新型冠状病毒信息简报

第 20 期（2020 年 4 月 7 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

联系人：蒋立春 jianglch@shanghaitech.edu.cn

内容介绍

分类	标题名称
疫情播报	1. 2020 年 4 月 6 日疫情
流行病学	2. ACE2 变异是意大利人群个体间变异和 COVID-19 易感性的基础 3. 病毒基因组学数据揭示华盛顿州 SARS-COV-2 的潜伏传播 4. Nextstrain，一个开源的病原基因组学数据展示工具和网站
疾病检测	5. 用血清学方法来检测人类血清中 SARS-CoV-2 的阳性情况 6. COVID-19 康复患者血清中抗 SARS-CoV-2 中和抗体的检测及其临床价值
临床病理	7. 重症 COVID-19 预后的病毒学和临床症状：中国武汉的一项回顾性观察研究
临床试验	8. 人工肝血液净化系统是一种有前途的抗细胞风暴靶向治疗 COVID-19的方法
基础研究	9. ACE2 和 TMPRSS2 基因主要表达在支气管瞬态分泌型细胞中 10. SARS-CoV-2 和 SARS-CoV 的细胞偏好性和药物敏感性存在差异

1. 2020年4月6日疫情

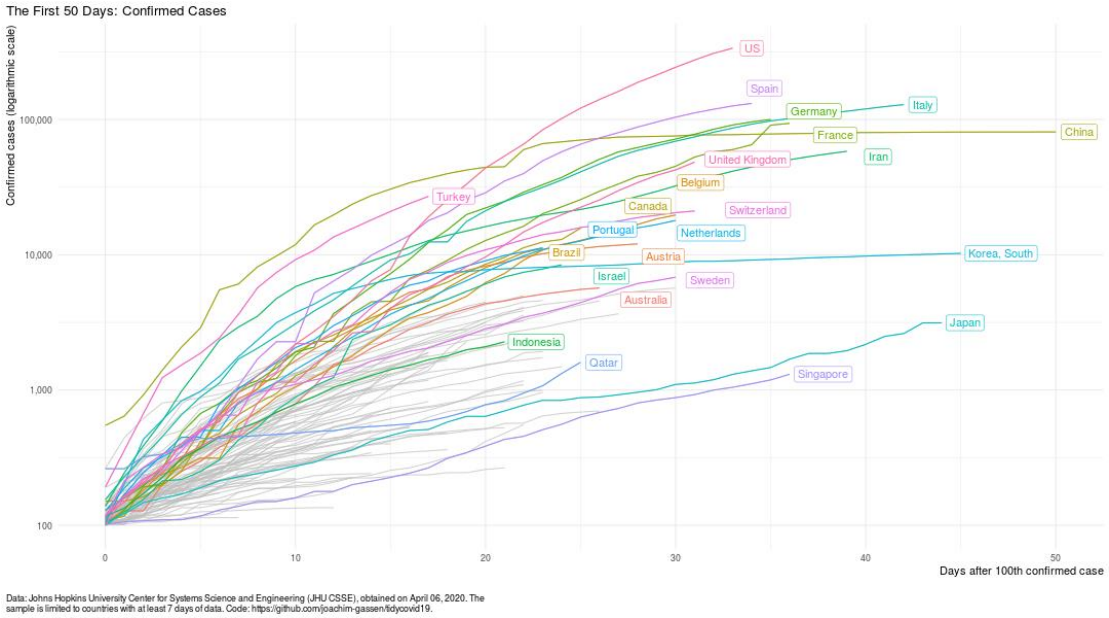
数据来源：WHO

发布时间：2020年4月6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6日全球累计确诊新型冠状病毒病人1210956例，当日新增确诊77200例，累计死亡67594例，当日新增死亡4810。

中国累计确诊83005例，累计死亡3340例，当日新增确诊75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6日北京时间下午4点）

2. ACE2变异是意大利人群个体间变异和COVID-19易感性的基础

ACE2 variants underlie interindividual variability and susceptibility to COVID-19 in Italian population

来源：medrxiv

发布时间：2020-04-06

来源链接：https://www.medrxiv.org/content/10.1101/2020.04.03.20047977v1

作者单位：锡耶纳大学，Azienda Ospedaliera Universitaria Senese等单位

通讯作者：Alessandra Renieri

编译:王玮

内容摘要：

目前，COVID-19已迅速蔓延到世界各地。意大利是第一个出现COVID-19疫情的欧洲国家，且与亚洲国家相比，临床的严重程度出乎意料。最近的研究表明，2019-nCov利用宿主受体即血管紧张素转换酶2（ACE2）作为宿主受体和宿主蛋白进行细胞表面结合和内化。因此，遗传易感性背景可能与个体间疾病易感性和严重性有关。利用意大利基因组网络（Network of Italian Genomes，NIG），该研究从5个不同的中心挖掘了6984 份意大利人外显子测序数据（基因组DNA来自外周血中的白细胞），寻找ACE2变异。该研究发现了一些对蛋白质稳定性有潜在影响的变异。其中的3种错义突变，p.Asn720Asp，p.Lys26Arg，p.Gly211Arg（MAF 0.002～0.015），这些突变在东亚人群中从未报道过，且有可能会干扰蛋白质的分

裂和稳定。该研究还发现一些可能干扰内化过程的罕见缺失突变和一个错义突变p.Trp69Cys，预测可能会干扰2019-nCov刺突蛋白的结合。这些发现表明，遗传易感性背景可能有助于找到与COVID-19相关的个体间的临床变异。基于遗传证据的风险评估能够为个性化的预防措施和治疗选择开辟道路。

编者注

Minor allele frequency，MAF，次等位基因频率。Hapmap计划将MAF>0.05的SNPs作为首要研究目标，MAF广泛应用于复杂疾病的全基因组关联研究。（来源百度）

4月4日简报中“意大利 COVID -19 疫情严重的情况下，ACE2 和 TMPRSS2 的变体和表达水平可能是导致性别和国家差异的候选因素”中指出，没有发现明显的证据表明ACE2与意大利人群的疾病严重程度/性别差异相关，但证明TMPRSS2水平和遗传变异可能是潜在的疾病调节剂。该文研究的是ACE2基因中MAF>0.05的变异。

Abstract

In December 2019, an initial cluster of unexpected interstitial bilateral pneumonia emerged in Wuhan, Hubei province. A human-to-human transmission was immediately assumed and a previously unrecognized entity, termed coronavirus disease 19 (COVID-19) due to a novel coronavirus (2019-nCov) was suddenly described. The infection has rapidly spread out all over the world and Italy has been the first European Country experiencing the endemic wave with unexpected clinical severity in comparison with Asian countries. It has recently been shown that 2019-nCov utilizes host receptors namely angiotensin converting enzyme 2 (ACE2) as host receptor and host proteases for cell surface binding and internalization. Thus, a predisposing genetic background can give reason for interindividual disease susceptibility and/or severity. Taking advantage of the Network of Italian Genomes (NIG), here we mined around 7000 exomes from 5 different Centers looking for ACE2 variants. A number of variants with a potential impact on protein stability were identified. Among these, three missense changes, p.Asn720Asp, p.Lys26Arg, p.Gly211Arg (MAF 0.002 to 0.015), which have never been reported in the Eastern Asia population, were predicted to interfere with protein cleavage and stabilization. Rare truncating variants likely interfering with the internalization process and one missense variant, p.Trp69Cys, predicted to interfere with 2019-nCov spike protein binding were also observed. These findings suggest that a predisposing genetic background may contribute to the observed inter-individual clinical variability associated with COVID-19. They allow an evidence-based risk assessment opening up the way to personalized preventive measures and therapeutic options.

3. 病毒基因组学数据揭示华盛顿州SARS-COV-2的潜伏传播

Cryptic transmission of SARS-CoV-2 in Washington State

来源：medrxiv

发布时间：2020.4.6

链接:http://medrxiv.org/cgi/content/short/2020.04.02.20051417

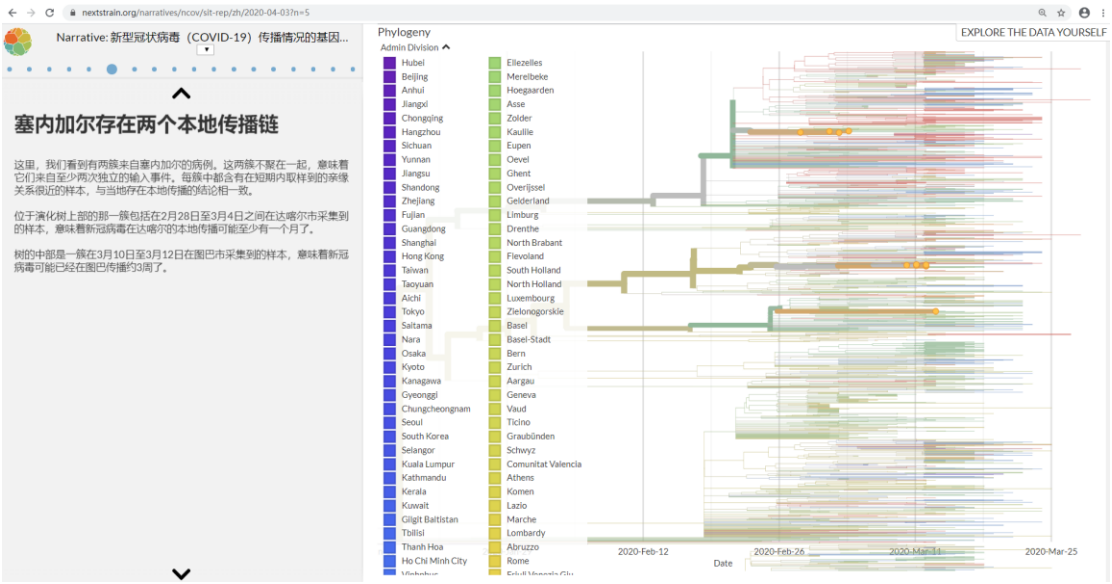
通讯作者：Trevor Bedford以及西雅图流感研究组成员Seattle Flu Study Investigators

通讯作者单位：Fred Hutchinson Cancer Research Center, Seattle, WA USA
编译：蒋立春
美国也是华盛顿州的第一例有记录的SARS-CoV-2病人是2020年1月15日从武汉旅行回去，并于1月19日去一家位于Snohomish县门诊并随后被确诊的病人。作者利用病毒基因组学数据重新构建了病毒的传播史。该研究分析了华盛顿州从2月20到3月15之间收集的感染病人的SARS-CoV-2病毒基因组数据。这段时间内绝大部分（346个中293例；85%）的SARS-CoV-2的感染看上去像一次1月晚些时间到2月早期的单一引入病例，在2月28日发现第一例社区传播比例之前已经在本地潜伏扩散了4-6周。根据基因组数据，我们推算病例的指数翻倍的时间是2.4到5.1天之间。这项研究表明了尽早鉴定病毒，广泛的进行检测以及被感染者立刻自我隔离的重要性。

Following its emergence in Wuhan, China, in late November or early December 2019, the SARS-CoV-2 virus has rapidly spread throughout the world. On March 11, 2020, the World Health Organization declared Coronavirus Disease 2019 (COVID-19) a pandemic. Genome sequencing of SARS-CoV-2 strains allows for the reconstruction of transmission history connecting these infections. Here, we analyze 346 SARS-CoV-2 genomes from samples collected between 20 February and 15 March 2020 from infected patients in Washington State, USA. We found that the large majority of SARS-CoV-2 infections sampled during this time frame appeared to have derived from a single introduction event into the state in late January or early February 2020 and subsequent local spread, strongly suggesting cryptic spread of COVID-19 during the months of January and February 2020, before active community surveillance was implemented. We estimate a common ancestor of this outbreak clade as occurring between 18 January and 9 February 2020. From genomic data, we estimate an exponential doubling between 2.4 and 5.1 days. These results highlight the need for large-scale community surveillance for SARS-CoV-2 introductions and spread and the power of pathogen genomics to inform epidemiological understanding.

4. Nextstrain，一个开源的病原基因组学数据展示工具和网站
https://nextstrain.org/
是一个实时追踪和展示病原体进化的工具和网站，共同创建者是上文的通讯作者Fred Hutchinson Cancer Research Center 的Trevor Bedford博士。
Nextstrain是一个开源的病原基因组学数据展示工具和网站。这个工具为公开数据提供强有力的分析和展示工具。目标是能能够让大家更好的理解感染性疾病的流行病学以及提高我们对疫情爆发的反应能力。
这也是一个典型的open science项目。数据来源于不同研究机构/医疗机构递交到GISAID数据库的病原物基因组。这个工具提供开源的数据分析和展示工具。科学家们可以根据分析来提出科学假设。这种open science的做法和前面一些科学家在基因组数据非常不足的情况下，提出不够成熟甚至可能是误导性的看法投递或者发表于学术杂志形成鲜明对比。

目前该网站提供即时的多语种情况报告
网站截屏范例：



以下是2020年4月3日该网站数据分析提供的主要观点

总结

我们发现了塞内加尔和刚果境内本地传播的证据。想要控制疫情在这些高风险地区的传播，相关国家必须迅速采取行动。我们目前还没有足够数据来评估非洲其他地区的情况。

日本近期的输入病例与邮轮旅行有关。

冰岛全面的测序工作凸显了旅行对疫情传播的影响，也揭示出奥地利境内很可能存在本地传播。

美国各地的样本在树上混杂排列，表明州与州之间的传播广泛存在。也有证据表明病毒在美国和加拿大之间跨境传播，另外，加拿大安大略省内也已经有本地传播的现象。

该工具通用于任何其他的有基因组数据的传染性疾病的研究。

5. 用血清学方法来检测人类血清中SARS-CoV-2的阳性情况

A serological assay to detect SARS-CoV-2 seroconversion in humans

来源：medRxiv

发表时间：2020-3-17

链接：https://www.medrxiv.org/content/10.1101/2020.03.17.20037713v1
通讯作者：Florian Krammer
作者单位：Icahn School of Medicine at Mount Sinai
编译：刘焕珍
文摘：
对于COVID19流行病来说，可以通过直接检测病毒遗传物质的分子来进行诊断，但是还需要对人的血液进行测试，以检测针对新型冠状病毒SARS-CoV-2的抗体。这种方法可以判断一个人过去是否曾被感染，这是因为人体保留了针对已被战胜的病原体的抗体，对医护人员进行筛查，以及鉴定已经免疫并且可以用于照顾感染患者的患者，从而最大程度地减少病毒传播给同事和其他患者的风险。作者开发出的SARS-CoV-2抗体测试的方法，该方法非常简单，可以迅速收集更多有关测试准确性和特异性的数据。作者首先设计了位于SARS-CoV-2外壳上的“刺突（spike）”蛋白的一个稍有变化的版本（这些变化使得这种蛋白可以更稳定地在实验室中使用），这种蛋白可以帮助这种病毒进入细胞，并且是人体对这种病毒产生的免疫反应中的一个关键靶标，这是因为人体会产生识别这种蛋白的抗体并标记这种病毒以便让它被破坏。他们还分离出刺突蛋白中的一个称为受体结合结构域（RBD）的短片段， SARS-CoV-2病毒利用RBD附着到它试图入侵的细胞上。他们随后使用细胞系来大量产生刺突蛋白的这种变化版本和RBD。在ELISA测试中，血液或血浆样品中的抗体在识别靶蛋白（此处为RBD或刺突蛋白）时会导致颜色变化。对三名确诊的COVID-19患者的四份血液样本以及在疫情爆发前存入的59份血清样本（作为对照）进行的初步测试表明该方法有效，这是因为SARS-CoV-2抗体与该测试中使用的蛋白结合。它仅对COVID-19患者显示阳性结果，而对所有对照血清均未显示。

Abstract
SARS-Cov-2 (severe acute respiratory disease coronavirus 2), which causes Coronavirus Disease 2019 (COVID19) was first detected in China in late 2019 and has since then caused a global pandemic. While molecular assays to directly detect the viral genetic material are available for the diagnosis of acute infection, we currently lack serological assays suitable to specifically detect SARS-CoV-2 antibodies. Here we describe serological enzyme-linked immunosorbent assays (ELISA) that we developed using recombinant antigens derived from the spike protein of SARS-CoV-2. These assays were developed with negative control samples representing pre-COVID 19 background immunity in the general population and samples from COVID19 patients. The assays are sensitive and specific, allowing for screening and identification of COVID19 seroconverters using human plasma/serum as early as 3 days post symptom onset. Importantly, these assays do not require handling of infectious virus, can be adjusted to detect different antibody types and are amendable to scaling. Serological assays are of critical importance to determine seroprevalence in a given population, define previous exposure and identify highly reactive human donors for the generation of convalescent serum as therapeutic. Sensitive and specific identification of Coronavirus SARS-Cov-2 antibody titers will also support screening of health care workers to identify those who are already immune and can be deployed to care for infected patients minimizing the risk of viral spread to colleagues and other patients.

6. COVID-19康复患者血清中抗SARS-CoV-2 中和抗体的检测及其临床价值

Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications

来源：medRxiv

发布时间：2020.04.06

链接：https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v1

通讯作者：黄竞荷

单位：上海公共卫生临床中心和医学分子重点实验室、复旦大学基础医学院

编译：孔娟

摘要：

近期，从SARS-CoV-2感染的康复病人体内分离出的多克隆抗体已经被用于治疗SARS-CoV-2感染，但还没有SARS-CoV-2特异性的nAbs被报道。本文研究者，使用了一种基于假型慢病毒载体的中和试验对175名COVID-19轻症患者恢复期血浆进行了抗SARS-CoV-2 中和抗体（NAbs）的检测。实验中以RBD、S1和S2蛋白为抗原进行酶联免疫吸附试验（ELISA）测定血浆中针对SARS-CoV2 S蛋白抗体,同时对其抗体的水平和动力学进行了检测。细胞水平结果显示血浆中SARS-CoV-2NAb能够特异性的抑制SARS-CoV-2对细胞的感染，但对SARS-CoV病毒没有抑制作用。此外血清学检测结果显示，在患病后的第10-15天，血清中检测到了SARS-CoV-2特异性抗体。NAb滴度与靶向S1、RBD和S2区域的抗S蛋白抗体有关，老年和中年患者的NAb滴度(P<0.0001)和S蛋白结合抗体(P=0.0003)明显高于青年患者。在这些患者中，有10例 NAb滴度低于最低检测水平(ID50:< 40)；两例显示出较高的NAb滴度ID50 :15989和21567。NAb滴度与血浆CRP水平呈正相关，与入院时患者淋巴细胞计数呈负相关。文中探索了与康复患者中NAbs水平相关的临床特征，其结果可能为SARS-CoV-2疫苗的开发提供一定的科学指导。

Abstract:

Plasma collected from 175 COVID-19 recovered patients with mild symptoms were screened using a safe and sensitive pseudotyped-lentiviral-vector-based neutralization assay. Spike-binding antibody in plasma were determined by ELISA using RBD, S1, and S2 proteins of SARS-CoV-2. The levels and the time course of SARS-CoV-2-specific NAbs and the spike-binding antibodies were monitored at the same time SARS-CoV-2 NAbs were unable to cross-reactive with SARS-CoV virus. SARS-CoV-2-specific NAbs were detected in patients from day 10-15 after the onset of the disease and remained thereafter. The titers of NAb among these patients correlated with the spike-binding antibodies targeting S1, RBD, and S2 regions. The titers of NAbs were variable in different patients. Elderly and middle-age patients had significantly higher plasma NAb titers (P<0.0001) and spike-binding antibodies (P=0.0003) than young patients. Notably, among these patients, there were ten patients whose NAb titers were under the detectable level of our assay (ID50: < 40); while in contrast, two patients, showed very high titers of NAb, with ID50 :15989 and 21567 respectively. The Nab titers were positive correlated with plasma CRP levels but negative correlated with the lymphocyte counts of patients at the time of admission, indicating an association between humoral response and cellular immune response.

7. 重症COVID-19预后的病毒学和临床症状：中国武汉的一项回顾性观察研究

Virologic and clinical characteristics for prognosis of severe COVID-19: a retrospective observational study in Wuhan, China

来源：medRxiv，预印本
发布时间：2020-04-06
来源链接：https://www.medrxiv.org/content/10.1101/2020.04.03.20051763v1

通讯作者及单位：Yi Ouyang（中南大学湘雅医院），Jianghai Chen（华中科技大学同济医学院附属协和医院）
编译者：宋张悦

内容摘要：
背景：严重的急性呼吸系统综合症冠状病毒2（SARS-CoV-2）已发展成为大流行病，其发病率和死亡率均很高。 世卫组织和美国疾病控制与预防中心（CDC）已发布确诊冠状病毒病（COVID-19）患者治疗的临时临床指南，但是关于重症COVID-19预后的病毒学和临床症状的数据仍非常有限。
方法：研究人员将50例重症COVID-19患者分为恢复良好组和恢复不良组。探讨了SARS-CoV-2病毒的动态脱落和血清学特征。确定了与恢复差和肺部病变有关的危险因素。此外，还探讨了病毒脱落、促炎症反应和肺部病变演变之间的潜在关系。
结果：总共58％的患者恢复较差，他们可能有更长的病毒脱落间隔。 最长的病毒脱落时间是症状出现后的57天。 研究发现高龄、高脂血症、低蛋白血症、使用皮质类固醇治疗、胸部计算机断层扫描(CT)实变以及SARS-CoV-2 IgM抗体阳性时间延长均与恢复不良有关。 此外，在低蛋白血症、高脂血症、IL-4和铁蛋白水平升高的患者中，肺部病变的可能性更高。 最后，病毒脱落和促炎反应与胸部CT上的肺部病变的演变密切相关。
结论：重症COVID-19患者有更长的SARS-CoV-2感染时间和病毒间歇脱落时间。高龄、高脂血症、低蛋白血症、使用皮质类固醇激素，以及SARS-CoV-2 IgM抗体阳性时间延长，可能被用作恢复不良患者的预后因子。

Abstract
Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has progressed to a pandemic associated with substantial morbidity and mortality. The WHO and the United States Center for Disease Control and Prevention (CDC) have issued interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19), but there is limited data on the virologic and clinical characteristics for prognosis of severe COVID-19. Methods: A total of 50 patients with severe COVID-19 were divided into good and poor recovery groups. The dynamic viral shedding and serological characteristics of SARS-CoV-2 were explored. The risk factors associated with poor recovery and lung lesion resolutions were identified. In addition, the potential relationships among the viral shedding, the pro-inflammatory response, and lung lesion evolutions were characterized. Results: A total of 58% of the patients had poor recovery and were more likely to have a prolonged interval of viral shedding. The longest viral shedding was 57 days after symptom onset. Older age, hyperlipemia, hypoproteinemia, corticosteroid therapy, consolidation on chest computed-tomography (CT), and prolonged SARS-CoV-2 IgM positive were all associated with poor recovery. Additionally, the odds of impaired lung lesion resolutions were higher in patients with hypoproteinemia, hyperlipemia, and elevated levels of IL-4 and ferritin.

Finally, viral shedding and proinflammatory responses were closely correlated with lung lesion evolutions on chest CT. Conclusions Patients with severe COVID-19 have prolonged SARS-CoV-2 infection and delayed intermittent viral shedding. Older age, hyperlipemia, hypoproteinemia, corticosteroid usage, and prolonged SARS-CoV-2 IgM positive might be utilized as predicative factors for the patients with poor recovery.

8. 人工肝血液净化系统是一种有前途的抗细胞风暴靶向治疗COVID-19的方法
A Promising Anti-Cytokine-Storm Targeted Therapy for COVID-19: The Artificial-Liver Blood-Purification System

来源：Engineering
发表时间：2020.3.20
链接：
https://www.sciencedirect.com/science/article/pii/S209580992030062X?via%3Dihub
通讯作者：李兰娟，中国工程院院士浙江大学教授、博士生导师
作者单位：传染病诊断与治疗国家重点实验室、国家传染病临床研究中心、传染病诊断协同创新中心，浙江大学医学院附属第一医院传染病防治研究所
编译：张怡
摘要：
已有研究揭示，冠状病毒或者流感病毒的致死率与过度和异常的免疫反应和严重的肺病理有关，常伴有致命的后果。人工肝血液净化系统已在浙江省应用，并在治疗出现细胞因子风暴的危重症COVID-19患者中，表现出良好的预后。
今后可能要进一步考虑以下几个方面：第一，需要抗细胞因子风暴的多中心临床，通过考察患者清除促炎细胞因子（如TNF-a、IL-1b、IL-2、IL-6、IL-18）的能力；第二，需要确认参与COVID-19患者细胞因子风暴的关键路径和免疫细胞类型，这将有助于了解人工肝净化系统，通过缓解细胞因子风暴来重新平衡免疫系统，逆转疾病进程。作为一种抗细胞因子风暴靶向治疗，人工肝血液净化系统在降低COVID-19感染的严重和危重患者的死亡率方面具有的潜力。
Studies revealed that the lethality of coronavirus or influenza virus is related to the induction of an excessive and aberrant immune response associated with severe lung pathology, with frequently fatal consequences. The artificial-liver blood-purification system was applied in Zhejiang province, China, and showed good prognosis in the treatment of severely or critically ill COVID-19 patients with cytokine storm.
Further investigations may be conducted in the near future and should consider the following aspects: First, there is a need for multicenter clinical studies of anti-cytokine-storm targeted therapy for COVID-19 by novel artificial-liver blood-purification systems with demonstrated abilities to clear pro-inflammatory cytokines (e.g., TNF-a, IL-1b, IL-2, IL-6, and IL-18). Second, investigations are needed regarding the key pathways and immune cell types involved in cytokine storm onset in COVID-19; these will benefit the understanding of artificial-liver support system treatment for alleviating cytokine storm to reverse the disease process in patients with severe COVID-19 infection by rebalancing the immune system. By acting as an anti-cytokine-storm

targeted therapy, artificialliver blood-purification systems hold excellent potential for reducing mortality in severely and critically ill patients with COVID-19 infection.

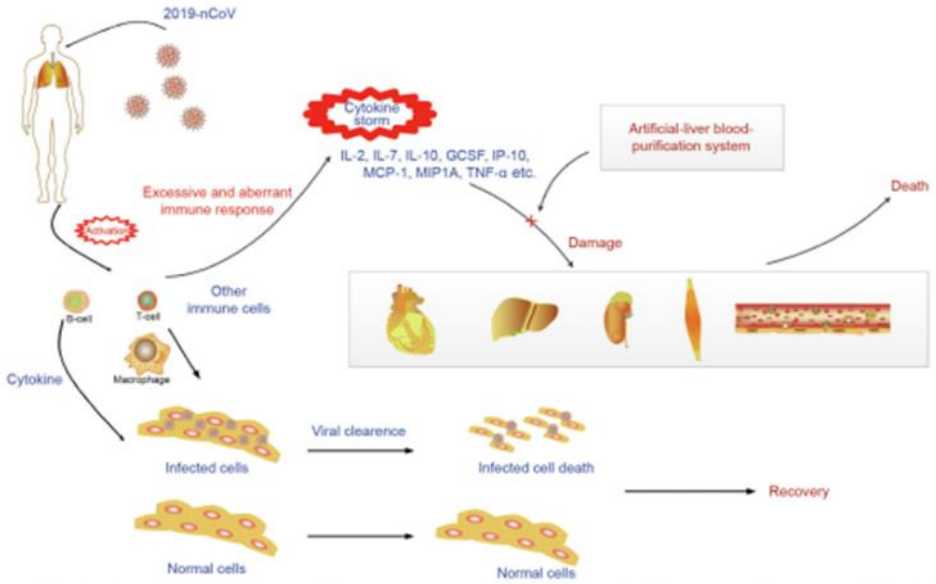


Fig. 1. The artificial-liver blood-purification system eliminates inflammatory cytokines/chemokines and alleviates cytokine-storm-induced damage in 2019-nCOV infection.

9. ACE2和TMPRSS2基因主要表达在支气管瞬态分泌型细胞中

SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells

来源：The EMBO Journal

发布时间：2020.4.4

通讯作者：Christian Conrad, Roland Elis

通讯作者单位：Freie Universität Berlin, Humboldt‐Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Heidelberg University Hospital and BioQuant, Heidelberg, Germany

链接：https://www.embopress.org/doi/abs/10.15252/embj.20105114

编译：宋珂

SARS-CoV-2流行病感染人类的呼吸系统，严重危害公共健康，迫切需要我们深入了解COVID-19的发病机理，特别是促使病毒感染和复制的宿主因素。据文献报道，SARS-CoV-2侵入细胞的过程，首先需要与ACE2结合，再通过TMPRSS2启动。在本文中，作者分别使用单细胞核与单细胞RNA测序方法，研究了ACE2和TMPRSS2在肺部组织的多种细胞类型（12名捐献者，39778个细胞）和支气管亚段分离出的细胞（4名捐献者，17521个细胞）中的表达水平和分布情况。作者发现，TMPRSS2在以上两种组织中均有表达。在支气管亚段中，ACE2在瞬时分泌细胞（这种细胞显示介于杯状细胞和纤毛细胞之间的细胞状态）中表达非常显著。有趣的是，这种瞬时分化的细胞中基因表达在RHO GTPase功能和调节病毒过程相关的通路中存在富集现象，表明这种细胞可能SARS-CoV-2更易感。本文为未来研究COVID-19的感染和发病机理提供了丰富的数据。

肺部组织细胞的基因表达使用了单细胞核RNA测序方法，样本来自于肺癌患者的健康、未感染的肺部组织。

针对支气管亚段样本，采用了单细胞RNA测序方法。样本来自于4名健康捐献者的人类支气管上皮细胞(HBECs)。
由于单细胞核RNA测序和单细胞RNA测序可能存在的技术差异，肺部组织和HBECs的CPM(counts per million)不具备数值的可比性。

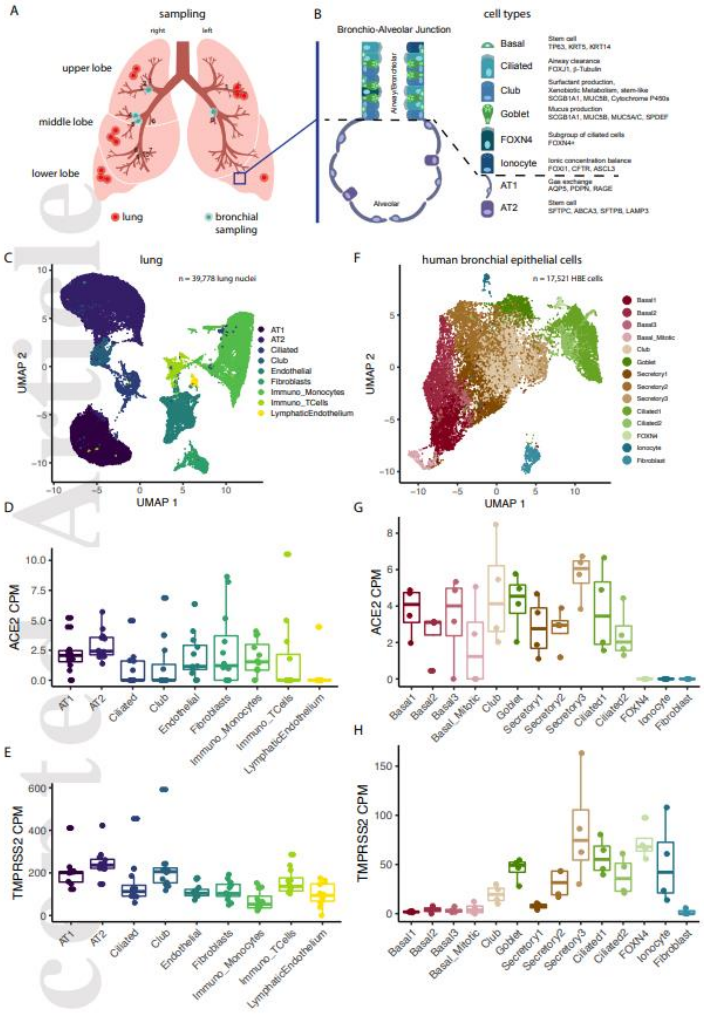


Figure 1. ACE2 and TMPRSS2 are expressed in specific cell types in lungs and HBECs.
A Sampling location of the surgical lung specimens and human bronchial epithelial cells (HBECs) used in this study. Blue rectangle is zoomed in B.
B Overview of the major cell types in the lung and airways.
C Uniform manifold approximation and projection (UMAP) of primary lung samples single nuclei RNA sequencing. Cell types are color-coded.
D Expression values of ACE2 in the cell types of primary lung samples.
E Expression values of TMPRSS2 in the cell types of primary lung samples.
F UMAP projections of HBE single cell RNA sequencing data. Cell types are colorcoded.
G Expression values of ACE2 in the cell types of HBECs.
H Expression values of TMPRSS2 in the cell types of HBECs.

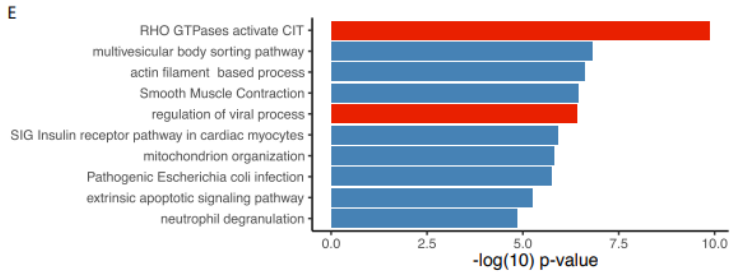


Figure 2. E Pathway enrichment values for secretory3-specific marker genes.

Abstract: The SARS - CoV - 2 pandemic affecting the human respiratory system severely challenges public health and urgently demands for increasing our understanding of COVID - 19 pathogenesis, especially host factors facilitating virus infection and replication. SARS - CoV - 2 was reported to enter cells via binding to ACE2, followed by its priming by TMPRSS2. Here, we investigate ACE2 and TMPRSS2 expression levels and their distribution across cell types in lung tissue (twelve donors, 39,778 cells) and in cells derived from subsegmental bronchial branches (four donors, 17,521 cells) by single nuclei and single cell RNA sequencing, respectively. While TMPRSS2 is expressed in both tissues, in the subsegmental bronchial branches ACE2 is predominantly expressed in a transient secretory cell type. Interestingly, these transiently differentiating cells show an enrichment for pathways related to RHO GTPase function and viral processes suggesting increased vulnerability for SARS - CoV - 2 infection. Our data provide a rich resource for future investigations of COVID - 19 infection and pathogenesis.

10. SARS-CoV-2和SARS-CoV的细胞偏好性和药物敏感性存在差异
SARS-CoV-2 and SARS-CoV differ in their cell tropism and drug sensitivity profiles
发布时间：2020.4.5
来源：biorxiv
通讯作者： Martin Michaelis, Mark N. Wass，Jindrich Cinatl jr
通讯作者单位：School of Biosciences, University of Kent, Canterbury, UK, School of Biosciences, University of Kent, Canterbury, UK, Institute for Medical Virology, University Hospital, Goethe University Frankfurt am Main, Germany,
链接：https://www.biorxiv.org/content/10.1101/2020.04.03.024257v1
这篇文章对SARS-CoV-2和SARS-CoV从基因组，细胞的偏好性以及药物敏感性方面进行了比较。通过对所有公布的SARS-CoV病毒基因组和直到2020年3月27日的SARS-CoV-2的基因组进行比较分析，发现这两种病毒里面存在各自独特的保守氨基酸。作者测试了SARS-CoV和SARS-CoV2对4种结肠癌细胞系Caco2, CL14, HT-29, 以及 DLD-1感染偏好性差异。从图1可以看出，细胞的ACE2（SARS-CoV-2的宿主细胞受体）和TMPRSS2（切割S蛋白始得病毒得以进入宿主细胞）的蛋白水平并不能可靠地预测细胞对SARS-CoV-2的敏感度。SARS-CoV-2对药物的敏感度也和SARS-CoV不一样。所以必须用SARS-CoV-2本身来做测试以鉴定有效药物。 作者进一步用细胞证明药物蛋白酶抑制剂抑肽酶（aprotinin）在目前临床使用的浓度下有抑制SARS-CoV-2的活性。治疗浓度的质子泵奥美拉唑（omeprazole）联用可以进一

步提高抑制剂抑肽酶（aprotinin）和remdesivir(瑞德西韦)的抗病毒活性（抑肽酶2.7倍，瑞德西韦10倍）。

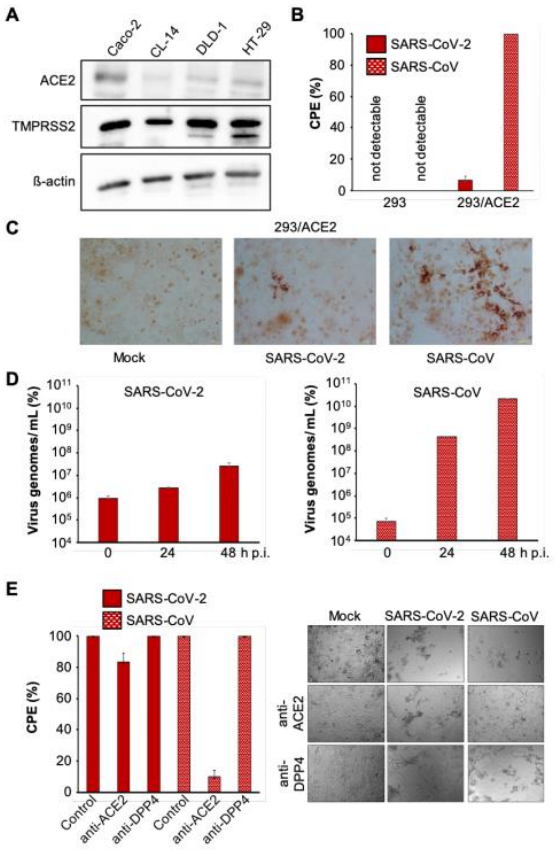


Figure 3. N A) Western blots indicating cellular ACE2 and TMPRSS2 protein levels. B) CPE formation in SARS-CoV and SARS-CoV-2 (MOI 0.01)-infected ACE2-negative 293 cells and 293 cells stably expressing ACE2 cells (293/ACE2) 48h post

SARS-CoV-2 is a novel coronavirus currently causing a pandemic. We show that the majority of amino acid positions, which differ between SARS-CoV-2 and the closely related SARS-CoV, are differentially conserved suggesting differences in biological behaviour. In agreement, novel cell culture models revealed differences between the tropism of SARS-CoV-2 and SARS-CoV. Moreover, cellular ACE2 (SARS-CoV-2 receptor) and TMPRSS2 (enables virus entry via S protein cleavage) levels did not reliably indicate cell susceptibility to SARS-CoV-2. SARS-CoV-2 and SARS-CoV further differed in their drug sensitivity profiles. Thus, only drug testing using SARS-CoV-2 reliably identifies therapy candidates. Therapeutic concentrations of the approved protease inhibitor aprotinin displayed anti-SARS-CoV-2 activity. The efficacy of aprotinin and of remdesivir (currently under clinical investigation against SARS-CoV-2) were further enhanced by therapeutic concentrations of the proton pump inhibitor omeprazole (aprotinin 2.7-fold, remdesivir 10-fold). Hence, our study has also identified anti-SARS-CoV-2 therapy candidates that can be readily tested in patients.