新型冠状病毒信息简报

第 25 期（2020 年 4 月 12 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

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 11 日疫情
流行病学	2. SARS-CoV-2 在武汉医院病房中空气和物体表面的分布
疾病检测	3. 新型冠状病毒检测，美国实验室仍未满负荷运转 4. 冠状病毒最新消息：英国建立大规模诊断网络
临床病理	5. COVID-19 重症监护患者的分类：建立合理有效的临床分流
临床研究	6. COVID-19 是如何杀死人类的？不确定性阻碍了医生选择治疗方法 7. 血纤维蛋白溶酶原改善 COVID-19 患者的肺损伤和低氧血症 8. 在英国多中心进行的血管紧张素转换酶抑制剂治疗与 SARS-CoV-2 严重疾病的风险降低相关性的研究
	9. 人源单克隆抗体阻断 SARS-CoV-2 Spike 蛋白与受体 ACE2 的结合 10. 类 SARS 冠状病毒的多种潜在宿主以及改良的有效抵抗 SARS-CoV-2 和 SARS-CoV-1 病毒的 ACE2-Fc 变体 11. 当前可用的静脉内免疫球蛋白(Gamunex © -C 和 Flebogamma © DIF) 包含有能与 SARS-CoV-2 抗原反应的抗体
基础研究	12. 用系统生物学方法来分析 COVID-19 流行病 13. 整合网络生物学框架揭示 SARS-CoV-2 的致病机理

1. 2020 年 4 月 11 日疫情

编译:王玮

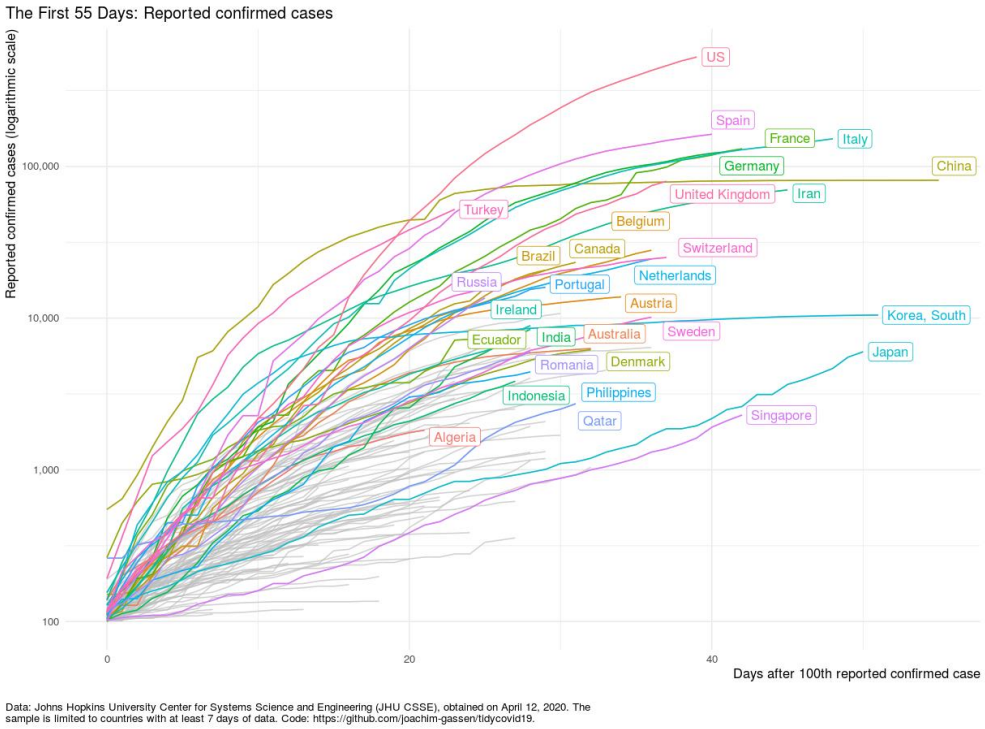
数据来源：WHO

发布时间：2020 年 4 月 11 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 11 日全球累计确诊新型冠状病毒病人 1610909 例，当日新增确诊 89657 例，累计死亡 99690 例，当日新增死亡 6892。

中国累计确诊 83369 例，累计死亡 3349 例，当日新增确诊 64 例，新增死亡 4 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 4 月 12 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11日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. SARS-CoV-2 在武汉医院病房中空气和物体表面的分布

Aerosol and Surface Distribution of Severe Acute Respiratory Syndrome Coronavirus 2 in Hospital Wards, Wuhan, China, 2020

来源：Emerg Infect Dis

发布时间：2020-04-10

通讯作者：Wei Chen, Bing Lu, and Yu-Wei Gao

通讯作者单位：中国人民解放军军事科学院军事医学研究院

链接：https://wwwnc.cdc.gov/eid/article/26/7/20-0885_article

编译:蒋立春

研究者在武汉的两家收治 COVID-19 病人的医院对病毒的分布进行了研究。他们总共研究了可以容纳 15 个病人的 ICU 和 24 个病人普通病房里的表面和空气样品。

该研究表明：

SARS-CoV-2 病毒广泛分布在 ICU 和普通病房的空气以及物体表面。这提示医护人员和其他密切接触者潜在的暴露风险高。

ICU 的环境病毒污染比普通病房高。

在普通病房里面病毒在空气的传播的大约为 4 米。

不过该研究没有测量收集到的环境样品里活病毒的量。另外，我们现在尚不了解最少多少病毒量可以造成感染。这些都是影响判断通过空气传播感染距离的因素。

Abstract:

To determine distribution of severe acute respiratory syndrome coronavirus 2 in hospital wards in Wuhan, China, we tested air and surface samples. Contamination was greater in intensive care units than general wards. Virus was widely distributed on floors, computer mice, trash cans, and sickbed handrails and was detected in air ≈4 m from patients.

3. 新型冠状病毒检测，美国实验室仍未满负荷运转

Thousands of coronavirus tests are going unused in US labs

来源：Nature

发布时间：2020-04-09

来源链接：

https://www.nature.com/articles/d41586-020-01068-3

编译:王玮

内容摘要：

美国实验室在为 COVID-19 检测重新配置设备方面付出了巨大努力，但仍没有满负荷运转。专家表示，很大程度上是由于缺乏国家战略。

一项对几所大学实验室进行的调查发现，这些实验室被监管、后勤和行政，以及支离破碎的美国医疗体系所阻碍。例如，当加州医院的检测积压越来越多时，诊所却拒绝了认证学术实验室提供的检测，因为他们没有使用兼容的健康记录软件，或者与医院没有合同。研究人员警告说，如果这些障碍仍然存在，那些试图加入抗击新型冠状病毒行动的实验室可能最终会陷入困境。一些实验室能在 12 小时到 24 小时内给出检测结果。但许多医院仍然坚持他们习惯的诊断公司。WHO 在 1 月份就开始警告各国政府为 COVID-19 做好准备。WHO 还审查并分发了德国开发的基于 PCR 的病毒检测方法。但是，美国 CDC 没有使用这种检测方法，而是开发了自己的检测系统。二月的大部分时间里，这是美国唯一允许的检测方法。2 月下旬，美国

FDA 披露 CDC 检测供不应求，存在缺陷，该局允许学术实验室开始进行新型冠状病毒检测。4 月 8 日，为了应对检测短缺和检测供应的问题，华盛顿特区的三位国会领导人致函卫生和公共服务部部长，要求制定一项国家检测战略。

Abstract
US labs that underwent huge efforts to retool for COVID-19 testing still aren’t operating at full capacity. Experts say the lack of a national strategy is largely to blame.

4. 冠状病毒最新消息：英国建立大规模诊断网络

Coronavirus latest: UK launches massive diagnostic network
来源：Nature
发布时间：2020-04-09
链接:
https://www.nature.com/articles/d41586-020-00154-w
编译:蒋立春
英国政府于 4 月 9 日开启了第一个大规模新冠病毒检测中心。除了这个位于 Milton Keynes 的第一个大规模诊断中心， 在 Glasgow 和 Alderley Park 的另外两个检测中心计划会在两周之内投入使用。英国政府在三月向全国的大学实验室征集了 PCR 仪来装备这些检测中心。

这些检测实验室将优先处理正在自我隔离的医护人员以帮助他们尽快返回工作岗位。
英国政府希望到 4 月底，每天的检测量可以达到 10 万。到目前为止，整个英国进行了不到 30 万新冠病毒检测。
全国各地的大学实验室也在进行新冠病毒的检测工作。

5. COVID-19 重症监护患者的分类：建立合理有效的临床分流

Classification of COVID-19 in intensive care patients: towards rational and effective clinical triage
来源：medRxiv，预印本
发布时间：2020-04-11
来源链接：https://www.medrxiv.org/content/10.1101/2020.04.09.20058909v1
通讯作者及单位：言方荣（中国药科大学，生物统计与计算药学研究中心）和王俊（苏州大学第一附属医院重症医学科）
编译：宋张悦
内容摘要：
目前关于 COVID-19 的研究主要集中在对确诊患者的综合信息上，很少有专门针对重症监护患者的数据，本文作者对重症监护患者进行了分类研究，帮助患者进行个体化评估，为治疗和管理提供有效的分诊。
本研究收集了武汉同济医院自 2020 年 1 月 25 日至 2 月 25 日，在重症监护室收治的共计 306 例 COVID-19 重症患者的病历资料，经筛选得到 151 例有完整病历的重症监护患者数据。研究人员构建了一个完全贝叶斯潜变量模型（fully Bayesian latent variable model），用于六类数据的综合聚类，包括人口统计学信息（年龄和性别）、症状（发烧、浑身乏力、干咳、厌食、肌痛、呼吸困难、咳痰和腹泻）、原始并发症（高血压、糖尿病、心血管疾病[CVD]、慢性阻塞性肺疾病[COPD]和恶性肿瘤）、生命体征（呼吸频率、心率、血压、血氧饱

和度[SpO2]和吸入氧体积分数[FiO2])、血常规检查（白细胞计数[WBC]、淋巴细胞、中性粒细胞、血小板和单核细胞、红血球分布宽度[RDW]）和炎症标志物检测（hs-CRP、IL-2R、IL-6、IL-8、IL-10 和 TNF-α）。通过分类研究在重症监护患者中确定了 COVID-19 的四种预后类型（Fig.1），在年龄、呼吸状况和炎症标志物上呈现阶梯式分布，提示这些指标的预后效果，与临床结果（重症监护病房入院后 28 天的死亡率）密切相关。研究人员还在文中指出，该报告可能是针对 COVID-19 重症监护患者分类的首次尝试，虽然研究者们认识到忽略治疗效果的局限性，但是本文的分类也有一定的启发意义，疾病的有效分类有利于早期进行患者管理，并在资源匮乏的地区优化医疗物资的分配。

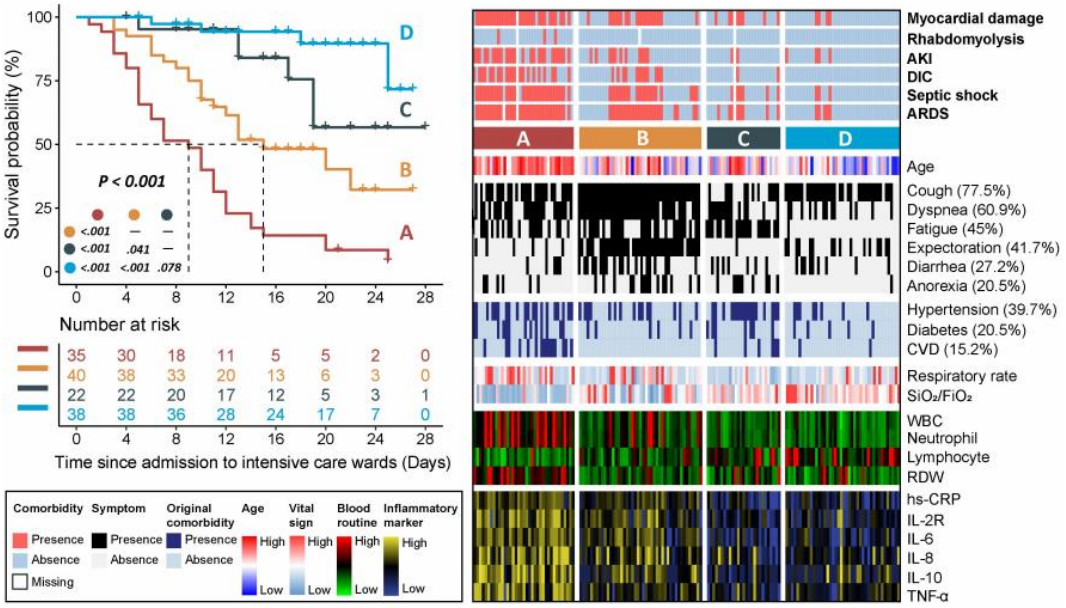


Fig.1. Clinical landscape of four prognostic types of COVID-19 in intensive care patients. Kaplan-Meier survival curves (left panel) showing differential survival rates; comprehensive heatmap (right panel) delineating clinical landscape of different types of COVID-19, with legend positioning in the left bottom panel. Survival was analyzed with log-rank test and pair-wise comparison was adjusted by Benjamini-Hochberg method. Labels of “high” and “low” were based on data interval instead of clinical reference values. AKI: acute kidney injury; DIC: disseminated intravascular coagulation; ARDS: acute respiratory distress syndrome; CVD: cardiovascular disease; SpO2: peripheral oxygen saturation; FiO2: fraction of inspired oxygen; WBC: white blood cell; RDW: red cell distribution width.

Abstract

The number of pertinent researches of COVID-19 has increased rapidly but they mainly focused on the description of general information of patients with confirmed infection. We aimed to bridge the gap between disease classification and clinical outcome in intensive care patients, data of which are scarce and such classification could help in individual evaluation and provide effective triage for treatment and management. Specifically, we collected and filtered out 151 intensive care patients with complete medical records from Tongji hospital

in Wuhan, China. We constructed a fully Bayesian latent variable model for integrative clustering of six data categories, including demographic information, symptoms, original comorbidities, vital signs, blood routine tests and inflammatory marker measurements. We identified four prognostic types of COVID-19 in intensive care patients, presenting a stepwise distribution in age, respiratory condition and inflammatory markers, suggesting the prognostic efficacy of these indicators. This report, to our knowledge, is the first attempt of dealing with classification of COVID-19 in intensive care patients. We acknowledge the limitation of ignoring the effect of treatment, but we believe such classification is enlightening for better triage, allowing for a more rational allocation of scarce medical resources in a resource constrained environment.

6. COVID-19 是如何杀死人类的？不确定性阻碍了医生选择治疗方法

How does COVID-19 kill? Uncertainty is hampering doctors' ability to choose treatments

来源：Nature

发布时间：2020-04-09

来源链接：

https://www.nature.com/articles/d41586-020-01056-7

编译:王玮

内容摘要：

医生们正在寻找抑制免疫反应的药物，但这些药物也会破坏人体自身对抗冠状病毒的能力。COVID-19 是如何杀死人类的？病毒本身还是人体免疫系统的反应最终击溃患者的器官，这一不确定性使得医生很难确定治疗冠状病毒危重患者的最佳方法。

临床数据表明，免疫系统在新冠状病毒感染者的衰亡过程中起着一定的作用，因此有了诸如类固醇等抑制免疫反应的治疗方法的发展。其中一些疗法广泛地抑制免疫系统，但这些疗法可能会妨碍人体控制病毒感染的能力。该文提到可能的疗法，包括类固醇，IL-6 抑制剂，以及联合疗法。

Abstract

Doctors are reaching for drugs that dampen the immune response — but these also undermine the body's own fight against the coronavirus.

7. 血纤维蛋白溶酶原改善 COVID-19 患者的肺损伤和低氧血症

Plasminogen improves lung lesions and hypoxemia in patients with COVID-19

来源：An International Journal of Medicine

发布时间：2020.4.10

链接

：https://academic.oup.com/qjmed/advance-article/doi/10.1093/qjmed/hcaa121/5818885

通讯作者：李季男

作者单位：深圳瑞建生命科学研究所基础研究室

编译：张鹏伟

内容摘要：

背景：COVID-19 患者的肺表现为典型的急性呼吸窘迫综合征（ARDS），主要由纤维蛋白组成

的透明膜形成和“毛玻璃”混浊症状。在此之前，作者发现纤溶酶原本身是纤维蛋白降解、伤口愈合和感染的关键调节因子。
方法：采用雾化吸入冻干纤溶酶原治疗 13 例临床中、重度或危重 COVID-19 患者。通过 CT 扫描和病人监护，比较患者治疗前后肺部病变程度、血氧饱和度和心率。
结果和结论：吸入纤溶酶原后，5 例临床中度患者的肺部病变情况迅速改善，表现为磨玻璃样阴影范围和密度减小。观察到 6 例临床重症患者血氧饱和度的改善情况。2 例危重病人在第一次吸入 1 小时后，氧含量从 79-82%显著增加到 91%。13 个病人中有 8 个心率减慢了。对于 5 名临床中度患者，这一差异具有统计学意义。此外，观察到患者胸闷有普遍缓解。
有报道称，成人 ARDS 患者血浆纤溶酶原显著升高，但本研究提示，在 COVID-19 感染期间，额外的血浆纤溶酶原治疗肺部病变和低氧血症可能是有效的。虽然还需要进一步的研究，但这项研究强调了有效应对这一快速流行病的可能希望。
Abstract：
Background: Lungs from patients with coronavirus disease 2019 (COVID-19) have shown typical signs of acute respiratory distress syndrome (ARDS), formation of hyaline membrane mainly composed of fibrin, and ‘ground-glass’ opacity. Previously, we showed plasminogen itself is a key regulator in fibrin degradation, wound healing and infection.
Method: Thirteen clinically moderate, severe or critical COVID-19 patients were treated with atomization inhalation of freeze-dried plasminogen. Levels of their lung lesions, oxygen saturation and heart rates were compared before and after treatment by CT scanning images and patient monitor.
Results and conclusions: After plasminogen inhalation, conditions of lung lesions in 5 clinically moderate patients have quickly improved, shown as the decreased range and density of ‘ground glass’ opacity. Improvements of oxygen saturation were observed in 6 clinically severe patients. In the 2 patients with critical conditions, the oxygen levels have significantly increased from 79-82% to 91% just about 1 hour after the first inhalation. In 8 of 13 patients the heart rates had slowed down. For the 5 clinically moderate patients, the difference is even statistically significant.
Whereas it is reported that plasminogen is dramatically increased in adults with ARDS, this study suggests that additional plasminogen may be effective and efficient in treating lung lesions and hypoxemia during COVID-19 infections. Although further studies are needed, this study highlights a possible hope of efficiently combating this rapid epidemic emergency.

8. 在英国多中心进行的血管紧张素转换酶抑制剂治疗与 SARS-CoV-2 严重疾病的风险降低相关性的研究

Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multi-site UK acute Hospital Trust
来源：medRxiv
发布日期：2020.04.07
链接：https://www.medrxiv.org/content/10.1101/2020.04.07.20056788v1
作者及单位：Daniel M Bean, Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King’s College London,

London, U.K
编译：孔娟
摘要:
SARS-CoV-2 能与机体下呼吸道中的受体 ACE2 血管紧张素转换酶 2 结合从而进入到肺部，已有研究表明，血管紧张素转换酶抑制剂(常用于心血管,高血压或糖尿病患者的治疗)可提高血管紧张素转换酶 2 水平，可能会增加严重 COVID-19 感染的风险。研究者在英国伦敦国王学院医院和皇家大学公主医院 205 例 COVID-19 住院患者的早期队列中评估了这一假设，主要观察终点是在症状出现后 7 天内死亡或转移到 ICU 病房。结果显示 205 名患者中有 53 名患者达到了主要终点,，研究者根据患者年龄、性别、共病(高血压、糖尿病、缺血性心脏病和心力衰竭)进行了调整。与假设相反，用血管紧张素转换酶抑制剂治疗与迅速恶化的严重疾病的风险降低有关。接受血管紧张素转换酶抑制剂 ORO.29(CI 0.10-0.75，p < 0.01)治疗的患者在 7 天内的死亡率或转到 ICU 的比率较低。
研究者表示，尽管研究可能受样本量较少的限制，但基于研究中并未发现血管紧张素转换酶抑制剂能够增加 COVID-19 疾病短期严重程度的证据，因此建议接受血管紧张素转换酶抑制剂治疗的患者应在 COVID-19 疾病期间继续使用这些药物。
Abstract:
Background: The SARS-Cov2 virus binds to the ACE2 receptor for cell entry. It has been suggested that ACE-inhibitors, which are commonly used in patients with hypertension or diabetes and which raise ACE2 levels, may increase the risk of severe COVID-19 infection. Methods: We evaluated this hypothesis in an early cohort of 205 acute inpatients with COVID-19 at King's College Hospital and Princess Royal University Hospital, London, UK with the primary endpoint being death or transfer to a critical care unit for organ support within 7-days of symptom onset. Findings: 53 patients out of 205 patients reached the primary endpoint. Contrary to the hypothesis, treatment with ACE-inhibitors was associated with a reduced risk of rapidly deteriorating severe disease. There was a lower rate of death or transfer to a critical care unit within 7 days in patients on an ACE-inhibitor OR 0.29 (CI 0.10-0.75, p<0.01), adjusting for age, gender, comorbidities (hypertension, diabetes mellitus, ischaemic heart disease and heart failure). Interpretation: Although a small sample size, we do not see evidence for ACE-inhibitors increasing the short-term severity of COVID-19 disease and patients on treatment with ACE-inhibitors should continue these drugs during their COVID-19 illness. A potential beneficial effect needs to be explored as more data becomes available.

9. 人源单克隆抗体阻断 SARS-CoV-2 Spike 蛋白与受体 ACE2 的结合

Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor
来源：medRxiv
发布时间：2020-04-11
链接：https://www.medrxiv.org/content/10.1101/2020.04.06.20055475v1
通讯作者：Zhaohui Qian，Yaokai Chen，Lilin! Ye
通讯作者单位：中国医学院和协和医科大学，重庆市公共卫生医疗救治中心 ，第三军医大学

编译:宋珂

由 SARS-CoV-2 导致的 COVID-19 已在全球范围流行。迄今为止，尚无预防性疫苗或批准的治疗性药物可用于应对这种高度传染性的疾病。日前，解放军第三军医大学和中国农科院哈尔滨兽医研究所联合国内多家大学、研究机构和医院，在 medRxiv 预印本网站上发表了其最新的成果。作者从最近康复的 3 名 COVID-19 患者的记忆 B 细胞中发现了两种单克隆抗体(mAb)，这两种 mAb 都能够特异性结合 SARS-CoV-2 的 Spike 蛋白(S)，阻断 SARS-CoV-2 的受体结构域(RBD)与人类血管紧张素转换酶 2(hACE2)的结合，有效中和假病毒的 S 蛋白。以上人源单克隆抗体的发现，有望对目前严重的 COVID-19 疫情的预防和治疗起到积极作用。

作者的研究发现所有康复的 COVID-19 病人都有抗 S1 和 RBD 的抗体，只有很少部分的抗体可以封闭 RBD 和 ACE2 受体的结合。作者选择了 3 位有更强封闭性的病人血清用于抗体的克隆。

Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic of novel corona virus disease (COVID-19). To date, no prophylactic vaccines or approved therapeutic agents are available for preventing and treating this highly transmittable disease. Here we report two monoclonal antibodies (mAbs) cloned from memory B cells of patients recently recovered from COVID-19, and both mAbs specifically bind to the spike (S) protein of SARS-CoV-2, block the binding of receptor binding domain (RBD) of SARS-CoV-2 to human angiotensin converting enzyme 2 (hACE2), and effectively neutralize S protein-pseudotyped virus infection. These human mAbs hold the promise for the prevention and treatment of the ongoing pandemic of COVID-19.

10. 类 SARS 冠状病毒的多种潜在宿主以及改良的有效抵抗 SARS-CoV-2 和 SARS-CoV-1 病毒的 ACE2-Fc 变体

Potential host range of multiple SARS-like coronaviruses and an improved ACE2-Fc variant that is potent against both SARS-CoV-2 and SARS-CoV-1

来源：bioRxiv

发布时间：2020-04-11

通讯作者：Guocai Zhong

通讯作者单位：深圳湾实验室

链接：https://www.biorxiv.org/content/10.1101/2020.04.10.032342v1

由 SARS-CoV-2 病毒引起的 COVID-19 疫情在全球肆虐。由于某些驯养物种可能会携带病毒，并再次传播给人类，因此，研究 SARS-CoV-2 病毒宿主的范围也尤为重要。此外，了解 SARS-CoV-2 和其他类 SARS 病毒如何利用动物里 ACE2 的同源基因进行传播，有可能为改进基于 ACE2 的病毒抑制剂提供结构上的启发。本文中，作者展示了一系列驯养和野生动物中 ACE2 的同源基因，够造成 SARS-CoV-2，SARS-CoV-1，蝙蝠冠状病毒 RaTG13，以及从穿山甲中分离出的冠状病毒侵入（文中采用假病毒测试）。其中一些物种，包括：骆驼，牛，马，山羊，绵羊，猪，猫和兔子可能是新的潜在的感染人的中间宿主。特别是兔子，还可以作为 COVID-19 的动物实验模型。作者发现，病毒 Spike 蛋白受体结构域重组 Ig Fc 融合蛋白(RBD-Fc)和可溶性 ACE2 (ACE2-Fc)可以有效阻断 SARS-CoV-2 和 SARS-CoV-1 的侵入。而且，发生 D30E 突变同时在 ACE2 的 740 号残基而不是 615 号残基处发生截断的 ACE2-Fc 变体阻止两种病毒侵入的效果均优于其他 ACE2-Fc 变体。现有数据表明，RBD-Fc 和 ACE2-Fc 可用于治疗和预防由 SARS-CoV-2 以及其他新病毒变体感染造成的流行病。

Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a currently uncontrolled pandemic and the etiological agent of coronavirus disease 2019 (COVID-19). It is important to study the host range of SARS-CoV-2 because some domestic species might harbor the virus and transmit it back to humans. In addition, insight into the ability of SARS-CoV-2 and SARS-like viruses to utilize animal orthologs of the SARS-CoV-2 receptor ACE2 might provide structural insight into improving ACE2-based viral entry inhibitors. Here we show that ACE2 orthologs of a wide range of domestic and wild animals support entry of SARS-CoV-2, as well as that of SARS-CoV-1, bat coronavirus RaTG13, and a coronavirus isolated from pangolins. Some of these species, including camels, cattle, horses, goats, sheep, pigs, cats, and rabbits may serve as potential intermediate hosts for new human transmission, and rabbits in particular may serve as a useful experimental model of COVID-19. We show that SARS-CoV-2 and SARS-CoV-1 entry could be potently blocked by recombinant IgG Fc-fusion proteins of viral spike protein receptor-binding domains (RBD-Fc) and soluble ACE2 (ACE2-Fc). Moreover, an ACE2-Fc variant, which carries a D30E mutation and has ACE2 truncated at its residue 740 but not 615, outperforms all the other ACE2-Fc variants on blocking entry of both viruses. Our data suggest that RBD-Fc and ACE2-Fc could be used to treat and prevent infection of SARS-CoV-2 and any new viral variants that emerge over the course of the pandemic.

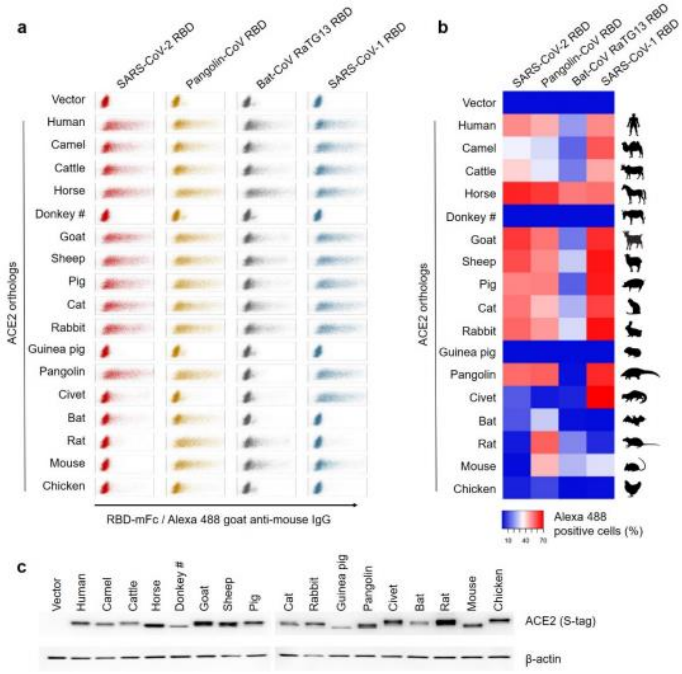


Fig. 2 | A wide range of ACE2 orthologs support binding to RBD proteins of four SARS-like coronaviruses. (a), 293T cells transfected with ACE2 genes of the indicated species were stained with RBD-mouse IgG2 Fc fusion proteins of SARS-CoV-2 WHU01, Pangolin-CoV, Bat-CoV RaTG13, and SARS-CoV-1 BJ01. The cells were then stained with Alexa 488 goat anti-mouse IgG secondary antibody and RBD-ACE2 binding was detected using flow cytometry. #,based on ACE2 protein sequence

alignment shown in the Extended Data Figure 1, around 20 residues (246- 268) of donkey ACE2 are missing in the sequence used in this study (NCBI Reference Sequence: XM_014857647.1). (b), Percentages of cells positive for RBD binding in panel a are presented as a heatmap according to the indicated color code. (c), Expression levels of the indicated ACE2 genes were detected using Western Blot. Data shown are representative of two independent experiments with similar results.

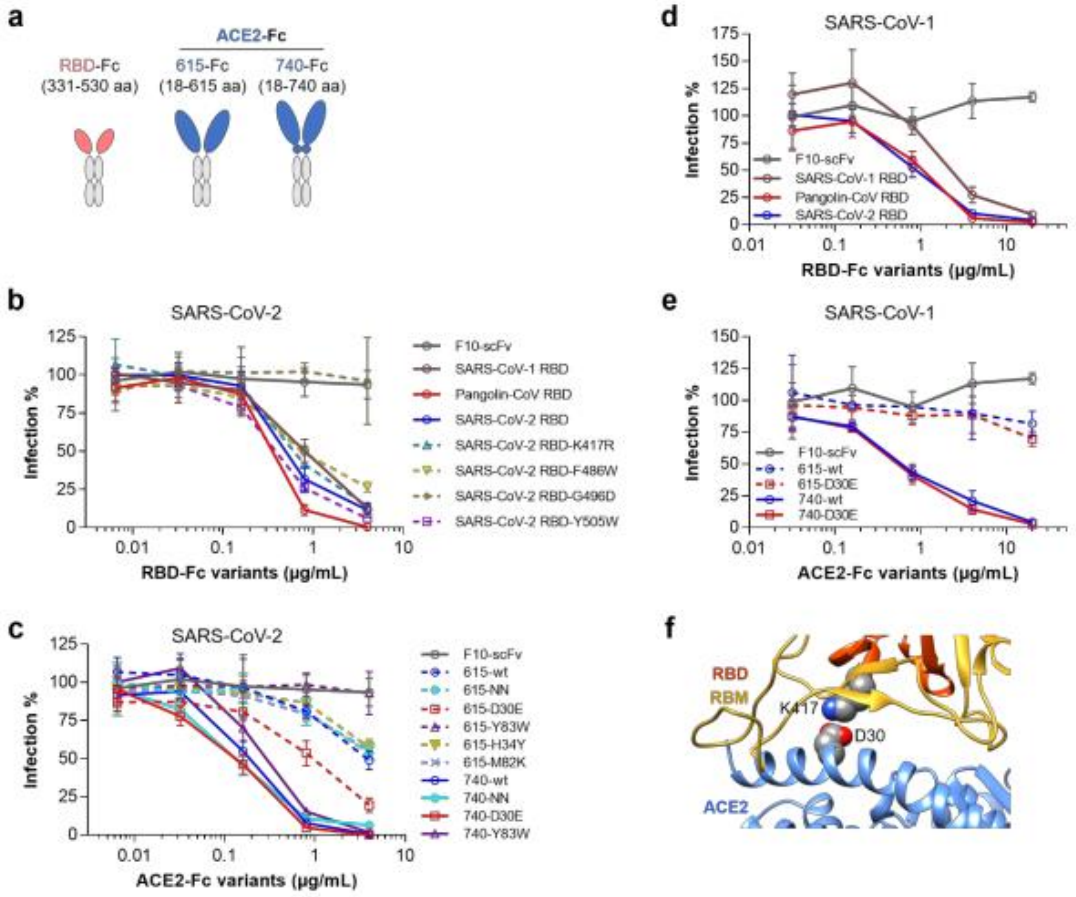


Fig. 4 | Recombinant RBD-Fc and ACE2-Fc variants efficiently block entry of SARS-CoV-2 and SARS-Cov-1. (a), Diagrams of RBD-Fc and ACE2-Fc fusion proteins used in the following studies. ACE2-expressing 293T cells were infected with SARS-CoV-2 spike-pseudotyped retrovirus in the presence of purified recombinant RBD-Fc (b) and ACE2-Fc (c) fusion proteins at the indicated concentrations. Viral entry was measured by the luciferase reporter at 48 hours post infection. Note that all the 740-version variants showed significantly better potency than the 615-version variants (two-tailed two-sample t-test, $p<0.001$). d-e, Experiments similar to that of panels b and c, except that the indicated RBD-Fc (d) and ACE2-Fc (e) variants were tested against SARSCoV-1 pseudovirus. (f), The ACE2 residue D30 forms a salt bridge with the SARS-CoV-2 RBD residue K417 (PDB code 6M0J). Data shown are representative of three experiments independently performed by three different people with similar results, and data points represent mean ± s.d. of four biological replicates.

11. 当前可用的静脉内免疫球蛋白（Gamunex © -C 和 Flebogamma © DIF）包含有能与 SARS-CoV-2 抗原反应的抗体

Currently available intravenous immunoglobulin (Gamunex©-C and Flebogamma© DIF) contains antibodies reacting against SARS-CoV-2 antigens

来源：bioRxiv

发表时间：2020.4.10

链接：https://www.biorxiv.org/content/10.1101/2020.04.07.029017v1

通讯作者：José-María Díez

作者单位：基立福（Grifols）研发

编译：雷颖

摘要：

背景：目前迫切需要可以立即用于控制 COVID-19 疾病传播的有效疗法。在这项研究中，作者评估了目前市售的静脉内免疫球蛋白（IVIG）产品，以检测可能与 SARS-CoV-2 病毒发生交叉反应的人类普通冠状病毒的抗体。

方法：Gamunex © -C 和 Flebogamma ©使用 ELISA 技术测试了 DIF（Grifols）IVIG 对几种 β 冠状病毒的抗原：HCoV（不确定抗原），HCoV-HKU1（N 蛋白），SARS-CoV（培养物裂解液），MERS-CoV（N 蛋白；S1 蛋白/ RBD；S 蛋白）和 SARS-CoV-2（S1 蛋白）。

结果：两种 IVIG 产品均对被测病毒的成分表现出一致的反应性。在 SARS-CoV，MERS-CoV 和 SARS-CoV-2 中观察到阳性交叉反应。对于 SARS-CoV-2，在 IVIG 浓度下观察到阳性反应，浓度范围从 Gamunex-C 用 100 μg/ mL 到 Flebogamma 5%DIF 用 1 mg / mL。

结论：Gamunex-C 和 Flebogamma DIF IVIG 含有与 SARS-CoV-2 抗原反应的抗体。这些制剂可立即用于治疗 COVID-19 疾病。

Abstract

Background: There is a critical need for effective therapies that are immediately available to control the spread of COVID-19 disease. In this study, we assessed currently marketed intravenous immunoglobulin (IVIG) products for antibodies against human common coronaviruses that may cross-react with the SARS-CoV-2 virus.

Methods: Gamunex©-C and Flebogamma© DIF (Grifols) IVIG were tested against several betacoronaviruses antigens using ELISA techniques: HCoV (undetermined antigen), HCoV-HKU1 (N protein), SARS-CoV (culture lysate), MERS-CoV (N protein; S1 protein/RBD; S protein), and SARS-CoV-2 (S1 protein).

Results: Both IVIG products showed consistent reactivity to components of the tested viruses. Positive cross-reactivity was seen in SARS-CoV, MERS-CoV, and SARS-CoV-2. For SARS-CoV-2, positive reactivity was observed at IVIG concentrations ranging from 100 μg/mL with Gamunex-C to 1 mg/mL with Flebogamma 5% DIF.

Conclusion: Gamunex-C and Flebogamma DIF IVIG contain antibodies reacting against SARS-CoV-2 antigens. These preparations may be useful for immediate treatment of COVID-19 disease.

12. 用系统生物学方法来分析 COVID-19 流行病

Confronting the COVID-19 Pandemic with Systems Biology

来源：biorxiv

发布时间：2020-04-06

链接：https://www.biorxiv.org/content/10.1101/2020.04.06.028712v1

通讯作者：Daniel Jacobson, Oak Ridge National Laboratory, University of Tennessee Knoxville.

编译：刘焕珍

文摘：

尽管 COVID-19 流行病的死亡率低于 SARS 和 MERS，但全球疫情爆发，已经导致更多病人的死亡。为了解决这种疾病的复杂性，系统生物学方法可以提供有关病毒生物学和疾病机理的见解。转录组和蛋白质组学数据表明 ACE2 在肺组织中几乎没有表达。分子建模模拟支持 ACE2 作为 SARS-CoV-2 的受体，但是 ACE 可能也充当病毒的受体，并且可能对 SARS-CoV-1 进入细胞起到很重要的作用。来自 COVID-19 患者的支气管肺泡灌洗样本的基因表达数据可识别肾素，血管紧张素和血管紧张素 1-7 受体 MAS 的上调以及与肺实质组织大规模溶解相一致的细胞情况，可能包括所有肺上皮组织细胞类型以及淋巴管内皮细胞，但通常缺少宿主防御必需的细胞（例如巨噬细胞）。作者分析表明，SARS-CoV-2 通过在肺中表达的 ACE2 进入宿主细胞的公认观点不太可能，因为在该处无法检测到 ACE2。更有可能的情况表明，鉴于 ACE2 阳性的鼻，口腔和胃肠道组织的目标空间更大，这些组织中的初始感染之后是通过淋巴系统和血液向肺微血管的迁移而继发的感染。COVID-19 肺样本中巨噬细胞的清除和活化细胞因子标记的完全缺乏表明，SARS-CoV-2 毒力的主要成分是其引起功能性免疫缺陷综合症的净效应。我们对 SARS-CoV-2 蛋白质组的结构分析表明，高度保守的 nsp5 蛋白的参与是抑制核因子转录因子 kappa B（NF-κB）途径，消除宿主细胞基于干扰素的抗病毒反应的主要机制的一部分。

Background: The magnitude and severity of the COVID-19 pandemic cannot be overstated. Although the mortality rate is less than SARS and MERS, the global outbreak has already resulted in orders of magnitude more deaths. In order to tackle the complexities of this disease, a Systems Biology approach can provide insights into the biology of the virus and mechanisms of disease.

Methods: Using a Systems Biology approach, we have integrated genomic, transcriptomic, proteomic, and molecular evolution data layers to understand its impact on host cells. We overlay these analyses with high-resolution structural models and atomistic molecular dynamics simulations conducted on the Summit supercomputer at the Oak Ridge National Laboratory.

Findings: Transcriptomic and proteomic data indicate little to no expression of ACE2 in lung tissue. Molecular modeling simulations support ACE2 as the receptor for SARS-CoV-2, but ACE may also act as a receptor for the virus and may be important for entry of SARS-CoV-1. Gene expression data from bronchoalveolar lavage samples from COVID-19 patients identify upregulation of renin, angiotensin, and the angiotensin 1-7 receptor MAS as well as a cellular landscape consistent with large-scale dissolution of lung parenchyma tissues, likely comprised of all lung epithelial cell types as well as lymphatic endothelial cells, but an absence of cells, such as macrophages, normally essential for host defense.

Interpretation: Our analyses indicate that the commonly accepted view that SARS-CoV-2 enters host cells via ACE2 expressed in the lung is unlikely because ACE2 is undetectable there. Instead, given the greater target space of ACE2-positive nasal, oral, and gastrointestinal tissues, a more likely scenario suggests initial infection in those tissues is followed by a secondary infection via

migration through the lymphatic system and bloodstream to the lung microvasculature. The elimination of macrophages and complete lack of activated cytokine signature in COVID-19 lung samples suggest that a major component of SARS-CoV-2's virulence is its net effect of causing a functional immune deficiency syndrome. Our structural analysis of the SARS-CoV-2 proteome suggests involvement of the highly conserved nsp5 protein as part of a major mechanism that suppresses the nuclear factor transcription factor kappa B (NF-κB) pathway, eliminating the host cell's interferon-based antiviral response.

13. 整合网络生物学框架揭示 SARS-CoV-2 的致病机理

Integrative Network Biology Framework Elucidates Molecular Mechanisms of SARS-CoV-2 Pathogenesis

来源：biorxiv

发布时间:2020-04-11

通讯作者：Mohammad Athar， M. Shahid Mukhtar

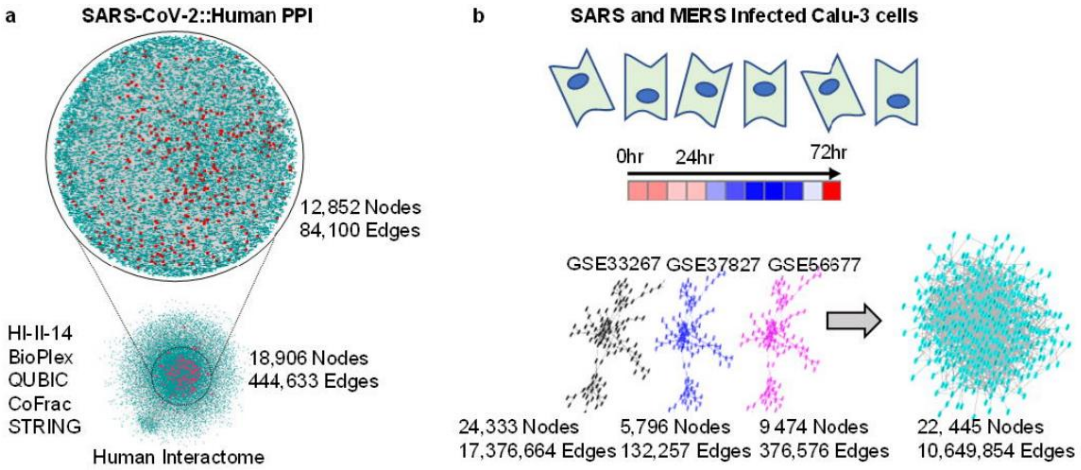
通讯作者单位：University of Alabama at Birmingham

链接:https://www.biorxiv.org/content/10.1101/2020.04.09.033910v1.full.pdf

编译:蒋立春

SARS-CoV-2 的病理生理学很复杂而我们对此所知甚少。研究者们采用了网络生物学的方法，整合多组学数据以及人细胞里的相互作用组构建了一个培养的人气道上皮细胞特异性的人-SARS-CoV-2 的相互作用组（CSI，Fig.1）。拓扑聚类分析以及通路富集分析表明 SARS-CoV-2 靶向作用于宿主病毒网络的核心节点。网络中心度分析发现了 28 个很有价值的 SARS-CoV-2 靶点（Fig.3.g）。这些靶点可能参与到病毒感染和疾病传播过程中病毒的入侵，复制以及存活等过程。

研究者建立的概率模型框架阐释了和 COVID-19 相关的关键基因调控回路以及分子事件。总体来讲，该研究中以网络为中心的分析揭示了全新的分子组成，解释了分子水平的结构和功能模块，为 SARS-CoV-2 的病理生理学提供了分子水平的线索。



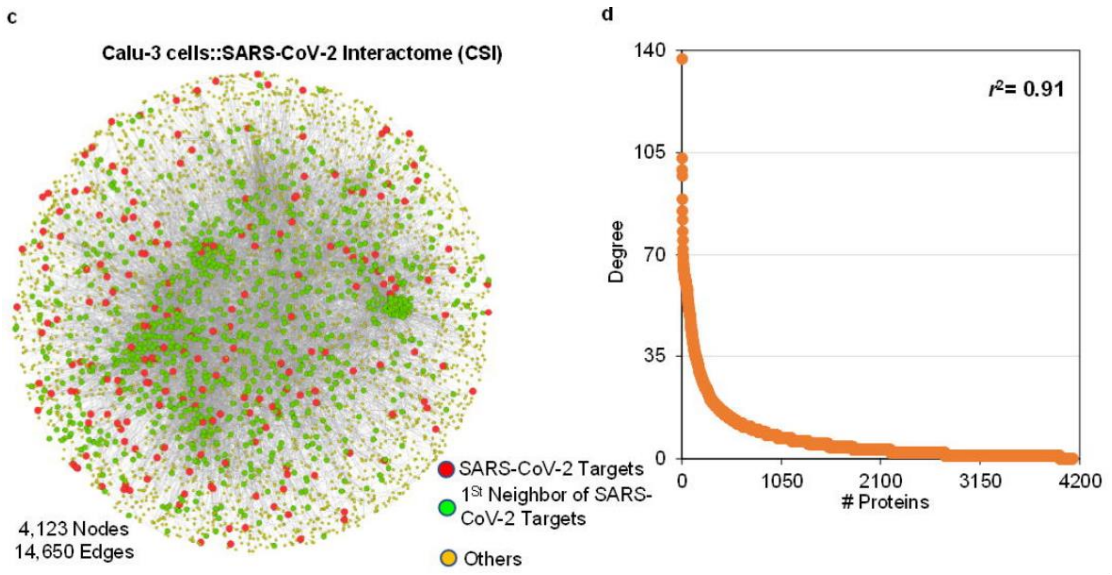


Figure 1: Integrative multi-omics analysis identified Calu-3-specific human-SARSCoV-2 Interactome (CSI). a Human interactomes (HI-II-14, BioPlex , QUBIC, CoFrac, and STRING) connections and 373 SARS-CoV-2 Interacting Proteins (SIPs) were used to extract the "SARS-CoV2::Human PPI" (12,852 Nodes and 84,100 Edges) including all possible interactions. b Weighted gene co-expression network (WGCNA) construction of SARS and MERS Infected Calu-3 cells gene expressions profiles from NCBI GEO datasets. The merged co-expression network has 22,445 Nodes and 10,649,854 Edges. c Calu-3-specific
human-SARS-CoV-2 Interactome (CSI) with 4,123 Nodes and 14,650 Edges (Red: 214 SIPs, Green: 1st Neighbor of SARS-CoV-2 Interacting Proteins (SIPs), Yellow: other proteins). d Degree of CSI nodes displays power law (r 2 =0.91) distribution and follow scale free property.

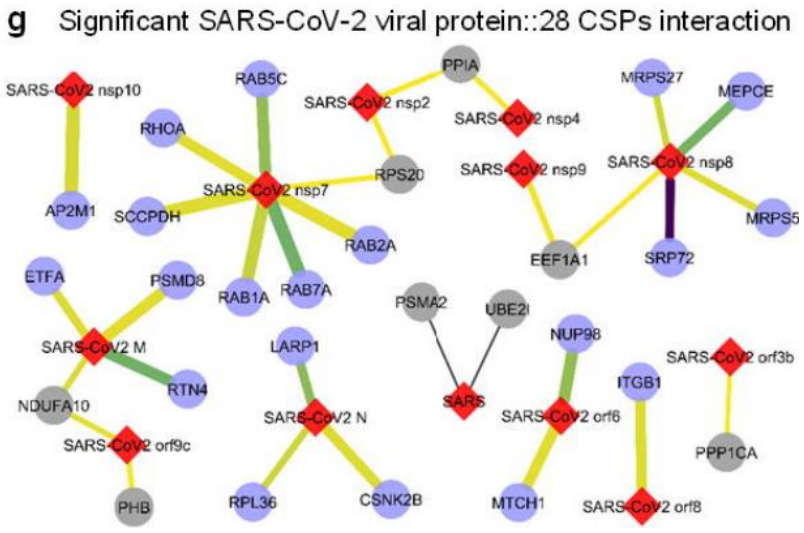


Fig. 3. g
Network representation of significant SARS-CoV-2 viral protein interaction with 28 CSPs (Nodes: Red= viral proteins, Blue= CSPs significantly targeted by viral

protein, grey= CSPs with insignificant viral protein interaction; edge width= MIST score, edge color= AvgSpec).

Abstract

Abstract COVID-19 (Coronavirus disease 2019) is a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While the pathophysiology of this deadly virus is complex and largely unknown, we employ a network biology-fueled approach and integrated multiomics data pertaining to lung epithelial cells-specific coexpression network and human interactome to generate Calu-3-specific human-SARSCoV-2 Interactome (CSI). Topological clustering and pathway enrichment analysis show that SARS-CoV-2 target central nodes of host-viral network that participate in core functional pathways. Network centrality analyses discover 28 high-value SARS-CoV-2 targets, which are possibly involved in viral entry, proliferation and survival to establish infection and facilitate disease progression. Our probabilistic modeling framework elucidates critical regulatory circuitry and molecular events pertinent to COVID-19, particularly the host modifying responses and cytokine storm. Overall, our network centric analyses reveal novel molecular components, uncover structural and functional modules, and provide molecular insights into SARS-CoV-2 pathogenicity.