日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 新闻：上科大等联合攻关团队科研成果荣登Nature——解析新冠病毒主蛋白酶三维结

构，发现候选药物

来源：Nature

发布时间：2020-04-09

链接：https://www.nature.com/articles/s41586-020-2223-y

编译:雷颖

北京时间4月9日下午5点，经国际权威学术刊物Nature诚邀约稿，上海科技大学饶子和/杨海涛团队与合作者组成的“抗新冠病毒攻关联盟”在该期刊上联合发表了新冠病毒的重要研究成果“Structure of Mpro from COVID-19 virus and discovery of its inhibitors”，率先在国际上成功解析新型冠状病毒关键药物靶点——主蛋白酶（Mpro）的高分辨率三维空间结构，并综合利用三种不同的药物发现策略，找到针对新冠病毒的潜在药物。

在从头设计的研究策略中，攻关“联盟”发现迈克尔受体N3是一个主蛋白酶的强效抑制剂，并率先解析了2.1Å的“主蛋白酶-N3”的高分辨率复合物结构（随后又提高至1.7Å），这也是世界上第一个被解析的新冠病毒蛋白质的三维空间结构。为方便相关的科技工作者第一时间开发以该酶为靶点的抗病毒药物，攻关“联盟”第一时间公开了研究成果，并在PDB蛋白质结构数据库（Protein Data Bank, PDB）公开了结构坐标。自1月26日起，团队已为国内外300多家高校、研究机构及企业的实验室直接提供了数据。该结构被PDB蛋白质结构数据库选为2020年2月的明星分子（February Molecule of the Month），并被PDB撰文报道。

此后，攻关“联盟”继续联合利用虚拟筛选和高通量筛选策略相结合的方式，在上海科技大学免疫化学研究所高通量筛选平台的协助下对酶促动力学相关参数及检测体系的微量化进行了快速优化，利用平台高通量筛选整合系统建立了针对该主蛋白酶在384微孔板中的的高通量筛选模型，最终对10000多个老药、临床药物以及天然活性产物进行筛选，发现了数种对主蛋白酶有显著抑制作用的先导药物，其中包括双硫仑（disulfiram）、卡莫氟（carmofur）、依布硒（ebselen）、紫草素（shikonin）、Tideglusib和PX-12等。后续的抗新冠病毒实验显示，依布硒和N3均能在细胞水平显著抑制新冠病毒的复制。值得一提的是，依布硒已用于治疗听力障碍等多种疾病的临床试验（完成临床二期），并具有很好的安全性表现。上述研究成果，为迅速开发具有临床潜力的抗新冠肺炎的药物奠定了重要基础。

A new coronavirus (CoV) identified as COVID-19 virus is the etiological agent responsible for the 2019-2020 viral pneumonia outbreak that commenced in Wuhan1–4. Currently there are no targeted therapeutics and effective treatment options remain very limited. In order to rapidly discover lead compounds for clinical use, we initiated a program of combined structure-assisted drug design, virtual drug screening and high-throughput screening to identify new drug leads that target the COVID-19 virus main protease (Mpro). Mpro is a key CoV enzyme, which plays a pivotal role in mediating viral replication and transcription, making it an attractive drug target for this virus5,6. Here, we identified a mechanism-based inhibitor, N3, by computer-aided drug design and subsequently determined the crystal structure of COVID-19 virus Mpro in complex with this compound. Next, through a combination of structure-based virtual and

high-throughput screening, we assayed over 10,000 compounds including approved drugs, drug candidates in clinical trials, and other pharmacologically active compounds as inhibitors of Mpro. Six of these compounds inhibited Mpro with IC50 values ranging from 0.67 to 21.4 μM. Ebselen also exhibited promising antiviral activity in cell-based assays. Our results demonstrate the efficacy of this screening strategy, which can lead to the rapid discovery of drug leads with clinical potential in response to new infectious diseases for which no specific drugs or vaccines are available.

3. 是否可以在消毒后重复使用N95口罩？能重复使用多少次？

来源：medRxiv

发布时间：2020-04-08

通讯作者：崔屹

通讯作者单位：Stanford University, USA

链接：https://www.medrxiv.org/content/10.1101/2020.04.01.20050443v1

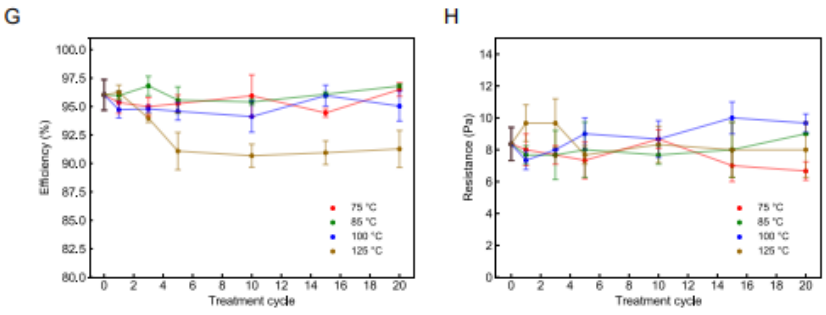
编译：宋珂

对于有机会接触到病毒的医护人员和公众来说，N95口罩能够为其提供基本的防护。然而COVID-19疫情的爆发导致了N95口罩严重短缺。因此，有必要测试安全重复使用口罩并保证个人防护水平的允许条件。作者发现，利用现代医院的基础设施，在各种湿度条件下（75° C时，最高相对湿度为100%RH），采用低于100° C的高温；或紫外线（UV）辐照，是最有效的口罩消毒、重复使用的处理方法（最多重复使用达20次），纤维对颗粒的过滤效率仍大于等于95%。需要谨慎选用液体和蒸气的消毒的方法，由于蒸汽、酒精和漂白剂均会导致过滤效率下降，使用这样处理过的口罩易受到病毒气溶胶的攻击。

表1. 一次消毒处理后，熔喷纤维（N95口罩材料，不是N95口罩）的过滤效果

Treatment	Mode of application	Treatment time (min)	Filtration efficiency (%)	Pressure drop (Pa)
Initial samples			96.52 ± 1.37	8.7 ± 1.0
Dry heat (75 °C)	Static-air oven	30	96.21	7.00
Steam	Beaker of boiling water	10	94.74	8.00
Ethanol (75%)	Immersion and air dry	Until dry	56.33	7.67
Chlorine-based (2%)	Light spray and air dry	5	73.11	9.00
UVGI (254 nm, 17 mW/cm^2)	Sterilization cabinet	30	95.50	7.00

图 4. RH<30%时，各温度下消毒处理20次后的过滤效果（G）效率（H）压力差



Abstract: The Coronavirus Disease 2019 (COVID-19) pandemic has led to a major shortage of N95 respirators, which protect healthcare professionals and the public who may come into contact with the virus. It is necessary to determine the conditions that would allow the safe reuse respirators and personal

protection in this crisis. We found that heating (<100 °C) under various humidities (up to 100% RH at 75 °C) and ultraviolet (UV) irradiation were the most promising candidates for mask reuse in the modern hospital infrastructure (up to 20 cycles), when tested on a fabric with particle filtration efficiency ≥95%. Treatments involving certain liquids and vapors may require caution, as steam, alcohol, and bleach all led to degradation in filtration efficiency, leaving the user vulnerable to viral aerosols.

4. 使用医院标准消毒技术进行N95口罩消毒

来源：medRxiv
发布时间：2020-04-08
通讯作者：Jay Krishnan
通讯作者单位：University of Manitoba, Canada
链接：https://www.medrxiv.org/content/10.1101/2020.04.05.20049346v1
编译：宋珂

为应对COVID-19疫情，全球都出现了个人防护用品严重短缺的局面。在某些情况严重的国家，N95口罩不得不采用配给制供应，医护人员也必须延长口罩的使用时间。本文中，作者针对4个不同品牌的N95口罩，以SARS-CoV-2或水疱性口炎病毒（VSV）作为测试样本，对比了4种不同的消毒方法，包括：高压灭菌器处理，环氧乙烷气体，雾化的离子化过氧化氢和过氧化氢蒸汽的消毒效果。作者还进一步测试了在承受多次消毒后，口罩能否保持结构和功能的完整性。结果显示，使用上述4种方法处理一次，都可以有效地对口罩进行消毒，并且不会导致结构和功能的损坏。使用过氧化氢蒸汽消毒方式，可以保证口罩至少循环使用5次。值得注意的是，对于3褶样式的口罩，采用标准的高压灭菌器消毒，在保证结构和功能完整性的同时，可以重复使用至少10次。但是，模具成型的N95口罩只能承受1次。由于卫生机构中普遍配备有高压灭菌设备，使用其对N95口罩进行消毒和重复使用，在全球范围内都是行之有效的方法。

表 1. 消毒效果

	Mean virus recovery post-decontamination ($LogTCID_{50}$ ± SD) compared to drying controls						
	Mask	Positive Control	Autoclave	Positive Control	EtO	iHP	VHP
			Treated		Treated	Treated	Treated
VSV	3M 1860	ND	ND	6.1 ± 0.3	0	0	0
	3M Aura 1870	ND	ND	6.5 ± 0.8	0	0	0
	3M Vflex 1804	ND	ND	6.4 ± 0.2	0	0	0
	AO Safety 1054	ND	ND	6.5 ± 0.3	0	0	0
SARS-CoV-2	3M 1860	5.2 ± 0.6	0	ND		ND	0
	3M Aura 1870	5.2 ± 0.6	0	ND		ND	0
	3M Vflex 1804	6.0 ± 0.7	0	ND		ND	0
	AO Safety 1054	6.3 ± 0.7	0	ND		ND	0

注：EtO（环氧乙烷气体），iHP（雾化的离子化过氧化氢），VHP（过氧化氢蒸汽）
ND = not done, 0 = no growth
Positive Control: small coupons cut from the masks were inoculated with virus on their exterior and allowed to dry for 1-2 hours

Abstract: The response to the COVID19 epidemic is generating severe shortages of personal protective equipment around the world. In particular, the supply of N95 respirator masks has become severely depleted with supplies having to be rationed and health care workers having to use masks for prolonged periods in

many countries. We sought to test the ability of 4 different decontamination methods including autoclave treatment, ethylene oxide gassing, ionized hydrogen peroxide fogging and vaporized hydrogen peroxide exposure to decontaminate 4 different N95 masks of experimental contamination with SARS-CoV-2 or vesicular stomatitis virus as a surrogate. In addition, we sought to determine whether masks would tolerate repeated cycles of decontamination while maintaining structural and functional integrity. We found that one cycle of treatment with all modalities was effective in decontamination and was associated with no structural or functional deterioration. Vaporized hydrogen peroxide treatment was tolerated to at least 5 cycles by masks. Most notably, standard autoclave treatment was associated with no loss of structural or functional integrity to a minimum of 10 cycles for the 3 pleated mask models. The molded N95 mask however tolerated only 1 cycle. This last finding may be of particular use to institutions globally due to the virtually universal accessibility of autoclaves in health care settings.

5. 25例出院患者COVID-19 RT-PCR检测再次阳性

PCR Assays Turned Positive in 25 Discharged COVID-19 Patients

来源：Clinical Infectious Diseases

发布时间：2020-4-8

链接：https://doi.org/10.1093/cid/ciaa398

通讯作者：Yanchao Pan

作者单位：深圳市第三人民医院传染病诊疗研究实验室

编译：孔娟

摘要：

研究者报告了出院后COVID-19患者中有14.5%（25/172）的RT-PCR检测再次阳性，进一步研究了实验室参数与治疗持续时间（r = -0.637; p = 0.002）和病毒复发时间（r = 0.52; p = 0.008）之间的相关性。

文中报道出院后再次检测阳性的25例患者其中24例首次发病时为非重症型，在住院期间均接受利托那韦/洛匹那韦和IFN-α的治疗，潜在的抗病毒治疗时间为13.33±3.93天，实验室参数与其他147例患者无明显差异。再次入院时，只有8 患者(32%)有轻度咳嗽。12例患者的原病变较出院前有所改善，另外8例患者的原病变较出院前无恶化。在平均2.73天的再次住院期间，鼻咽拭子和泄殖腔拭子标本中病毒基因检测的逆转录聚合酶链反应结果均为阴性。

相关分析表明，与持续阴性的147名出院者不同的是这25名患者(r=-0.637，p=0.002)的出院前血清D-二聚体水平与治疗持续时间之间存在显著的负相关，此外，这25名患者出院前的淋巴细胞浓度与病毒再次出现的时间间隔显著正相关(r=0.52，p=0.008)。

文中指出间隔24小时的两次阴性逆转录聚合酶链反应检测可能不足以评估病毒清除率。重复的RT-PCR反应检测间隔延长，如48小时，这是至关重要的，以确保病毒实际上已经清除，出院的病人不再传播病毒。另一方面，作者建议某些免疫学指标，如D-二聚体、绝对淋巴细胞计数，甚至抗体试验都应与RT-PCR阴性试验相结合以确保受感染患者完全康复并可以出院。

Abstract

We report the observation that 14.5% of COVID-19 patients had positive RT-PCR

testing again after discharge. We describe correlations between laboratory parameters and treatment duration (r= -0.637; p=0.002) and time to virus recrudescence (r= 0.52; p=0.008) respectively, suggesting the need for additional measures to confirm illness resolution in COVID-19 patients Subsequently, correlation analysis indicated that there was a significant inverse correlation existed between serum D-Dimer level before discharging and the duration of treatment in these 25 patients (r=-0.637, p=0.002), instead of the rest 147 patients. Furthermore, lymphocyte concentrations before these 25 patient leaving the hospital were significantly positively correlated (r=0.52, p=0.008) with the time interval for virus reappearing.

导读：由于全球感染人数急剧增加，超过100万，给检测带来巨大挑战。全球各地科学家都在考虑将样品组成样品池以扩大检测能力，降低费用的方法。

6. LAMP-Seq：利用压缩条码空间进行人群大规模COVID-19诊断

LAMP-Seq: Population-Scale COVID-19 Diagnostics Using a Compressed Barcode Space

来源：bioRxiv，预印本

发布时间：2020-04-08

链接：https://www.biorxiv.org/content/10.1101/2020.04.06.025635v1

通讯作者及单位：张锋（Broad Institute of MIT and Harvard Cambridge）

编译：宋张悦

内容摘要：

早期的证据表明，隔离措施可以减缓COVID-19的指数级传播，但这些措施给社会带来了巨大的负担。而且一旦隔离限制被取消，指数级的传播可能会重新出现。有人提出，大规模的检测可以帮助打破隔离和传播的循环，但目前的检测方法无法进行如此大规模的处理。张锋团队在本文中提出了LAMP-Seq——是一种条形码标记的反转录环介导的等温扩增(RT-LAMP)方法，可以显著降低大规模检测的成本和复杂性。

在这一方法中，单个样本在一个加热温度下反应，产生条形码标记的扩增子，这些扩增子被转运到一个测序中心，混合后一起分析，可以实现大规模并行深度测序和标准计算分析，显著降低成本和人力。文中介绍实现大规模测序可以使用Illumina NextSeq测序仪，另外，作者还建议如果只是测试方法或小规模样本可以使用MiSeq测序仪。LAMP-Seq的步骤及原理如图1所示。

研究人员估计，根据现有产品的列表价格(不包括人工和仪器成本)，每个样品的成本将低于7美元（详细如图2所示），通过酶的优化生产，有可能进一步降低4倍的成本。鉴于新一代测序的低成本和可扩展性，研究人员认为这种方法可以通过现有的测序基础设施，合理地扩展规模，每天分析数百万个样本。

注：本文中的方法在含有SARS-CoV-2 N-基因的质粒中进行实验，未通过临床样本验证。为了促进与感兴趣人士的合作，共同推进抗击当前冠状病毒大流行的斗争，本文的研究人员在www.LAMP-Seq.org上建立了一个公共论坛。

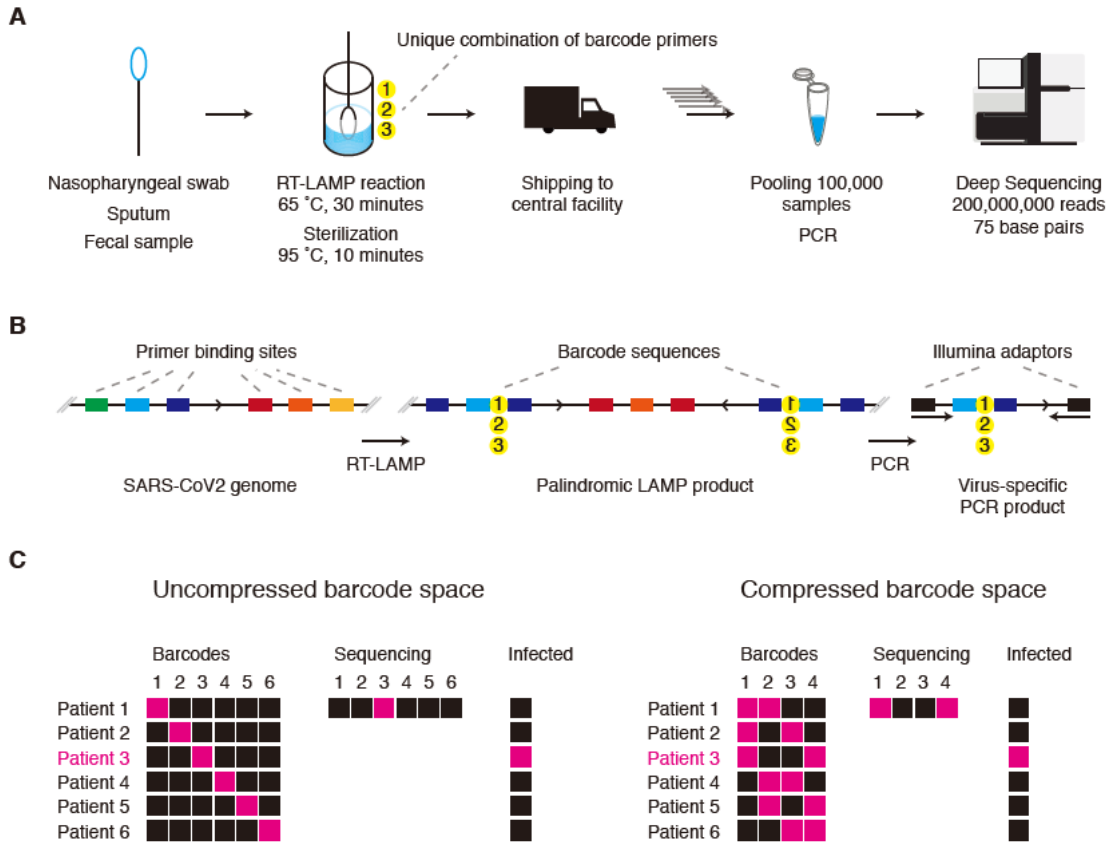


图1. LAMP-Seq的步骤及原理示意图。(A) LAMP-Seq的步骤概要。(B)预期的酶促反应和反应产物的示意图。(C)压缩条码空间的示意图，通过组合条形码可标记数百万个样品，同时最大限度地减少条形码引物的使用数量。

Item	Cost per sample
Matrix tubes	0.5 $
Bst 3.0 polymerase	5.68 $
Pipette tips	0.5 $
Pooling containers	0.02 $
PCR reagents	0.006 $
Sequencing kits	0.02 $
Computation power	0.1 $
TOTAL	6.83 $ / sample

图2. LAMP-Seq的单个样本成本核算

Abstract

The ongoing COVID-19 pandemic has already caused devastating losses. Early evidence shows that the exponential spread of COVID-19 can be slowed by restrictive isolation measures, but these place a tremendous burden on society. Moreover, once these restrictions are lifted, the exponential spread is likely to re-emerge. It has been suggested that population-scale testing can help break the cycle of isolation and spread, but current detection methods are not

capable of such large-scale processing. Here we propose LAMP-Seq, a barcoded Reverse-Transcription Loop-mediated Isothermal Amplification (RT-LAMP) protocol that could dramatically reduce the cost and complexity of population-scale testing. In this approach, individual samples are processed in a single heat step, producing barcoded amplicons that can be shipped to a sequencing center, pooled, and analyzed en masse. Using unique barcode combinations per sample from a compressed barcode space enables extensive pooling, significantly reducing cost and organizational efforts. Given the low cost and scalability of next-generation sequencing, we believe that this method can be affordably scaled to analyze millions of samples per day using existing sequencing infrastructure.

7. SARS-CoV-2通过spike蛋白介导的膜融合感染T淋巴细胞

SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion

来源：Cellular & Molecular Immunology

发表时间：2020.4.7

链接：https://www.nature.com/articles/s41423-020-0424-9

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编译：张丽双

摘要：

众所周知，SARS-CoV-2可以通过spike蛋白结合ACE2感染人体细胞，同时T细胞减少是COVID-19的一个常见临床特征，那么ACE2表达极低的T细胞是否可以被SARS-CoV-2感染，过程是怎样的，这篇文章就回答了这个问题。根据假病毒和活病毒感染的结果，证明了：（1）SARS-CoV-2可以感染T细胞，但基本不能复制，类似于MERS-CoV；（2）SARS-CoV-2通过受体依赖、S蛋白介导的膜融合感染T细胞；（3）EK1肽（已被报道能通过与HR1结合形成6-HB，阻断spike蛋白介导的膜融合）可以抑制T细胞感染。由于作者观察到hACE2在T细胞中的表达水平很低，这里进一步提出一种新的受体可能介导SARS-CoV-2进入T细胞，如T淋巴细胞表面的CD147，这是最近报道的SARS-CoV-2的一种新的侵袭途径。

Abstract

Based on the results of pseudovirus and live virus infection, here we proved that (1) SARS-CoV-2 could infect T cells, (2) SARS-CoV-2 infected T cells through receptor-dependent, S protein-mediated membrane fusion, and (3) infection could be inhibited by EK1 peptide. However, we observed a very low expression level of hACE2 in T cells; therefore, we further proposed that a novel receptor might mediate SARS-CoV-2 entry into T cells. Similar to MERS-CoV, SARS-CoV-2 infection of T cells is abortive.

8. 在中国武汉地区COVID-19患者急性肾损伤：同一中心回顾性观察研究

Acute kidney injury in patients hospitalized with COVID-19 in Wuhan, China: A single-center retrospective observational study

来源：medRxiv

发布时间：2020.4.6

链接：https://www.medrxiv.org/content/10.1101/2020.04.06.20055194v1
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编译：张鹏伟
内容摘要：
背景：肾脏可能受到冠状病毒2019疾病（COVID-19）的影响。本研究评估了COVID-19患者急性肾损伤（AKI）的预测因子和预后。
方法：这项观察研究从2020年1月5日至3月8日包括武汉汉口医院所有临床确诊的COVID-19患者的数据。数据来自临床和实验室记录。后续调查于2020年3月8日进行审查。
这是同一中心的回顾性观察研究。纳入的患者从2020年1月5日至3月8日在武汉汉口医院住院的临床确诊COVID-19的患者。我们使用logistic回归模型评估AKI和COVID-19疾病的发病率变化与临床结果之间的关系。
结果：共有287例患者，55例有AKI，232例无AKI，纳入分析。与无AKI的患者相比，AKI患者年龄较大，以男性为主，更易出现缺氧，并有高血压和脑血管疾病。此外，AKI患者的白细胞、D-二聚体、天冬氨酸转氨酶、总胆红素、肌酸激酶、乳酸脱氢酶、降钙素原、C-反应蛋白水平较高，高血钾患病率较高，淋巴细胞计数较低，胸部CT评分较高。1期AKI发生率为14.3%，2、3期AKI发生率为4.9%。AKI患者的死亡率明显较高。
结论：AKI是COVID-19的重要并发症。年龄大、男性、多发性既往合并症、淋巴细胞减少、感染指标增加、D-二聚体升高、心和肝功能受损是AKI的危险因素。进展到2期或3期的AKI患者死亡率较高。对COVID-19患者，AKI的预防和肾功能的监测是非常重要的。
Abstract
Background: The kidney may be affected in coronavirus-2019 disease (COVID-19). This study assessed the predictors and outcomes of acute kidney injury (AKI) among individuals with COVID-19.
Methods: This observational study, included data on all patients with clinically confirmed COVID-19 admitted to Hankou Hospital, Wuhan, China from January 5 to March 8, 2020. Data were extracted from clinical and laboratory records. Follow-up was censored on March 8, 2020.
This is a single-center, retrospective, observational study. Patients clinically confirmed COVID-19 and admitted to Hankou Hospital, Wuhan, China from January 5 to March 8, 2020 were enrolled. We evaluated the association between changes in the incidence of AKI and COVID-19 disease and clinical outcomes by using logistic regression models.
Results: A total of 287 patients, 55 with AKI and 232 without AKI, were included in the analysis. Compared to patients without AKI, AKI patients were older, predominantly male, and were more likely to present with hypoxia and have pre-existing hypertension and cerebrovascular disease. Moreover, AKI patients had higher levels of white blood cells, D-dimer, aspartate aminotransferase, total bilirubin, creatine kinase, lactate dehydrogenase, procalcitonin, C-reactive protein, a higher prevalence of hyperkalemia, lower lymphocyte counts, and higher chest computed tomographic scores. The incidence of stage 1 AKI was 14.3%, and the incidence of stage 2 or 3 AKI was 4.9%. Patients with AKI had substantially higher mortality.
Conclusions: AKI is an important complication of COVID-19. Older age, male,

multiple pre-existing comorbidities, lymphopenia, increased infection indicators, elevated D-dimer, and impaired heart and liver functions were the risk factors of AKI. AKI patients who progressed to stages 2 or 3 AKI had a higher mortality rate. Prevention of AKI and monitoring of kidney function is very important for COVID-19 patients.

9. 和COVID-19相关的血浆中代谢组和脂质组学改变

Plasma Metabolomic and Lipidomic Alterations Associated with COVID-19

来源：medrxiv

发布时间：2020-04-07

通讯作者：You Shang, Xi Zhou等

通讯作者单位：华中科技大学同济医学院、武汉金银潭医院；武汉病毒所等

链接：https://www.medrxiv.org/content/10.1101/2020.04.05.20053819v1

编译：陈文章

本文采用代谢组和脂质组学的手段研究了新冠病人的血浆。新冠病人的病情从初期到严重期，发展非常迅速。我们对这个过程中的生理变化却了解很少。先前的研究表明EBOLA病人的代谢组和脂质组变化非常大。本文的研究也表明代谢组和脂质组变化很大，尤其同肝功能相关的。本文共研究了34个病人（其中9人最终不治，4个时间点；11人严重，14轻症，各两个时间点）和10个健康对照。病人来自金银潭医院。代谢物分子采用液质联用分析，偏最小二乘法((OPLS-DA)最后用来对病人正常人做预测。研究者鉴定了431和代谢物和698脂类分子。其中87个代谢物分子的丰度有明显变化。

研究者发现在9个死亡患者中，氨基酸的丰度在病人中明显降低（编译者注：我们4月8日简报中报道的西湖大学研究结果吻合）。氨基酸是免疫巨吞噬细胞用来对抗炎症感染的能量和物质，表明氨基酸被大量消耗，免疫系统是时处于激活状态。核酸和有机酸的代谢则比较复杂，部分丰度上调，而另外一部分丰度下调（比如次黄嘌呤）。后者表明次黄嘌呤-鸟嘌呤磷酸核糖转移酶在死亡患者中有严重的缺陷。氨基甲酰磷酸的下调表明肝功能严重受损。

此外，研究者还定量的比较了轻症和重症患者间的代谢组。大多数丰度产生变化的代谢物是丰度下调。此外，刚刚治愈患者的代谢组尚未回复正常。

总之：氨基酸，核酸，有机酸和碳水化合物的丰度都有大幅度下调；而同
甘油脂代谢相关的脂类分子的丰度却有所上调以保证身体所需的能量，最终也有利于病毒的复制。这表明新冠病毒有可能劫持了细胞的代谢。此外，本研究所发现的一些丰度明显变化的代谢物如L-苹果酸，木酮糖-5-磷酸，氨基甲酰磷酸，3-磷酸甘油，磷脂，溶血磷脂酰胆碱同病情变化有强相关性，而且同肝功能相关。L-苹果酸和氨基甲酰磷酸的下调会导致氨的不正常累积，造成病情恶化。嘌呤和甲状腺激素也有显著变化，妨碍肝功能。

此外，甘油磷脂的丰度有显著变化（编译者注：我们4月8日简报中报道的西湖大学研究结果吻合），作者认为会妨碍心血管功能。

Abstract

The pandemic of the coronavirus disease 2019 (COVID-19) has become a global public health crisis. COVID-19 is marked by its rapid progression from mild to severe conditions, particularly in the absence of adequate medical care. However, the physiological changes associated with COVID-19 are barely understood. In this study, we performed untargeted metabolomic and lipidomic analyses of plasma from a cohort of COVID-19 patients who had experienced

different symptoms. We found the metabolite and lipid alterations exhibit apparent correlation with the course of disease in these COVID-19 patients, indicating that the development of COVID-19 affected patient metabolism. Moreover, many of the metabolite and lipid alterations, particularly ones associated with hepatic functions, have been found to align with the progress and severity of COVID-19. This work provides valuable knowledge about blood biomarkers associated with COVID-19 and potential therapeutic targets, and presents important resource for further studies of COVID-19 pathogenesis

10. 真实世界数据表明靶向儿茶酚胺-细胞因子轴可能可以预防SARS-CoV-2引起的细胞因子风暴

Targeting the catecholamine-cytokine axis to prevent SARS-CoV-2 cytokine storm syndrome

来源：medrix

发布时间：2020-04-08

链接：https://www.medrxiv.org/content/10.1101/2020.04.02.20051565v1

通讯作者：Joshua T. Vogelstein, Susan Athey, Shibin Zhou, Chetan Bettegowda

通讯作者单位：The Johns Hopkins University, USA

编译：蒋立春

#However, given the cost, immunosuppression, and potential adverse reactions of tocilizumab, this strategy will likely be restricted to select patients in developed countries.

COVID-19导致的死亡看上去是由于急性呼吸窘迫综合征（ARDS）以及免疫失调引起的。逐渐有更多证据证明一部分病人的特征是细胞因子风暴，根据IL-6水平可以预测COVID-19的严重性和住院致死率。靶向炎症过激可能对降低COVID-19的病死率的一个关键因素。尽管目前已经有三个临床研究已经开始采用IL-6的抗体比如妥珠单抗来治疗COVID-19，有初步数据证明了其有效性。作者认为由于这个药物价格贵、会引起免疫抑制以及可能的副作用，这个药物在发展中国家的使用很可能会局限于少数病人。

作者之前的研究表明儿茶酚胺可以通过一个前馈作用自我放大一个依赖于alpha-1肾上腺素受体（α1-AR）的通路来促进免疫细胞产生IL-6以及其他细胞因子，从而加剧免疫损害（Nature. 2018 Dec; 564(7735): 273–277.）。预先给予小鼠拮抗α1-AR的药物哌唑嗪（prazosin）可以降低小鼠中儿茶酚和细胞因子的反应。这样处理过的小鼠在被给予超炎刺激时，生存率显著提高（图1）。为了研究α1-AR的拮抗剂对预防急性呼吸窘迫综合征（ARDS）出现不好结果中的可能作用，研究者们对住院急性呼吸窘迫综合征（ARDS）的病人进行了一个回溯性研究。作者从Truven Health MarketScan 研究数据库中找到了12673名年龄在45-64岁之间的急性呼吸窘迫综合征（ARDS）男性病人。这些病人中有1189（9.4%）在上一年中被医生开了α1-AR的拮抗剂药物。采用逻辑回归模型，研究者们发现之前服用过α1-AR的拮抗剂的ARDS病人使用介入性机械通气的概率更低，死亡率也更低（图2，adjusted odds ratio-AOR 0.80, 95%置信区间0.69-0.94, p=0.008）。

这些数据和临床前动物实验中的发现一致，支持将α1-AR的拮抗剂用在临床中以预防急性呼吸窘迫综合征ARDS和局部以及系统性免疫失调。研究者们建议通过开展随机临床试验来研究在症状加重之前给病人服用α1-AR拮抗剂（比如哌唑嗪）是否可以预防细胞因子风暴发生以此降低死亡率。

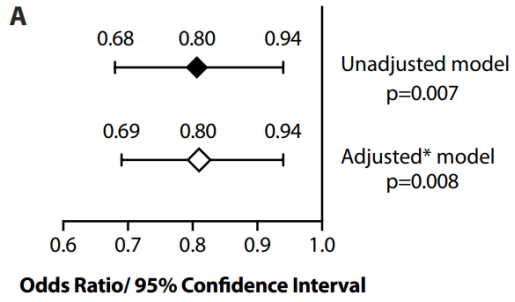
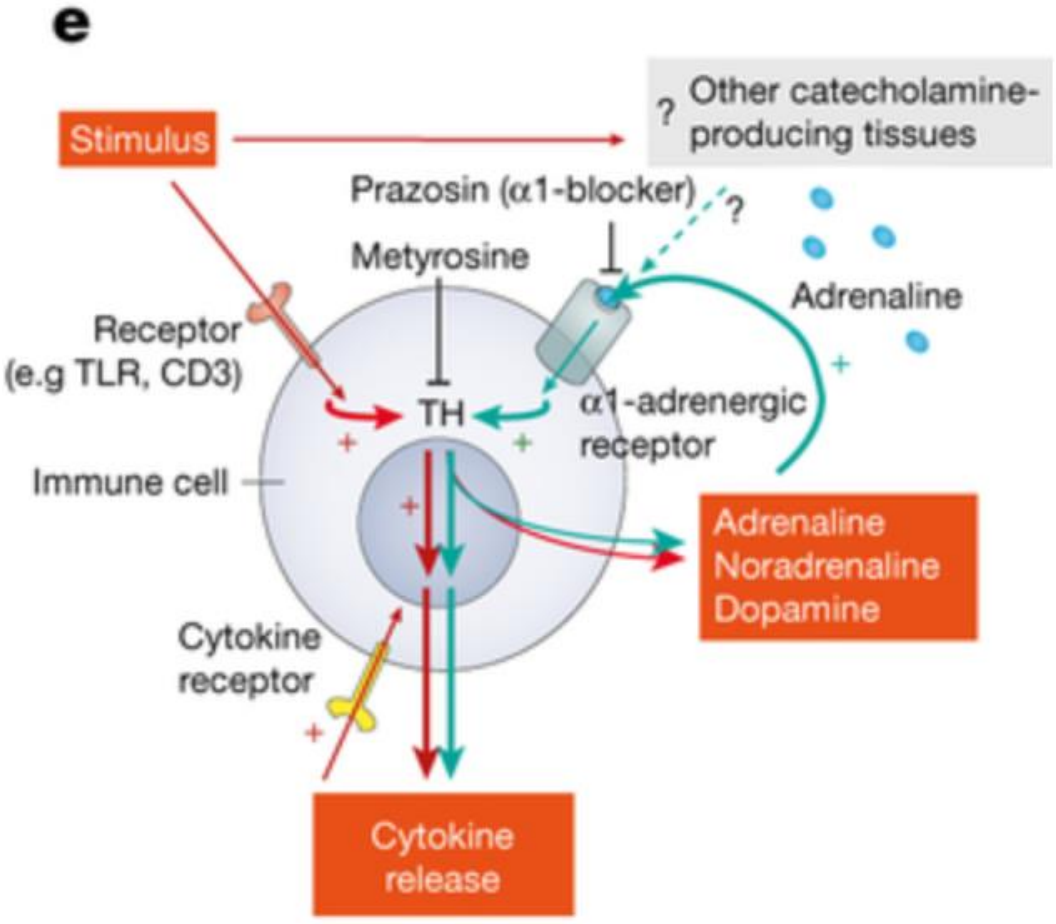


Figure 1. Logistic regression of the composite of invasive mechanical ventilation and in-hospital mortality

图一. 关于是否需要介入性机械通气以及住院期间病亡率的逻辑回归



图二Scheme showing how inhibition of the catecholamine pathway may reduce CRS. TLR, toll-like receptor. （Fig.5 Nature. 2018 Dec; 564(7735): 273–277.）

Abstract

The mortality of Coronavirus disease 2019 (COVID-19) appears to be driven by acute respiratory distress syndrome (ARDS) and a dysregulated immune response to SARS-CoV-2. Emerging evidence suggests that a subset of COVID-19 is characterized by the development of a cytokine storm syndrome (CSS), and interleukin (IL)-6 levels are predictors of COVID-19 severity and in-hospital mortality. Targeting hyper-inflammation in COVID-19 may be critical for

reducing mortality. Catecholamines enhance inflammatory injury by augmenting the production of IL-6 and other cytokines through a self-amplifying feed-forward loop in immune cells that requires alpha-1 adrenergic receptor (α1-AR) signaling. Prophylactic inhibition of catecholamine synthesis with the α1-AR antagonist prazosin reduced catecholamines and cytokine responses in mice, and resulted in markedly increased survival following various hyper-inflammatory stimuli.

These findings offer a rationale for studying α1-AR antagonists in the prophylaxis of patients with COVID-19-CSS and ARDS. As high infection rates threaten to overwhelm hospital capacity during this pandemic, preventative approaches that ameliorate COVID-19 severity and reduce excessive mortality are desperately needed. We hypothesize that treatment with prazosin of individuals who test positive for SARS-CoV-2 could reduce catecholamine surges, secondary cytokine dysregulation, and mortality. To investigate a potential role for α1-AR antagonists in preventing poor outcomes in ARDS, we conducted a retrospective analysis of hospitalized patients diagnosed with ARDS. Using data from the Truven Health MarketScan Research Database (2010-2017), we identified 12,673 men (age 45-64) with ARDS, of whom 1,189 patients (9.4%) were prescribed α1-AR antagonists in the previous year. Applying logistic regression models, we found that patients with prior use of α1-AR antagonists had lower odds of the composite of need for invasive mechanical ventilation and mortality compared to non-users (AOR 0.80, 95% CI 0.69-0.94, p=0.008). Mirroring findings from pre-clinical models, these data support a clinical rationale to study α1-AR antagonists in the prophylaxis of ARDS and states of local and systemic immune dysregulation. Prospective, randomized clinical trials of alpha-1 receptor antagonists (e.g. prazosin) administered prior to the onset of severe symptoms are needed to assess their efficacy in preventing CSS and reducing mortality in COVID-19.

11. Nelfinavir抑制SARS-CoV-2的体外复制

Nelfinavir inhibits replication of severe acute respiratory syndrome coronavirus 2 in vitro

来源：bioRxiv

发布时间：2020.4.6

链接：https://www.biorxiv.org/content/10.1101/2020.04.06.026476v1

通讯作者：Naoki Yamamoto日本著名艾滋病专家

作者单位：日本东京大学医学院

编译：张鹏伟

内容摘要：

2019年12月，在中国湖北省武汉市出现了严重急性呼吸综合症冠状病毒2（SARS-CoV-2）。到目前为止，还没有针对2019年冠状病毒病（COVID-19）的特异性治疗方法。因此，迫切需要寻找有效的抗病毒药物来治疗该病，并对几种已获批准的药物如lopinavir进行了评价。本文中，作者报道了一种HIV-1蛋白酶抑制剂nelfinavir，它能有效地抑制SARS-CoV-2

的复制。Nelfinavir 50%和90%的抑制有效浓度（EC50和EC90）分别为1.13μM和1.76μM，是包括lopinavir在内的9种HIV-1蛋白酶抑制剂中最低的。Nelfinavir血药浓度的峰谷值是该药EC50的3～6倍。这些结果表明，nelfinavir是治疗COVID-19的潜在候选药物，应在COVID-19患者中进行评估。

Abstract

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, Hubei Province, China. No specific treatment has been established against coronavirus disease-2019 (COVID-19) so far. Therefore, it is urgently needed to identify effective antiviral agents for the treatment of this disease, and several approved drugs such as lopinavir have been evaluated. Here, we report that nelfinavir, an HIV-1 protease inhibitor, potently inhibits replication of SARS-CoV-2. The effective concentrations for 50% and 90% inhibition (EC50 and EC90) of nelfinavir were 1.13 μM and 1.76 μM respectively, the lowest of the nine HIV-1 protease inhibitors including lopinavir. The trough and peak serum concentrations of nelfinavir were three to six times higher than EC50 of this drug. These results suggest that nelfinavir is a potential candidate drug for the treatment of COVID-19 and should be assessed in patients with COVID-19.

12. 开源/众包项目介绍

全球健康药物研发中心药物发现社区的公共信息共享门户和数据存储库

https://ghddi-ailab.github.io/Targeting2019-nCoV/

一个综合的COVID-19信息资源结库

https://covidbase.com/

主要针对帮助科学家进行科学攻关的志愿者（志愿者不一定需要是科学家）对接的平台

https://crowdfightcovid19.org/

github上COVID-19相关的开源社区项目

https://github.blog/2020-03-23-open-collaboration-on-covid-19/

实验方法开源项目

https://www.protocols.io/groups/coronavirus-method-development-community

COVID-19病人为主的CT影像数据

https://github.com/ieee8023/covid-chestxray-dataset

NIH2018年公布的32000张胸部CT图像数据

https://www.nih.gov/news-events/news-releases/nih-clinical-center-releases-dataset-32000-ct-images

https://nihcc.app.box.com/v/DeepLesion

从物资调度等方面帮助武汉抗疫的开源项目

https://community.wuhan2020.org.cn/zh-cn/

Wuhan2020社区：医院、工厂、采购等信息实时同部的数据服务。可以看到后续加入了帮助受疫情影响的企业和个人招聘和找工作等功能