新型冠状病毒信息简报

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上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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免责申明：
本简报仅作为科研参考之用，不构成医疗建议，如您怀疑自己感染新型冠状病毒，请去正规医院或者咨询医生。

1. 2020 年 5 月 5 日疫情

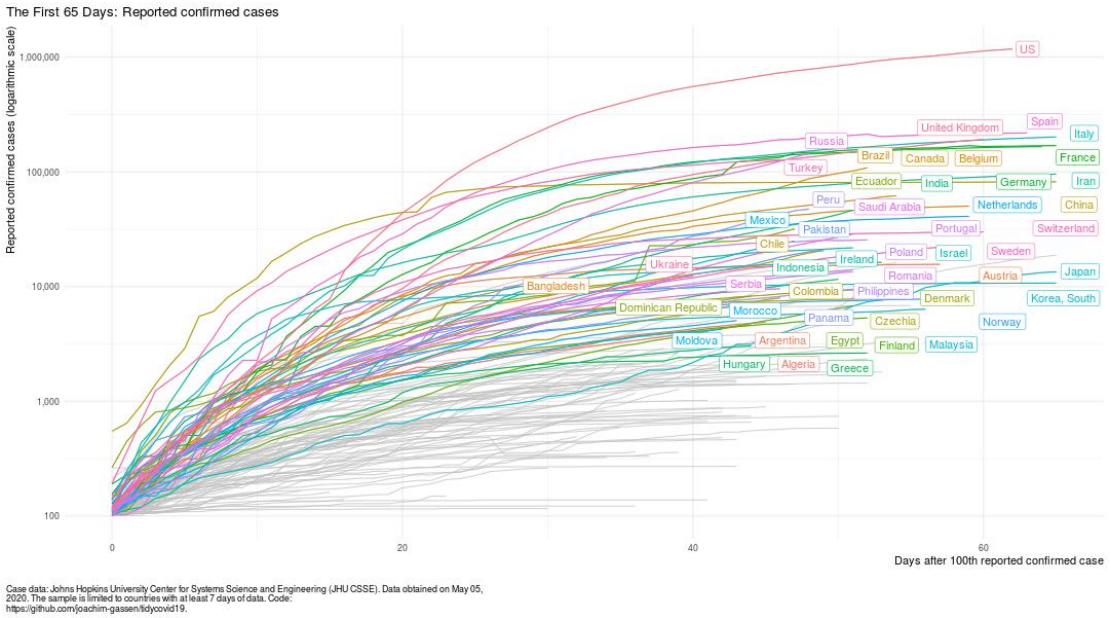
数据来源：WHO

发布时间：2020 年 5 月 5 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 5 月 5 日全球累计确诊新型冠状病毒病人 3517345 例，当日新增确诊 81454 例，累计死亡 243401 例，当日新增死亡 3797。

中国累计确诊 84404 例，累计死亡 4643 例，当日新增确诊 4 例，新增死亡 0 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 5 月 5 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（5月5日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 纽约住院病人中，人种和病亡率无关

分析西奈山健康系统里的住院的 COVID-19 病人的电子病例发现了和预后相关的因素，虽然有色人种感染率显著高于人群，但是人种和病亡率无关

analysis of hospitalized COVID-19 patients in the Mount Sinai Health System using electronic medical records (EMR) reveals important prognostic factors for improved clinical outcomes

来源： medrxiv

发布时间： 2020-05-04

链接： https://www.medrxiv.org/content/10.1101/2020.04.28.20075788v1

3. 商用标准 RNA 浓度标得过低，导致检测试剂盒的灵敏度人为假性提高

加州理工研究人员发现美国 CDC 推荐的确定 COVID-19 检测试剂盒的商用标准 RNA 浓度标得过低，导致检测试剂盒的灵敏度人为假性提高

Commercial stocks of SARS-CoV-2 RNA may report low concentration values, leading to artificially increased apparent sensitivity of diagnostic assays

来源： medrxiv

发布时间： 2020-05-04

链接： https://www.medrxiv.org/content/10.1101/2020.04.28.20077602v1

4. COVID-19 无症状携带者的早期病毒清除及抗体动力学

Early viral clearance and antibody kinetics of COVID-19 among asymptomatic carriers

来源： medRxiv

发布时间： 2020-05-02

链接： https://www.medrxiv.org/content/10.1101/2020.04.28.20083139v1

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DOI 或 PUBMED ID： preprint

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中文摘要：

总结： 目前的研究发现，无症状携带者更年轻，有早期 RNA 转阴，轻度实验室改变和胸部 CT 表现，检测不到 IgM 以及中度水平的 IgG。

背景： 无症状携带者有助于 2019 年冠状病毒病（COVID-19）的传播，但其临床特征、病毒动力学和抗体反应尚不清楚。

方法： 共纳入 56 例入院时无症状的 COVID-19 患者和 19 例年龄相匹配的有症状患者。用 RT-PCR 方法检测 SARS-CoV-2 RNA，用化学发光微粒免疫法检测抗 SARS-CoV-2 的总抗体（Ab）、IgG、IgA 和 IgM。

结果： 在整个随访期间，56 例入院时无症状的 COVID-19 患者中，33 例出现症状，23 例仍无症状。43.8%的无症状携带者为儿童，除一名 64 岁的患者外，所有无症状病例的 C 反应蛋白或白细胞介素-6 均无明显变化。无症状携带者的鼻咽中 SARS-CoV-2 的初始 Ct 阈值与症状发生前的患者和有症状患者相似，但无症状携带者的传染期(9.63 天)短于症状发生前的患者(13.6 天)--采用鼻咽鼻咽拭子中 RNA 阳性代表可传染。三组间总抗体、IgG、IgA 的血清阳性转化率无明显差异，但 IgM 转化率差异较大。无症状组 IgG 和 IgM COI 平均峰值分别

为3.5和0.8，这也低于有症状组IgG和IgM COI峰值分别为4.5和2.4 (p <0.05)。三组病例的抗体动力学如Figure 5所示。

结论：年轻的COVID-19患者似乎更可能是无症状的病例，这些无症状病例的SARS-CoV-2病毒清除早，IgM生成水平较低，但总抗体、IgG和IgA水平较高。本研究的发现为无症状的COVID-19患者的病毒清除和抗体动力学提供了经验信息。

Abstract:

Summary: Asymptomatic carriers were found to be younger, with an early negative conversion of RNA, mild laboratory changes and chest CT manifestations, undetectable IgM and moderate levels of IgG.

Background Asymptomatic carriers contribute to the spread of Coronavirus Disease 2019 (COVID-19), but their clinical characteristics, viral kinetics, and antibody responses remain unclear.

Methods A total of 56 COVID-19 patients without symptoms at admission and 19 age-matched symptomatic patients were enrolled. RNA of SARS-CoV-2 was tested using transcriptase quantitative PCR, and the total antibodies (Ab), IgG, IgA and IgM against the SARS-CoV-2 were tested using Chemiluminescence Microparticle Immuno Assay.

Results Among 56 patients without symptoms at admission, 33 cases displayed symptoms and 23 remained asymptomatic throughout the follow-up period. 43.8% of the asymptomatic carriers were children and none of the asymptomatic cases had recognizable changes in C-reactive protein or interleukin-6, except one 64-year-old patient. The initial threshold cycle value of nasopharyngeal SARS-CoV-2 in asymptomatic carriers was similar to that in pre-symptomatic and symptomatic patients, but the communicable period of asymptomatic carriers (9.63 days) was shorter than pre-symptomatic patients (13.6 days). There was no obvious differences of the seropositive conversion rate of total Ab, IgG, and IgA among the three groups, though the rates of IgM varied largely. The average peak IgG and IgM COI of asymptomatic cases was 3.5 and 0.8, respectively, which is also lower than those in symptomatic patients with peaked IgG and IgM COI of 4.5 and 2.4 (p <0.05).

Conclusion Young COVID-19 patients seem to be asymptomatic cases with early clearance of SARS-CoV-2 and low levels of IgM generation but high total Ab, IgG and IgA. Our findings provide empirical information for viral clearance and antibody kinetics of asymptomatic COVID-19 patients.

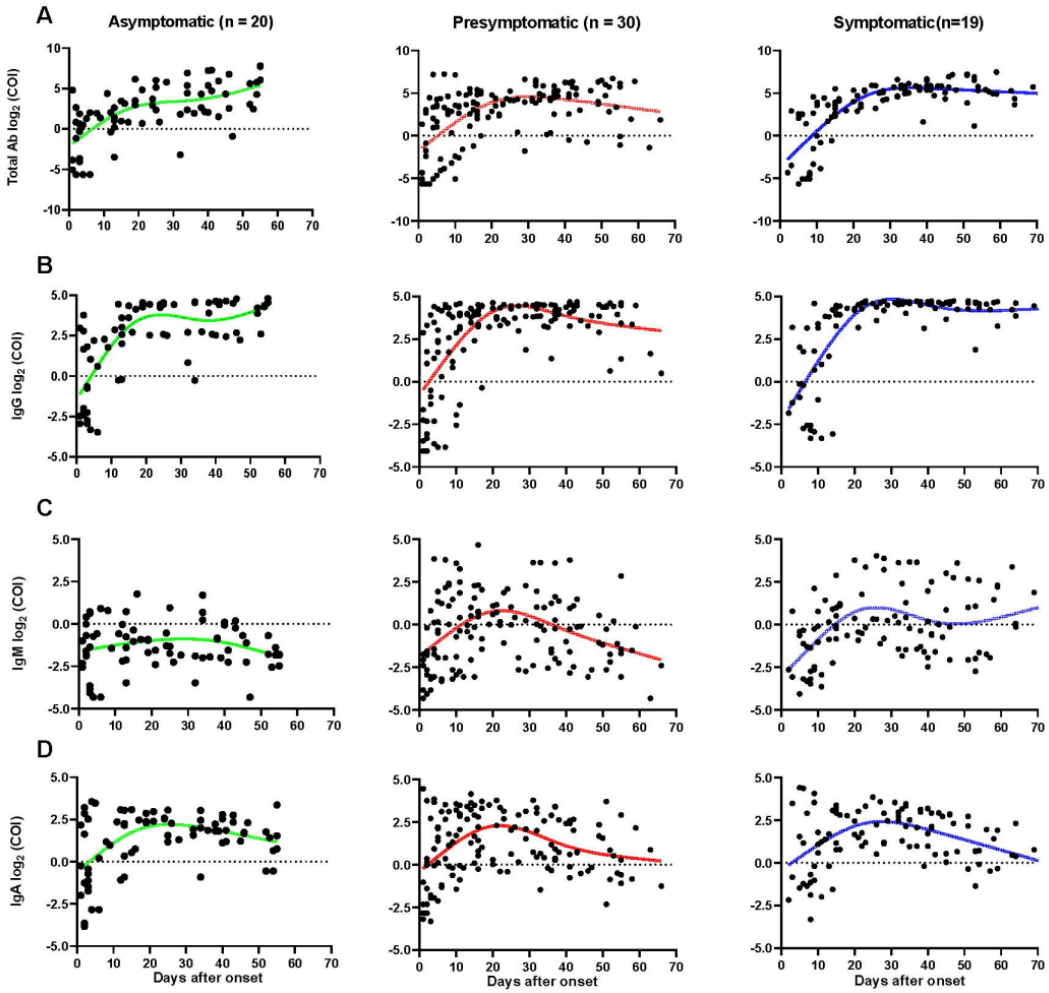

Figure 5. Dynamics of SARS-CoV-2 specific antibodies. The levels of total Ab (A), IgG (B), IgM (C), and IgA (D) of different patients after onset. The relative antibody level was estimated using log2 (COI). Each dot represents a sample, curves represent best fit line. Patients with totally negative antibodies or only one sample was excluded. Negative results are shown below the dotted horizontal lines.

5. 通过一种新型超高通量蛋白组学方法对COVID-19感染者进行临床分类

Clinical classifiers of COVID-19 infection from novel ultra-high-throughput proteomics

来源：medRxiv

发布时间：2020-04-29

链接：https://www.medrxiv.org/content/10.1101/2020.04.27.20081810v1

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中文摘要：

COVID-19是一场空前的全球挑战，它的出现、传播与临床表现都具有高变异性，因此急需一种即时的诊断分类方法。本文作者设计了一种新型的基于质谱的低成本、高通量平台，包括新的样品制备流程和短梯度高流速的液相色谱-质谱分析方法；该方法有利于临床应用，并且可以提高分析通量和定量准确度。通过对一定规模的血清、血浆样品的快速评估，作者报道了区分轻型和重型COVID-19感染的27种生物标志物，其中有些可能可作为潜在治疗靶点。这些蛋白强调了补体因子、凝血系统、炎症机制以及白细胞介素6的上下游的促炎信号通路。该方法的应用将蛋白组学从一个研究工具转变为一种响应快、可临床操作的技术工具，适用于检测爆发性感染。

Summary

The COVID-19 pandemic is an unprecedented global challenge. Highly variable in its presentation, spread and clinical outcome, novel point-of-care diagnostic classifiers are urgently required. Here, we describe a set of COVID-19 clinical classifiers discovered using a newly designed low-cost high-throughput mass spectrometry-based platform. Introducing a new sample preparation pipeline coupled with short-gradient high-flow liquid chromatography and mass spectrometry, our methodology facilitates clinical implementation and increases sample throughput and quantification precision. Providing a rapid assessment of serum or plasma samples at scale, we report 27 biomarkers that distinguish mild and severe forms of COVID-19, of which some may have potential as therapeutic targets. These proteins highlight the role of complement factors, the coagulation system, inflammation modulators as well as pro-inflammatory signalling upstream and downstream of Interleukin 6. Application of novel methodologies hence transforms proteomics from a research tool into a rapid-response, clinically actionable technology adaptable to infectious outbreaks.

6. 转载：新冠病毒感染者出现的五类皮疹

Hanson 临床科研微信公众号

发布时间：2020-05-05

公众号文章链接：

https://mp.weixin.qq.com/s?__biz=MzUxODkzODQxMA==&mid=2247489032&idx=2&sn=9057fcc94473379cd7236ab8f3b2e17b&chksm=f9801c4dcef7955b92358da5abadbf270b151949a0edf21080756fe1f7f3c70d13a426ff74c2&mpshare=1&scene=1&srcid=&sharer_sharetime=1588636849103&sharer_shareid=a3b2167cca65f3faf18e9be218ac9684&key=acb88000024cc52fb0fe33df7928c3164092654d7725988c746a7ebd86c0211e06bf33b64ddd86c3e3c7d8d694808c358e1f7b9978618296ac2ffda529077cc755d50d73787766b8fb224dbf768cca25&ascene=1&uin=MjgxMjY4NjgxNQ%3D%3D&devicetype=Windows+10&version=62080085&lang=zh_CN&exportkey=A5fPATygqXnSHrC7D7zWPUM%3D&pass_ticket=ImX31OhB1SyBllfUolLttmYgefeMt%2FlKIu%2FtzxEVynu2kXhXg7oAmzRXrcAkbI%2FD

推荐：赵素文

原文：

Classification of the cutaneous manifestations of COVID‐19: a rapid prospective nationwide consensus study in Spain with 375 cases

原文链接：https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.19163

7. 重症 COVID-19 患者的辅助免疫治疗

Adjunct immunotherapies for the management of severely ill COVID-19 patients

来源：Cell Reports Medicine (cell 旗下的开放获取杂志)

发布时间：2020-04-29

链接：https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30021-5

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DOI 或 PUBMED ID：https://doi.org/10.1016/j.xcrm.2020.100016

编译者：张丽双

中文摘要：

目前还没有 COVID-19 的特异性治疗方法。现在数据清楚地证实了细胞因子风暴和活化的免疫细胞迁移到肺部是 COVID-19 的免疫反应，如单核细胞源性巨噬细胞（FCN1+）增多、中性粒细胞激增、CD8+T 细胞比例增加、Treg 减少、I 型干扰素诱导基因的强烈上调、血浆 CRP 升高和 IL6 升高等等，过度的免疫反应介导了严重肺损伤和 ARDS。鉴于免疫抑制疗法如皮质类固醇可能的副作用，包括继发感染的风险，作者建议免疫疗法作为辅助治疗重症 COVID-19 患者。这种免疫疗法基于中和炎性细胞因子、免疫调节和被动病毒中和，不仅可以减轻炎症、炎症相关的肺损伤或病毒载量，而且可以同时减少对资源有限的重症监护病房和机械通气的过度依赖。

Abstract:

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has infected millions with more than 181,000 fatal cases as of 22nd April 2020. Currently, there are no specific COVID-19 therapies. Most patients depend on mechanical ventilation. Current COVID-19 data clearly highlight that cytokine storm and activated immune cell migration to the lungs characterize the early immune response to COVID19 that causes severe lung damage and development of acute respiratory distress syndrome. In view of uncertainty associated with immunosuppressive treatments such as corticosteroids and their possible secondary effects, including risks of secondary infections, we suggest immunotherapies as an adjunct therapy in severe COVID-19 cases. Such immunotherapies based on inflammatory cytokine neutralization, immunomodulation and passive viral neutralization, not only reduce inflammation, inflammation-associated lung damage, or viral load, but could also prevent intensive care unit hospitalization and dependency on mechanical ventilation both of which are limited resources.

8. 氯喹治疗 COVID-19 的安全性和有效性的多中心前瞻性观察研究的初步证据

Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19

来源：medRxiv

发布时间：2020-04-26

链接：https://www.medrxiv.org/content/10.1101/2020.04.26.20081059v1

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DOI 或 PUBMED ID：Preprint
编译者：孔娟
中文摘要：

背景： SARS -CoV-2 大流行迫切需要有效的治疗方法。氯喹已被证明具有体外抗冠状病毒的作用。文中研究者旨在评估不同剂量氯喹治疗 COVID-19 的有疗效和安全性。
方法：在这项多中心前瞻性观察研究中，研究者在广东和湖北的 12 家医院招募了 197 名 18 岁以上已确诊 SARS-CoV-2 感染的非重症患者，入组患者每天口服一次（半剂量）或两次（全剂量）500mg 氯喹磷酸盐。176 位接受非氯喹治疗的患者作为历史对照。
结果：
1：疗效分析：
首先，比非氯喹组相比，氯喹组患者病毒 RNA 清除得更快，中位时间提前了 5.4 天。其次，在开始治疗后的第 10 天和第 14 天，氯喹组中检测不到病毒 RNA 的患者占比分别为 91.4%和 95.9%，显著高于非氯喹组，分别为 57.4%和 79.6%。
第三，在临床症状方面，曾有发烧症状的患者中，氯喹组的发热持续时间显著短于非氯喹组，几何平均比率 0.6，但要注意的是，该结果可能部分得益于氯喹的解热作用。
两组患者的住院时间无显著差异，均无患者死亡或入住 ICU。氯喹组中有 1 名患者进展为重症，而非氯喹组中有 9 名。但至研究结束，这 10 名患者最终病毒 RNA 均转阴。
2：亚组分析：
氯喹临床获益较广泛，但对于重症 COVID-19 患者，以及症状发作后 14 天才接受治疗的患者，其临床获益并不显著。
在亚组分析中，与非氯喹组相比，氯喹组在第 10 天和第 14 天胸部 CT 改善的患者占比更高，但差异无统计学意义，这可能因样本量小以及胸部 CT 延迟吸收所致。
氯喹组中出现了 3 位“复阳”患者，出院后 7 天内，他们的呼吸道样本中病毒 RNA 检测呈阴性，但粪便样本中病毒 RNA 检测呈阳性。而非氯喹组中未发现复阳者。
3：安全性分析：
在研究期间，氯喹组中共有 53 例患者（26.9%）发生不良反应，非氯喹组中有 57 例（32.4%）。与非氯喹组相比，氯喹组中胃肠道事件（包括呕吐、腹胀、恶心、食欲下降和口渴）和神经系统不良事件（包括头晕和睡眠障碍）更常见。此外，氯喹组患者比非氯喹组患者更容易出现焦虑情绪。研究组观察到半剂量氯喹组的不良事件少于全剂量氯喹组。对血清氯喹浓度进行监测，结果发现其平均浓度逐渐升高，在用药期间最高达到 1.80 (±0.49) μmol/ L，在停用氯喹的 28 天内降至 0.13 (±0.08) μmol/L。
结论：尽管随机试验需要进一步评估，但这项研究为氯喹在 COVID-19 中的安全性和有效性提供了证据，并表明氯喹可能是对抗 COVID-19 大流行的一种经济有效的疗法。

Abstract:

Background: Effective therapies are urgently needed for the SARS-CoV-2 pandemic. Chloroquine has been proved to have antiviral effect against coronavirus in vitro. In this study, we aimed to assess the efficacy and safety of chloroquine with different doses in COVID-19.
Method: In this multicenter prospective observational study, we enrolled patients older than 18 years old with confirmed SARS-CoV-2 infection excluding

critical cases from 12 hospitals in Guangdong and Hubei Provinces. Eligible patients received chloroquine phosphate 500mg, orally, once (half dose) or twice (full dose) daily. Patients treated with non-chloroquine therapy were included as historical controls. The primary endpoint is the time to undetectable viral RNA. Secondary outcomes include the proportion of patients with undetectable viral RNA by day 10 and 14, hospitalization time, duration of fever, and adverse events.

Results: A total of 197 patients completed chloroquine treatment, and 176 patients were included as historical controls. The median time to achieve an undetectable viral RNA was shorter in chloroquine than in non-chloroquine (absolute difference in medians -6.0 days; 95% CI -6.0 to -4.0). The duration of fever is shorter in chloroquine (geometric mean ratio 0.6; 95% CI 0.5 to 0.8). No serious adverse events were observed in the chloroquine group. Patients treated with half dose experienced lower rate of adverse events than with full dose

Conclusions

Although randomised trials are needed for further evaluation, this study provides evidence for safety and efficacy of chloroquine in COVID-19 and suggests that chloroquine can be a cost-effective therapy for combating the COVID-19 pandemic.

备注：

1.武汉同济医院汪道文团队于 2020 年 5 月 1 日在 medRxiv 上发表的 Hydroxychloroquine application is associated with a decreased mortality in critically ill patients with COVID-19，也报道了通过减轻炎性细胞因子风暴，羟氯喹治疗与重症 COVID-19 患者的死亡率降低显著相关。

https://www.medrxiv.org/content/10.1101/2020.04.27.20073379v1

2.中文部分转载自以下链接：

https://mp.weixin.qq.com/s?src=11&timestamp=1588740369&ver=2321&signature=LmEPnudPmA*6FTux3099QLgf268JawH5Bin7nhu4NvWYyUA63hTsf4hNBLBtwvWbDIRoutZnkIsUverXAMw9HjfPCnzZb4gFBQMxSGtS7Go*SQSrGCSz9zkkInaJh4NY&new=1

9. 骆驼科动物单域抗体有效中和β-冠状病毒的结构基础

Structural Basis for Potent Neutralization of Betacoronaviruses by Single-domain Camelid Antibodies

来源：cell

发布时间：2020-05-05

链接：https://www.cell.com/cell/fulltext/S0092-8674(20)30494-3

3 月 29 日简报第 9 条报道过该工作的预印本

10. 阻断 SARS-CoV-2 感染的人类单克隆抗体

A human monoclonal antibody blocking SARS-CoV-2 infection

来源：Nature COMMUNICATIONS

发布时间：2020-05-04

链接：https://www.nature.com/articles/s41467-020-16256-y

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DOI 或 PUBMED ID：doi.org/10.1038/s41467-020-16256-y
编译者：张鹏伟
中文摘要：
新型人冠状病毒 SARS-CoV-2 在世界范围内引起了呼吸系统疾病（COVID-19）的流行。目前缺乏治疗这种疾病的疫苗和靶向疗法。作者在此报告了一种在细胞培养中能中和 SARS-CoV-2（和 SARS-CoV）的人单克隆抗体。这种交叉中和抗体以这些病毒的共同表位为靶点，可能为 COVID-19 的预防和治疗提供潜力。
为了鉴定 SARS-CoV-2 中和抗体，采用了转基因 H2L2 小鼠(编码人可变重链和轻链以及大鼠来源恒定区域编码嵌合免疫球蛋白)的抗体上清液进行 ELISA（交叉）反应性评估。47D11 表现出 SARS-S 和 SARS2-S 假型 VSV 感染的交叉中和活性。通过将人可变重链和轻链区域克隆到人 IgG1 等型骨架中，将嵌合的 47D11 H2L2 抗体重组为全人免疫球蛋白。47D11 抗体对 SARS-S 和 SARS2-S 假型 VSV 感染 VeroE6 细胞有较强的抑制作用，IC_{50}值分别为 0.061 和 0.061μg/ml。用 SARS-CoV 和 SARS-CoV-2 对 VeroE6 细胞的真实感染已被中和，IC_{50}值为 0.19 和 0.57μg/ ml。47D11 靶向 SARS2-S-$S1_B$结构域中的保守表位。
Abstract:
The emergence of the novel human coronavirus SARS-CoV-2 has caused a worldwide epidemic of respiratory disease (COVID-19). Vaccines and targeted therapeutics for treatment of this disease are currently lacking. Here we report a human monoclonal antibody that neutralizes SARS-CoV-2 (and SARS-CoV) in cell culture. This cross-neutralizing antibody targets a communal epitope on these viruses and may offer potential for prevention and treatment of COVID-19.
In order to identify SARS-CoV-2-neutralizing antibodies, ELISA-(cross) reactivity was assessed of antibody-containing supernatants from immunized transgenic H2L2 mice that encode chimeric immunoglobulins with human variable heavy and light chains and constant regions of rat origin. 47D11 exhibited cross-neutralizing activity of SARS-S and SARS2-S pseudotyped VSV infection.The chimeric 47D11 H2L2 antibody was reformatted to a fully human immunoglobulin, by cloning of the human variable heavy and light chain regions into a human IgG1 isotype backbone. The 47D11 antibody was found to potently inhibit infection of VeroE6 cells with SARS-S and SARS2-S pseudotyped VSV with IC 50 values of 0.061 and 0.061 μg/ml respectively. Authentic infection of VeroE6 cells with SARS-CoV and SARS-CoV-2 was neutralized with IC 50 values of 0.19 and 0.57 μg/ml. 47D11 targets a conserved epitope in the SARS2-S-$S1_B$ domain.
备注：南京医科大学团队于 2020 年 5 月 3 日在 bioRxiv 上发表的 Isolating multiple formats of human monoclonal neutralizing antibodies against SARS-CoV-2 by in vitro site-directed antibody screening，报道了作者通过定点抗体筛选分离了多种形式的 SARS-CoV-2 中和抗体，伪病毒和真实的 SARS-CoV-2 中和试验表明四种抗体都能有效地保护宿主细胞免受病毒感染。
https://www.biorxiv.org/content/10.1101/2020.05.03.074914v1

11. 利用人多能干细胞来源的结肠类器官鉴定阻断新冠病毒感染的药物

Identification of Drugs Blocking SARS-CoV-2 Infection using Human Pluripotent Stem Cell-derived Colonic Organoids

来源：bioRxiv

发布时间：2020-05-02

链接：https://www.biorxiv.org/content/10.1101/2020.05.02.073320v1

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DOI 或 PUBMED ID：https://doi.org/10.1101/2020.05.02.073320

编译者：刘焕珍

中文摘要：

hPSC 衍生的结肠类器官不仅表达 ACE2 和 TMPRS2S2，还可以感染 SARS-CoV-2 假病毒。目前还缺乏能够进行药物筛选的新冠肺炎疾病的生理相关模型。先前的研究是基于临床数据或转基因动物。然而，这些转基因动物未能完全再现人类细胞的细胞表型和宿主反应。作者采用 hPSC 衍生的结肠类器官这个平台进行高通量药物筛选，筛选了 1280 个 FDA 批准的化合物，并鉴定了 MPA（霉酚酸）和 QNHC（盐酸阿的平）这两种能阻止 SARS-CoV-2 假病毒进入人体细胞的药物。值得注意的是，在本实验中，MPA 和 QNHC 阻断病毒进入的功效比氯喹高 5 倍以上，氯喹是 FDA 最近批准用于紧急治疗新冠肺炎患者的药物，MPA 和 QNHC 均可作为新冠肺炎治疗的临床试验候选药物。

Abstract:

We report that hPSC-derived COs（human pluripotent stem cell-derived colonic organoids） express ACE2 and TMPRS2S2 and are permissive to SARS-CoV-2 pseudo-entry virus infection. There is currently a lack of physiologically relevant models for COVID-19 disease that enable drug screens. Previous studies were based on clinical data or transgenic animals. However, such transgenic animals fail to fully recapitulate the cellular phenotype and host response of human cells. We adapted a hPSC-derived CO platform for high throughput drug screening, we screened 1280 FDA-approved compounds and identified MPA（Mycophenolic acid） and QNHC, two drugs that can block the entry of SARS-CoV-2 into human cells. Strikingly, in this assay, the efficacies of MPA and QNHC for blocking viral entry are more than 5 times higher than chloroquine, a drug recently authorized by the FDA for emergency use to treat COVID-19 patients.Both MPA and QNHC can be considered candidates for clinical trials of COVID-19 therapy.

12. SARS-CoV-2 快速适应 BALB/c 小鼠：一个新的测试疫苗有效性的小鼠模型

Rapid adaptation of SARS-CoV-2 in BALB/c mice: Novel mouse model for vaccine efficacy

来源：biorxiv

发布时间：2020-04-29

链接： https://www.biorxiv.org/content/10.1101/2020.05.02.073411v1

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DOI：preprint
编译者：蒋立春
中文摘要：
野生型小鼠对 SARS-CoV-2 不敏感，而转人 ACE2 的转基因小鼠使用成本高，给疫苗研发中的动物学试验带来挑战。该文报道了 SARS-CoV-2 病毒快速适应了 BALB/c 小鼠，因此该小鼠可以为疫苗研发测试提供经济有效的小动物模型。作者们通过将人里分离的 SARS-COV-2 病毒感染老年小鼠的肺部，并且将小鼠肺部取出的病毒依次感染下一批老年小鼠肺部作为 P1 代，一直传到第 6 代。作者们发现适应小鼠的第六代病毒 MACSp6 既可以有效感染年老的 BALB/c 小鼠，也可以有效感染年轻小鼠，并且导致中度的肺炎以及炎症反应。
适应小鼠的第六代病毒 MACSp6 中和原来的病毒相比，发生了 5 个变异，其中 4 个改变了氨基酸。作者通过结构对接等分析推测可能是位于 S 蛋白受体结合区域 RBD 的一个氨基酸变异 N501Y 加强了该病毒对小鼠的感染性。作者用对基于 S 蛋白 RBD 开发的疫苗进进行了体内中和活性检测。发现该疫苗可以高效中和阻断 MACSp6 对 BALB/c 的感染。作者认为这个小鼠模型是一个对疫苗的有效性进行体内实验的方便易得的有效模型。
编者注：病毒在小鼠里传代并累计突变的过程可能在这个研究里得到很好研究，可惜作者没有提到相关工作，也没有提供相关原始测序数据。
Abstract:
Coronavirus disease 2019 (COVID-19) threatens global public health and economy. In order to develop safe and effective vaccines, suitable animal models must be established. Here we report the rapid adaption of SARS-CoV-2 in BALB/c mice, based on which a convenient, economical and effective animal model was developed. Specifically, we found that mouse-adapted SARSCoV-2 at passage 6 (MACSp6) efficiently infected both aged and young wild-type BALB/c mice, resulting in moderate pneumonia as well as inflammatory responses.
The elevated infectivity of MACSp6 in mice could be attributed to the substitution of a key residue (N501Y) in the receptorbinding domain (RBD). Using this novel animal model, we further evaluated the in vivo protective efficacy of an RBD-based SARS-CoV-2 subunit vaccine, which elicited highly potent neutralizing antibodies and conferred full protection against SARS-CoV-2 MACSp6 challenge. This novel mouse model is convenient and effective in evaluating the in vivo protective efficacy of SARS-CoV-2 vaccine

13. 刺突蛋白分析流程揭示了一种更具传染性的 SARS-CoV-2 的出现

Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2

来源：biorxiv
发布时间：2020-05-05
链接：https://www.biorxiv.org/content/10.1101/2020.04.29.069054v2
第一作者：Bette Korber
通讯作者：Bette Korber
通讯作者单位：Theoretical Biology and Biophysics, Los Alamos National Laboratory, Los Alamos, NM87545 USA

DOI 或 PUBMED ID：preprint

编译者：王玮

中文摘要：

该研究开发了一个分析流程，以便于实时跟踪 SARS-CoV-2 的突变，最初的跟踪重点是刺突蛋白，因为刺突蛋白介导了人类细胞的感染，是大多数疫苗策略和抗体治疗的目标。SARS-CoV-2 基因组数据来自 GISAID，共获得 6,346 条刺突蛋白序列和 4,535 条基因组序列。到目前为止，已经鉴定出了 14 种正在积累的突变（表一）。突变是在更广泛的系统发育背景下，在地理上，并随着时间的推移，提供一个早期预警系统，揭示可能在传播或抵抗干预方面具有选择性优势的突变。对于每一个被评估为阳性选择的突变，该研究通过结构模型探讨了这些突变的含义。刺突蛋白 D614G 突变是一个值得关注的突变；在 2 月初开始在欧洲传播后，当它被引入新的地区时，它迅速成为主要的形式。此外，我们还提供了局部循环病毒株之间重组的证据，表明存在多个病毒株感染。这些发现对 SARS-CoV-2 的传播、发病机制和免疫干预具有重要意义。

Spike Mutation	Spike Location Possible Impact	04/13/20 Count	Geographic Sampling	Phylogenetic Pattern
D614G	SARS-CoV epitope Interprotomer stabilization	3577	Global	One main lineage & recurrent emergence
L5F	Signal Peptide	37	13 countries	Recurrent emergence
L8V/W	Signal Peptide	18	Hong Kong	
H49Y	S1 NTD domain	12	China	
Y145H/del	S1 NTD domain	10	6 countries	
Q239K	S1 NTD domain	8	Europe	
V367F	Up/Down conformations	12	Europe/Hong Kong	
G476S	Directly in the RBD	8	Washington, USA	
V483A	Up/Down conformations	21	Washington, USA	
V615I/F	In SARS-CoV ADE epitope	13	Wales	
A831V	Potential fusion peptide in S2	28	Iceland	One lineage
D839Y/N/E	S2 subunit	27	Europe	
P1263L	Cytoplasmic Tail	49	UK/Iceland/Australia	One lineage
Mutational cluster 934-940:	Fusion core of HR1	65	Different forms in 9 countries	

Table 1. Table summarizing the mutations we are following in Spike. With the exception of D614G, all other mutations in Spike remain rare; we will nonetheless monitor them for potential immunological impact and/or for increased frequencies regionally or globally as the pandemic progresses. The NTD is the N-terminal domain, S2 is a membrane fusion subunit, and HR1 the first heptad repeat region (Lv et al., 2020). Up/Down conformations refer to a change in state in which the up conformation exposes the RBD (Kirchdoerfer et al., 2016; Kirchdoerfer et al., 2018). The SARS-CoV epitope was identified from the first SARS epidemic, and is the immunodominant linear antibody epitope observed in natural infection

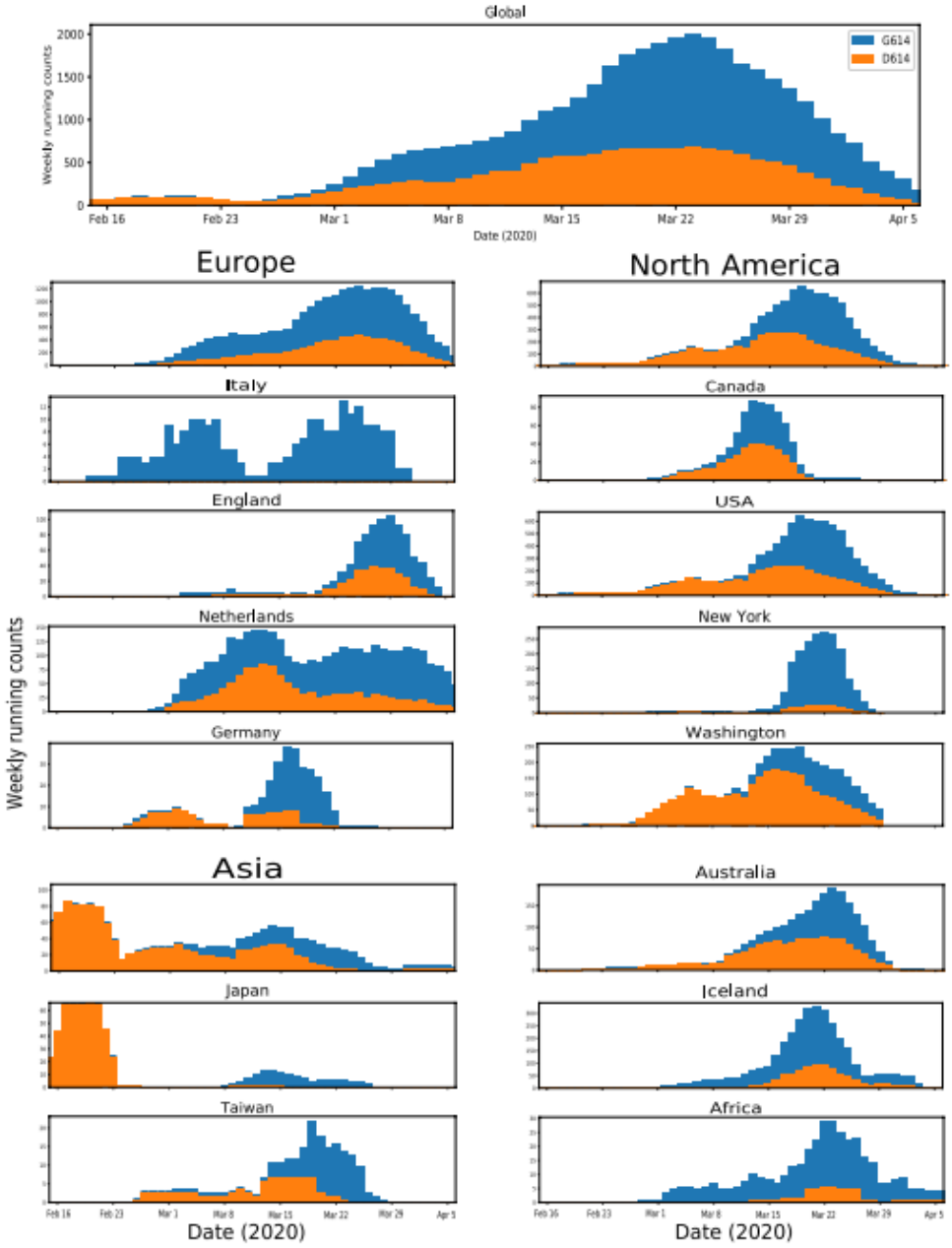

Fig. 3. Running weekly average counts showing the relative amount of D614 (orange) and G614, (blue) in different regions of the world. In almost every case soon after G614 enters a region, it begins to dominate the sample. Fig. S3 shows the same data, illustrated as a daily cumulative plot. Plots were generated with Python Matplotlib (Hunter, 2007). The plots shown here and in Fig. S3 can be recreated with contemporary data from GISAID at www.cov.lanl.gov.

编者注：

相关文章:

Molecular Architecture of Early Dissemination and Evolution of the SARS-CoV-2 Virus in Metropolitan Houston, Texas

https://www.biorxiv.org/content/10.1101/2020.05.01.072652v2.full.pdf

该研究对德克萨斯州休斯顿市（一个有 700 万居民的多民族地区）的 COVID-19 患者的 320 株 SARS-CoV-2 进行了基因组测序。这些病毒基因组来自休斯顿大流行的早期阶段。在该研究所测序的病毒株中，有 70%（320 株中的 224 株）发生了 D614G 突变。

Abstract:

We have developed an analysis pipeline to facilitate real-time mutation tracking in SARS-CoV-2, focusing initially on the Spike (S) protein because it mediates infection of human cells and is the target of most vaccine strategies and antibody-based therapeutics. To date we have identified fourteen mutations in Spike that are accumulating. Mutations are considered in a broader phylogenetic context, geographically, and over time, to provide an early warning system to reveal mutations that may confer selective advantages in transmission or resistance to interventions. Each one is evaluated for evidence of positive selection, and the implications of the mutation are explored through structural modeling. The mutation Spike D614G is of urgent concern; after beginning to spread in Europe in early February, when introduced to new regions it repeatedly and rapidly becomes the dominant form. Also, we present evidence of recombination between locally circulating strains, indicative of multiple strain infections. These finding have important implications for SARS-CoV-2 transmission, pathogenesis and immune interventions.

在 https://bigd.big.ac.cn/ncov 数据信息系统中，也可以观察到以上两篇文章提到的突变。在中国境内发生的该变异占比例很低，主要是后期传入少数病例的病毒为该基因型。

14. 恢复期病人免疫细胞单细胞测序

Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing

来源： cell discovery

发布时间： 2020-05-04

链接： https://www.nature.com/articles/s41421-020-0168-9

3 月 28 日简报第 5 条报告过该文章的预印本

15. 用合成基因组平台快速构建一个 SARS-CoV-2 病毒

Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform

来源： nature

发布时间： 2020-05-04

链接： https://www.nature.com/articles/s41586-020-2294-9

4 月 4 日简报第 8 条编者注讲到过这篇文章的预印本

16. SARS-CoV-2 刺突蛋白的一个多碱基酶切位点是对人肺细胞感染至关重要

A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells

来源： molecular cell

发布时间： 2020-05-01

链接：

https://www.sciencedirect.com/science/article/pii/S1097276520302641?via%3Dihub

4 月 22 日简报第 5 条报道了该文章的预印本

17. 瑞德西韦抑制 SARS-CoV-2 病毒 RNA 依赖 RNA 聚合酶的结构基础

Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-

CoV-2 by remdesivir

来源： Science

发布时间： 2020-05-01

链接： https://science.sciencemag.org/content/early/2020/04/30/science.abc1560

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DOI 或 PUBMED ID： 10.1126/science.abc1560

编译者： 宋珂

中文摘要：

由 SARS-CoV-2 病毒导致的 COVID-19 疫情已发展为全球性的危机。SARS-CoV-2 病毒需要利用 RNA 依赖 RNA 聚合酶（RdRp）才能完成复制，这正是抗病毒药物“瑞德西韦”的靶点。本文中，作者使用冷冻电镜解析了 SARS-CoV-2 RdRp apo 状态的结构，分辨率为 2.8Å。同时还解析了 RdRp 与包含 50 个碱基的模板-引物 RNA 链和“瑞德西韦”形成的复合物结构，分辨率为 2.5Å。通过分析复合物结构，作者发现部分双链 RNA 模板插入了 RdRp 的中央通道。在第一对碱基复制的位置，“瑞德西韦”通过共价键与引物链结合，终止了 RNA 链的生长。解析出的结构为了解病毒 RNA 的复制机制提供了重要的信息，并为研发抗病毒感染的药物提供了合理的模板。

译者注：与《Structure of the RNA-dependent RNA polymerase from COVID-19 virus》和《Structure of replicating SARS-CoV-2 polymerase》的异同。

这三篇文章都利用 Cryo-EM 解析了 SRAR-CoV-2 nsp12(RdRp)-nsp7-nsp8 复合物的结构。本文在解析了 apo 状态的 RdRp 结构基础上，还解析了 RdRp 与 template-primer RNA 和 Remdesivir 的复合物机构。从结构上揭示了 Remdesivir 阻断病毒 RNA 复制的机制。

《Structure of the RNA-dependent RNA polymerase from COVID-19 virus》文中，解析了 nsp12(RdRp)-nsp7-nsp8 复合物的结构，并根据 sofosbuvir 与 HCV ns5b 的结合模式，推测出了 Remdesivir 与 RdRp 的结合形式。

《Structure of replicating SARS-CoV-2 polymerase》一文解析了 RdRp 与 template-primer RNA 的复合物结构。（译者水平有限，如有错误，请读者批评指正！）

Abstract:

The pandemic of Corona Virus Disease 2019 (COVID-19) caused by SARS-CoV-2 has become a global crisis. The replication of SARS-CoV-2 requires the viral RNA-

dependent RNA polymerase (RdRp), a target of the antiviral drug, Remdesivir. Here we report the cryo-EM structure of the SARS-CoV-2 RdRp either in the apo form at 2.8 Å resolution or in complex with a 50-base template-primer RNA and Remdesivir at 2.5 Å resolution. The complex structure reveals that the partial double-stranded RNA template is inserted into the central channel of the RdRp where Remdesivir is covalently incorporated into the primer strand at the first replicated base pair and terminates chain elongation. Our structures provide critical insights into the mechanism of viral RNA replication and a rational template for drug design to combat the viral infection.

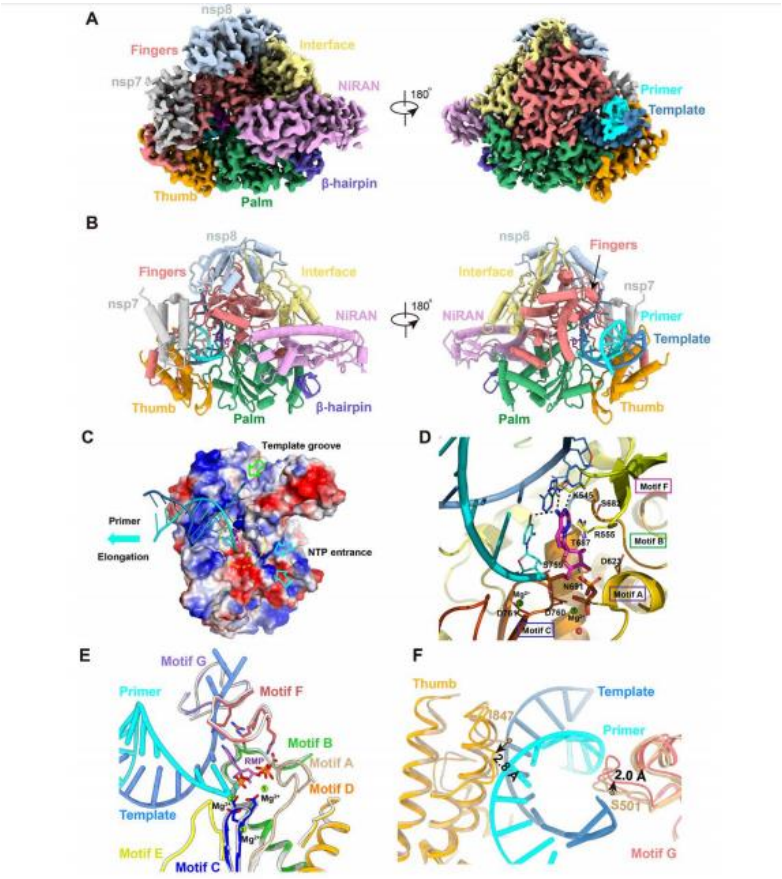

Fig. 3. Cryo-EM Structure of the Remdesivir and RNA bound RdRp complex. (**A** and **B**) Two views of cryo-EM map (A) and structure (B) of the nsp12-nsp7-nsp8 in complex with template-primer RNA and Remdesivir. (**C**) Surface view of the RdRp active site with the electrostatic potential from red (negative) to blue (positive). For clarity, residues 410-442, 834-919 of nsp12 and nsp8 are excluded from the figure. The covalently bound Remdesivir in the monophosphate form and the product, pyrophosphate, are shown. The active site is emphasized with a yellow dashed circle. The template groove, the entrance for NTP and the elongation direction are annotated with different colored arrows. (**D**) A close view of the RdRp active site, showing the covalently bound RMP, pyrophosphate, and magnesium ions. Key residues and bases that interact with Remdesivir are shown. (**E** and **F**) Superposition of the conserved RdRp motifs (A to G) of the RNA bound complex with the apo structure colored in gray, with a close view at the active site (E) and at the exit of the template and primer strand (F).

18. 重症 SARS-CoV-2 患者表现为滤泡外 B 细胞活化的狼疮样特征

Critically ill SARS-CoV-2 patients display lupus-like hallmarks of extrafollicular B cell activation

来源： medRxiv

发布时间：2020-05-03
链接：https://www.medrxiv.org/content/10.1101/2020.04.29.20083717v1
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通讯作者：Ignacio Sanz
通讯作者单位：美国埃默里大学洛万斯人体免疫学中心风湿科医学系
DOI 或 PUBMED ID：Preprint
编译者：雷颖

中文摘要：
疾病过程从无症状传播到呼吸衰竭和死亡的广泛异质性已成为 SARS-CoV-2 大流行病的标志。虽然这种临床进程有很好的记录，但它的免疫基础仍不太清楚。因此，作者进行了 B 细胞反应的研究，因为它们参与早期效应反应和记忆形成的开始。在效应反应方面，作者最近在耀斑性红斑狼疮（flaring SLE）中阐述了滤泡外通路（EF）的参与和临床相关性。在这种全身性自身免疫性疾病中，EF 途径是由新激活的幼稚 B 细胞（aN）启动的，通过产生表观基因启动的 B 细胞前体，导致产生自身抗体的抗体分泌细胞的大量扩增，这种前体是幼稚（IgD）和记忆标记物（CD27）的双阴性（DN）并缺乏 CXCR5 和 CD21（DN2）的表达。这些高活化的 D2 细胞也可以通过 CD11c 和 T-bet 的高表达来区分，而且它们是 TLR7 驱动的。在病毒清除中，由 ssRNA 触发的 TLR7-刺激，以及由它们在小鼠中的对应部分（通常被描述为年龄相关的 B 细胞）发挥的中心作用，都有力地支持了 DN2 细胞和全体 EF 通路可能显著参与 COVID-19 患者的假设。同样值得注意的是，EF-B 细胞激活在非裔美国人的 SLE 患者中尤为突出，在重症 COVID-19 中这一群体不成比例。在这项研究中，作者发现危重病人的 COVID-19 有力地上调了滤泡外通路的成分，产生了大量的抗体分泌细胞，并失去了独特的过渡 B 细胞群体，且与阳性预后相关。这一患者集群与不良结果的生物标志物密切相关，并表现出较高的死亡率。因此，这种 B 细胞表型可能可以在早期阶段作为严重 COVID 感染的免疫学标志，从而可以确定一个病人子集，他们可能可以从旨在减轻疾病负担的靶向免疫调节治疗中受益。

Abstract
Wide heterogeneity of disease course ranging from asymptomatic spread to respiratory failure and death has become a hallmark of the SARS-CoV-2 pandemic. While this clinical spectrum is well documented, its immunologic underpinnings are less clear. We have therefore, initiated studies of the B cell responses as they would participate in both early effector responses and in the initiation of memory formation. In terms of effector responses, we were particularly interested in the engagement and clinical correlates of the extra-follicular pathway (EF), we recently described in flaring SLE. In this systemic autoimmune disease, the EF pathway is initiated by newly activated naive B cell (aN) leading to large expansion of autoantibody-producing antibody-secreting cells through the generation of an epigenetically primed B cell precursor which are double negative (DN) for naive (IgD) and memory markers (CD27) and lacking expression of CXCR5 and CD21 (DN2). These highly activated D2 cells are also distinguished by high expression of CD11c and T-bet and are TLR7-driven. Both, TLR7-stimulation which is triggered by ssRNA and the central role played by their murine counterparts (typically characterized as Age-Associated B cells), in viral clearance, strongly supported the hypothesis that DN2 cells and the global EF pathway could be prominently engaged in COVID-19 patients. Also of note, EF B cell activation is particularly prominent in SLE patients of African-American ancestry, a population

disproportionately represented in severe COVID-19. In this study we find that critically-ill patients with COVID-19 robustly upregulate constituents of the extrafollicular pathway, produce enormous numbers of antibody secreting cells, and lose unique transitional B cell populations that correlate with positive prognosis. This patient cluster associates tightly with biomarkers of poor outcomes and exhibits high rates of mortality. Thus, this B cell phenotype might serve as an immunological marker of severe COVID infection at early stages and could therefore identify a patient subset likely to benefit from targeted immunomodulatory therapy aimed at alleviating disease burden.

19. 免疫致病机制在 COVID-19 进展中可能的作用

A possible role of immunopathogenesis in COVID-19 progression

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中文摘要：

背景：体液免疫和细胞免疫的效果决定了病毒感染的后果。适当的免疫反应可以起到保护的作用，然而在病毒感染中，过度的免疫反应与免疫介导的发病机制相关。本研究探讨不同严重程度的 COVID-19 患者的常规和 SARS-CoV-2 特异性细胞和体液免疫状态。

方法：在这项研究中，作者收录了 53 例 COVID-19 中、重度和危重患者临床表现，比较了循环免疫细胞、SARS-CoV-2 抗原特异性 T 细胞和体液免疫的数量、表型和功能特征。

结果：严重和/或危急 COVID-19 患者的 CD8+ T 细胞、CD4+和 CD8+ T 细胞亚群在循环中的分化记忆/效应表型和迁移能力明显低于中度疾病患者。重要的是，临床病程从严重到中度的改善伴随着 T 细胞亚群转变的改善。此外，他们发现，在首次使用 SARS-CoV-2 S-蛋白重叠肽刺激后，三组患者均出现了可检测的 SARS-CoV-2 的 T 细胞反应。值得注意的是，危急的 COVID-19 患者表现出更强的 SARS-CoV-2 的 T 细胞反应，产生了 Th1 相关的炎症性细胞因子。此外，抗体滴度与 SARS-CoV-2 反应性 CD4+频率之间的明显的相关性，强调了特异性免疫在疾病进程中的作用。

结论：作者的数据表明，激活的记忆表型循环 T 细胞的消耗和较强 SARS-CoV-2 特异性细胞和体液免疫与 COVID-19 疾病的严重程度有关。这一发现可能对诊断、治疗和预防 COVID-19 具有重要意义。

Abstract

Background: The efficacy of the humoral and cellular immunity determines the outcome of viral infections. An appropriate immune response mediates protection, whereas an overwhelming immune response has been associated with immune-mediated pathogenesis in viral infections. The current study explored the general and SARS-CoV-2 specific cellular and humoral immune status in patients with different COVID-19 severities.

Methods: In this prospective study, we included 53 patients with moderate, severe,

and critical COVID-19 manifestations comparing their quantitative, phenotypic, and functional characteristics of circulating immune cells, SARS-CoV-2 antigen specific T-cells, and humoral immunity.

Results: Significantly diminished frequencies of CD8+ T-cells, CD4+ and CD8+T-cell subsets with activated differentiated memory/effector phenotype and migratory capacity were found in circulation in patients with severe and/or critical COVID-19 as compared to patients with moderate disease. Importantly, the improvement of the clinical courses from severe to moderate was accompanied by an improvement in the T-cell subset alterations. Furthermore, we surprisingly observed a detectable SARS-CoV-2-reactive T-cell response in all three groups after stimulation with SARS-CoV-2 S-protein overlapping peptide pool already at the first visit. Of note, patients with a critical COVID-19 demonstrated a stronger response of SARS-CoV-2-reactive T-cells producing Th1 associated inflammatory cytokines. Furthermore, clear correlation between antibody titers and SARS-CoV-2-reactive CD4+ frequencies underscore the role of specific immunity in disease progression.

Conclusion: Our data demonstrate that depletion of activated memory phenotype circulating T-cells and a strong SARS-CoV-2-specific cellular and humoral immunity are associated with COVID-19 disease severity. This counter-intuitive finding may have important implications for diagnostic, therapeutic and prophylactic COVID-19 management.

20. UCSC SARS-CoV-2 基因组浏览器

The UCSC SARS-CoV-2 Genome Browser

来源： biorxiv

发布时间： 2020-05-04

链接: https://www.biorxiv.org/content/10.1101/2020.05.04.075945v1

除了 ucsc 常规基因组 browser(基因组注释、基因组保守性等等)内容之外，该网站还囊括了 nextstrain.org 里面的病毒全球展示链接，以及展示肺部单细胞测序的 cell browser。