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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1. 2020 年 5 月 6 日疫情

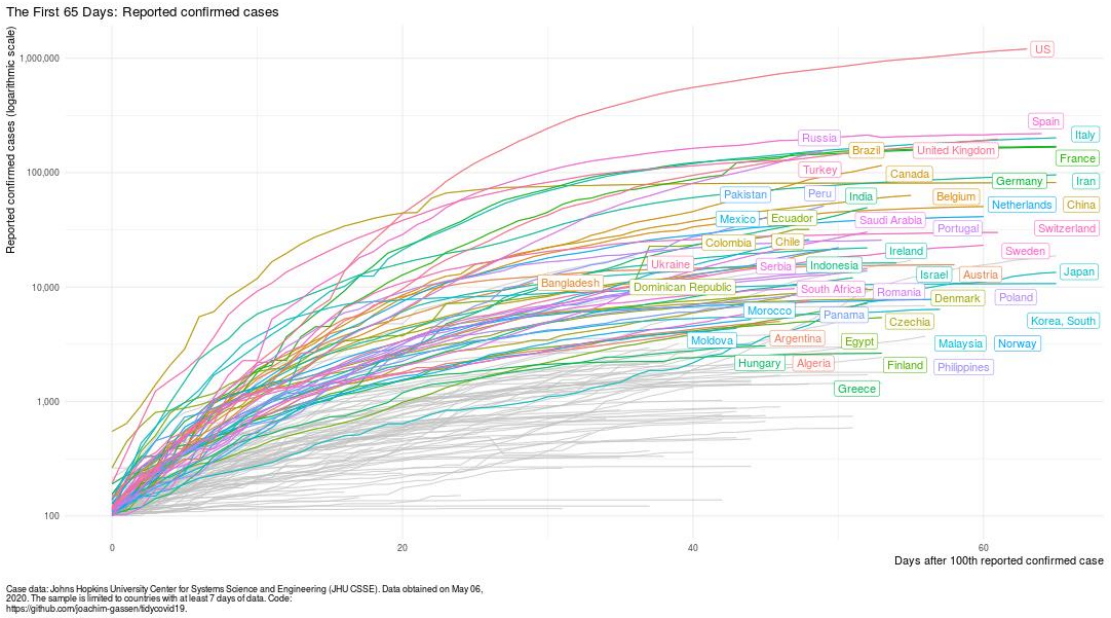
数据来源：WHO

发布时间：2020 年 5 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 5 月 6 日全球累计确诊新型冠状病毒病人 3588773 例，当日新增确诊 71463 例，累计死亡 247503 例，当日新增死亡 4102。

中国累计确诊 84406 例，累计死亡 4643 例，当日新增确诊 2 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 6 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6日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. SARS-CoV-2 与流感病毒共感染

SARS-CoV-2 and influenza virus co-infection

来源：The Lancet
发布时间：2020-05-05
链接：https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31052-7/fulltext

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DOI 或 PUBMED ID： 10.1016/S0140-6736(20)31052-7

编译者：宋张悦

中文摘要：

自 2019 年 12 月以来，2019 年冠状病毒病(COVID-19)已成为国际公共卫生突发事件。严重急性呼吸系统综合征冠状病毒 2 (SARS-CoV-2)在临床表现、传播机制和季节一致性方面与流感病毒相似。因此，两种病毒同时感染是可行的。据之前的报道，只有一例合并感染病例，诊断是相继发生的。本文中，研究人员报告了四例同时诊断为 SARS-CoV-2 和流感合并感染的病例。

患者 1-3 为男性，年龄分别为 53 岁、78 岁、56 岁，患者 4 为女性，年龄为 81 岁（详见下表）。4 例患者均有高血压病史。患者 1 和 4 有血液透析终末期肾病病史，患者 2 和 4 有 2 型糖尿病。4 例患者均因干咳、发热和呼吸困难而就诊于急诊科 3 天。

体格检查显示，除 3 号患者外，所有患者均出现呼吸急促和低氧饱和度支气管痉挛，其数值正常。2 例患者入院时胸部摄片呈病理性改变：患者 2 为双侧浸润，患者 4 为右双叶性肺炎。分析结果汇总在下表中。

患者 1 和 2 的甲型流感快速核酸扩增检测均为阳性。患者 3 的甲型和乙型流感检测均为阳性，患者 4 的乙型流感检测为阳性。按照 SARS-CoV-2 的本地诊断方案，同时进行 RT-PCR 检测，四名患者均为阳性。患者 3 于 48h 后出院，无治疗及并发症。然而，患者 1、2 和 4 的呼吸系统迅速恶化，需要口气管插管和机械通气。

初始治疗使用洛匹那韦-利托那韦 400/100 mg，每天两次，口服羟基氯喹 200 mg，每天两次（血液透析患者，每天两次 100 mg），口服奥司他韦 150 mg，每天两次（血液透析患者，每 48 小时 30 mg）。患者 2 和 4 每 48h 皮下注射干扰素 β-1b 8MU。患者 1 的临床症状有所改善，入院 72 小时后病情稳定，需氧量低。患者 2 和 4 入院 72h 后仍保持机械通气。

本文中，研究人员重点介绍了四例 SARS-CoV-2 和流感共感染病例，并说明了这种共感染可能产生的影响。这些患者的临床和分析过程与之前报道的 COVID-19 没有区别，但是，还需要更多的研究来评估 SARS-CoV-2 和流感共同感染对临床结局的影响。作者呼吁医学界提高警惕，即使病人的病因可能是其他病毒，也要将 COVID-19 作为一种潜在的诊断，尤其是在 COVID-19 疫情流行区。

	CRP (mg/dL [<1 mg/dL])			LDH (U/L [<234 U/L])			Ferritin (ng/mL [20-400])			D-dimer (ng/mL [<500])			Lymphocyte count (×10⁹ cells per L [0·9-4·5])			Platelets count (×10⁹ cells per L [130-400])			Ultrasensitive troponin I (ng/L [<45·2])		
	0 h	24 h	72 h	0 h	24 h	72 h	0 h	24 h	72 h	0 h	24 h	72 h	0 h	24 h	72 h	0 h	24 h	72 h	0 h	24 h	72 h
Patient 1 (man, 53 years)	4·3	10	10	NA	191	209	NA	905	1203	NA	700	1300	0·6	0·4	0·3	125	101	86	191	168	300
Patient 2 (man, 78 years)	14·0	15·0	3·6	314	340	283	NA	162	235	NA	NA	2100	0·3	0·3	0·5	60	60	81	NA	NA	NA
Patient 3 (man, 56 years)	2·1	3·18	NA	NA	NA	NA	280	305	NA	200	200	NA	1·2	1·8	NA	199	205	NA	2·8	2·9	NA
Patient 4 (woman, 81 years)	1·3	6·1	9·7	247	231	250	NA	NA	NA	200	NA	NA	0·5	0·5	0·7	99	78	78	1748	648	836

Numbers in square brackets correspond to the normal laboratory values. CRP=C-reactive protein. LDH=Lactate dehydrogenase. NA=not available.

Table: **Analytical findings of four patients with severe acute respiratory syndrome coronavirus 2 and influenza virus co-infection**

Abstract:
Since December, 2019, coronavirus disease 2019 (COVID-19) has been an international public health emergency. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mimics the influenza virus regarding clinical presentation, transmission mechanism, and seasonal coincidence. Thus, co-infection by both viruses is feasible. To the best of our knowledge, only one case of co-infection is known, although the diagnosis was sequential. Here, we present four cases of SARS-CoV-2 and influenza co-infection, diagnosed simultaneously.
Patients 1–3 were men aged 53, 78, and 56 years, respectively, and patient 4 was a woman aged 81 years (table). All four patients had a medical history of hypertension. Patients 1 and 4 had a history of end-stage kidney disease on haemodialysis, and patients 2 and 4 had type 2 diabetes. All four patients attended the emergency department because of non-productive cough, fever, and dyspnoea for 3 days.
Here we highlight four cases of SARS-CoV-2 and influenza co-infection and show the implications that such a co-infection can have. The clinical and analytical courses in these patients did not differ from those previously reported for COVID-19. However, more studies are needed to assess the effect of the SARS-CoV-2 and influenza co-infection in clinical outcomes. We call on the medical community to be aware and take COVID-19 into account as a potential diagnosis even in patients with other viral causes, especially in epidemic areas.

3. Covid-19 患者狼疮抗凝及异常凝血试验

Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19
来源：The new england journal of medicine
发布时间：2020-05-05
链接：https://www.nejm.org/doi/full/10.1056/NEJMc2013656
第一作者：Louise Bowles，Sean Platton
通讯作者：K. John Pasi
通讯作者单位：Royal London Hospital, London, United Kingdom
DOI 或 PUBMED ID：10.1056/NEJMc2013656
编译者：王玮
中文摘要：

Covid-19 患者具有严重的高凝状态，且常见复杂静脉血栓形成。在 Covid-19 患者中，凝血筛查出现异常，包括活化部分凝血活酶时间（aPTT）延长。这一发现被视为避免在治疗和预防剂量下使用抗凝剂的理由。

延长的 aPTT 可能说明凝血因子缺乏或存在特异性（如抗凝血因子 VIII 的抗体）或非特异性（如狼疮抗凝剂）的凝血抑制剂。狼疮抗凝剂可影响体外凝血试验，但通常与出血无关。作为抗磷脂综合征的一部分，狼疮抗凝剂与血栓形成风险相关。该研究调查了 Covid-19 患者 aPTT 延长的原因。

对 216 例 SARS-CoV-2 阳性患者的血液样品进行凝血筛查，发现 44 例（20%）aPTT 延长。

排除 9 例患者的样品，并进一步调查 35 例患者的样品。
结果摘要见表 1。中位年龄 57 岁，男性 24 例。肺栓塞 1 例，临床疑似血栓形成 1 例。具临床意义的出血或动脉血栓未见。

未发现任何患者存在因子 VIII 或因子 IX 的缺陷。在 5 名患者中，发现因子 XI 的边际降低，但不太可能具有临床意义。16 例患者的因子 XII 水平为 50 IU per deciliter 或更低。34 例患者行狼疮抗凝试验，阳性 31 例（91%）。34 例患者中有 18 例（53%）经稀释罗素毒液时间（DRVVT）和狼疮抗凝敏感 aPTT 检测，7 例（21%）经 DRVVT 检测，6 例（18%）经单独狼疮抗凝敏感 aPTT 检测，显示狼疮抗凝剂的存在。所有狼疮抗凝阳性标本均具有 50:50 混合的延长 aPTT（即，由 50%患者血浆和 50%正常血浆组成的样品）。

在 540 例接受狼疮抗凝试验的历史对照组中，43 例（8%）的 aPTT 为 30 秒或更长，其中 11 例（26%）的抗狼疮抗凝试验呈阳性。Covid-19 组狼疮抗凝剂阳性率明显高于对照组（P<0.001）。

在该研究中发现，大多数 Covid-19 患者住院时 aPTT 延长并对狼疮抗凝剂呈阳性（91%），并且常伴有相关的因子 XII 缺乏。值得注意的是，这两种现象都与出血倾向无关；凝血不需要因子 XII，如果狼疮抗凝剂持续存在，可能与抗磷脂综合征内的血栓倾向有关。需要进一步研究以确定狼疮抗凝剂在 Covid-19 血栓形成发病机制中的作用。

尽管我们在 35 份标本中检测到 28 份肝素，但 DRVVT 分析中含有肝素酶，它可以中和任何可能导致狼疮抗凝剂假阳性检测的肝素作用。狼疮抗凝剂与继发于因子 XII 抗体的获得性因子 XII 缺乏症之间的关系已在前面描述过。值得注意的是，在该研究中，尽管因子 VIII 显著升高会缩短 aPTT，但患者还是出现 aPTT 延长。

该研究建议延长 aPTT 不应成为 Covid-19 患者抗凝治疗预防和治疗静脉血栓形成的障碍。并认为，临床医生在等待进一步研究 aPTT 延长时，不应停止使用抗凝剂治疗血栓，也不应仅在 aPTT 延长的基础上，在面临高风险肺栓塞的情况下停止溶栓治疗。

Table 1. Demographic and Clinical Characteristics and Laboratory Findings in 35 Patients with Covid-19 and a Prolonged aPTT.*

Characteristic or Finding	Value in Patients (N=35)	Reference Range
Mean age (95% CI) — yr	56.6 (18.6–83.4)	—
Male sex — no. (%)	24 (69)	—
Taking oral anticoagulant at admission — no.	0	—
Thrombosis status — no. (%)		
Arterial	0	—
Venous, confirmed	1 (3)	—
Venous, suspected	1 (3)	—
Mean (95% CI) values on coagulation assay		
aPTT — sec	35.5 (30.0–54.6)	21–29
PT — sec	11.8 (10.2–14.1)	8.8–11.7
aPTT 50:50 — sec	32.6 (29.0–38.0)	21–29
Factor VIII level — IU/dl	199 (100–369)	52–153
Factor IX level — IU/dl	125 (62–205)	58–138
Factor XI level — IU/dl	81 (37–144)	58–148
Factor XII level — IU/dl	55 (26–100)	52–164
Anti–factor Xa heparin activity on heparin assay — no. (%)		
<0.05 IU/ml	7 (20)	—
0.05–0.19 IU/ml	7 (20)	—
0.20–0.40 IU/ml	14 (40)	—
0.41–0.50 IU/ml	5 (14)	—
>0.50 IU/ml	2 (6)	—
LA test result†		
Positive — no./total no. (%)	31/34 (91)	—
DRVVT — no.	7	—
LA-sensitive aPTT — no.	6	—
Both tests positive — no.	18	—
Negative — no./total no. (%)	3/34 (9)‡	—

* The abbreviation aPTT denotes activated partial-thromboplastin time, CI confidence interval, DRVVT dilute Russell's viper-venom time, LA lupus anticoagulant, and PT prothrombin time.

† Assays for lupus anticoagulant were performed with 34 of the specimens.

‡ The 3 specimens that were negative for lupus anticoagulant had levels of factor XII that were deemed sufficient to prolong the aPTT.

Abstract:
Patients with coronavirus disease 2019 (Covid-19) have a profound hypercoagulable state, and complicating venous thrombotic events are common.[1-3] Abnormalities in coagulation screening measures, including a prolonged activated partial-thromboplastin time (aPTT), have been reported in patients with Covid-19.[4] This finding could be seen as a reason to avoid the use of anticoagulation at both therapeutic and prophylactic doses.
A prolonged aPTT may indicate a clotting-factor deficiency or the presence of an inhibitor of coagulation that is either specific (e.g., antibody to factor VIII) or nonspecific (e.g., lupus anticoagulant). Lupus anticoagulant can affect in vitro tests of blood coagulation but typically is not associated with bleeding. As part of the antiphospholipid syndrome, lupus anticoagulant is associated with a thrombotic risk. We investigated the cause of prolonged aPTT in patients with Covid-19.
Blood specimens obtained from 216 patients who were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were received for coagulation screening, and 44 (20%) were found to have a prolonged aPTT. The specimens from 9 patients were excluded, and those from 35 patients were investigated further. (Details of the methods are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

4. 研究者们发现 COVID-19 病人血中循环的活内皮细胞以及前体细胞数目（CEPs/mL）要显著高于正常对照人群

Viable circulating endothelial cells and their progenitors are increased in Covid-19 patients
链接：https://www.medrxiv.org/content/10.1101/2020.04.29.20085878v1
第一作者： Patrizia Mancuso
通讯作者: Francesco Bertolini
通讯作者单位： European Institute of Oncology

5. 检测到针对 SARS-CoV-2 刺突蛋白及其受体结合区的 IgG 抗体并不表示会快速从 COVID-19 中恢复

Identification of IgG antibody response to SARS-CoV-2 spike protein and its receptor binding domain does not predict rapid recovery from COVID-19
来源：medRxiv
发布时间：2020-05-01
链接：https://www.medrxiv.org/content/10.1101/2020.05.01.20087684v1
第一作者：Kathleen M. McAndrews，Dara P. Dowlatshahi
通讯作者：Raghu Kalluri
通讯作者单位：University of Texas MD Anderson Cancer Center, Houston, TX, USA
DOI 或 PUBMED ID：Preprint
编译者：张鹏伟
中文摘要：

作者利用实验室制备的重组 SARS-CoV-2 的 RBD 和刺突蛋白，设计了检测循环血清抗体的定量 ELISA 方法。用 20 例 SARS-CoV-2 RT-PCR 确诊的 COVID-19 住院患者血清检测抗 SARS-CoV-2 刺突蛋白和 RBD 的循环 IgG 滴度。与对 RBD 有边缘抗体反应的患者相比，患者样本中对刺突糖蛋白或 RBD 的 IgG 抗体的定量检测并不总是与更快的恢复相关。一名完全康复的 COVID-19 患者没有对 RBD 产生抗体。当调查 99 份健康供者样本（于 2017 年至 2020 年 2 月期间获得）时，在一名来自 2020 年 2 月采集的供者中检测到了 RBD 抗体，另外三名供者表现出对刺突蛋白的抗体，而不是 RBD。总之，此项研究表明，需要更严格定量的分析，并采用大规模样本集，以确定抗 SARS-CoV-2 刺突蛋白或 RBD 抗体是否与 COVID-19 疾病恢复有关。还可以想象，对 SARS-CoV-2 刺突蛋白/RBD 的体液反应与决定 COVID-19 疾病的临床后遗症和严重程度的适应性 T 细胞反应相关。

Abstract:
Diagnostic testing and evaluation of patient immunity against the novel severe acute respiratory syndrome (SARS) corona virus that emerged last year (SARS-CoV-2) are essential for health and economic crisis recovery of the world. It is suggested that potential acquired immunity against SARS-CoV-2 from prior exposure may be determined by detecting the presence of circulating IgG antibodies against viral antigens, such as the spike glycoprotein and its receptor binding domain (RBD). Testing our asymptomatic population for evidence of COVID-19 immunity would also offer valuable epidemiologic data to aid health care policies and health care management. Currently, there are over 100 antibody tests that are being used around the world without approval from the FDA or similar regulatory bodies, and they are mostly for rapid and qualitative assessment, with different degrees of error rates. ELISA-based testing for sensitive and rigorous quantitative assessment of SARS-CoV-2 antibodies can potentially offer mechanistic insights into the COVID-19 disease and aid communities uniquely challenged by limited financial resources and access to commercial testing products. Employing recombinant SARS-CoV-2 RBD and spike protein generated in the laboratory, we devised a quantitative ELISA for the detection of circulating serum antibodies. Serum from twenty SARS-CoV-2 RT-PCR confirmed COVID-19 hospitalized patients were used to detect circulating IgG titers against SARS-CoV-2 spike protein and RBD. Quantitative detection of IgG antibodies to the spike glycoprotein or the RBD in patient samples was not always associated with faster recovery, compared to patients with borderline antibody response to the RBD. One patient who did not develop antibodies to the RBD completely recovered from COVID-19. In surveying 99 healthy donor samples (procured between 2017-February 2020), we detected RBD antibodies in one donor from February 2020 collection with three others exhibiting antibodies to the spike protein but not the RBD. Collectively, our study suggests that more rigorous and quantitative analysis, employing large scale sample sets, is required to determine whether antibodies to SARS-CoV-2 spike protein or RBD is associated with protection from COVID-19 disease. It is also conceivable that humoral response to SARS-CoV-2 spike protein or RBD works in association with adaptive T cell response to determine clinical sequela and severity of COVID-19 disease.

6. 辉瑞和 BioNTech 在两大洲首次测试 COVID-19 候选疫苗

Pfizer, BioNTech first to test COVID-19 vaccine candidate on two continents

来源：biocentury

发布时间：2020-05-06

文章链接：

https://www.biocentury.com/article/305112?editionId=ck9up12vc091r0171vuv48i5b&editionType=daily

作者：Steve Usdin

作者单位：Washington Editor

DOI 或 PUBMED ID：新闻

编译者：张怡

中文摘要:

周二，在美国健康志愿者从辉瑞公司和 BioNTech 公司获得了一种候选 RNA 疫苗，这标志着 COVID-19 疫苗首次进入两大洲的临床试验。

4 月 29 日，辉瑞公司和 BioNTech SE 在德国完成了 BNT162 候选疫苗 I/II 期临床试验的第一个剂量队列研究。

BioNTech 的一名发言人表示，BNT162 在中国的试验预计将“在监管机构批准后”开始。

两家公司正在全球联合开发和商业化 BNT162，但在中国是由 BioNTech 与复星医药集团有限公司联合开发。

两家公司正在测试四种 BNT162 候选疫苗：三种含有尿苷酸的 mRNA (uRNA)或核苷修饰 mRNA (modRNA)，第四种含有自扩增 mRNA (saRNA)。

I/II 期试验的剂量递增部分在德国和美国开展，目标一个剂量范围为 1μg 到 100μg。将对单剂和两剂方案进行测试。

辉瑞公司宣布计划加大疫苗的生产。该公司表示，它将有能力生产“数百万剂疫苗，到 2021 年将增加到数亿剂”。该公司说，将在美国的三个工厂生产 BNT162 在比利时的一个工厂，以及其他尚未选定的地点。

BioNTech 将从其欧洲 GMP 认证的 mRNA 制造工厂提供疫苗的临床供应。

Abstract:

The announcement Tuesday that healthy volunteers in the U.S. have received a candidate RNA vaccine from Pfizer and BioNTech marks the first COVID-19 vaccine to enter clinical testing on two continents.

Pfizer Inc. (NYSE:PFE) and BioNTech SE (NASDAQ:BNTX) completed the first dosing cohort of a Phase I/II trial of their BNT162 vaccine candidate in Germany on April 29.

A trial of BNT162 in China is expected to begin “upon regulatory approval,” a BioNTech spokesperson said.

The companies are jointly developing and commercializing BNT162 globally, with the exception of China, where BioNTech is partnered with Fosun Pharmaceutical Group Co. Ltd. (Shanghai:600196; HKEX:2196).

The companies are testing four BNT162 candidates: three that contain uridine containing mRNA (uRNA) or nucleoside modified mRNA (modRNA), and a fourth that contains self-amplifying mRNA (saRNA).

The dose escalation portion of the Phase I/II trials in Germany and the U.S.

will target a dose range of 1 μg to 100 μg. Single- and two-dose regimens will be tested.
Pfizer announced plans to ramp up production of the vaccine candidate at-risk. The company said it will have the capacity to produce “millions of vaccine doses increasing to hundreds of millions in 2021.” It said it will manufacture BNT162 at three sites in the U.S., at a plant in Belgium, and at additional sites that haven’t yet been selected.
BioNTech will provide clinical supply of the vaccine from its GMP-certified mRNA manufacturing facilities in Europe.

7. 一种 SARS-CoV-2 灭活疫苗的快速开发

Rapid development of an inactivated vaccine candidate for SARS-CoV-2
来源：science
链接：
https://science.sciencemag.org/content/early/2020/05/05/science.abc1932?rss=1
4 月 22 日简报第 8 条报道了该文的预印本

8. 利用人多能干细胞来源的肺类器官鉴定新冠肺炎的候选治疗药物

Identification of Candidate COVID-19 Therapeutics using hPSC-derived Lung Organoids
来源：bioRxiv
发布时间：2020-05-05
链接：https://www.biorxiv.org/content/10.1101/2020.05.05.079095v1
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DOI 或 PUBMED ID：Preprint
编译者：刘焕珍
中文摘要：

新冠病毒最主要攻击的目标器官是肺，新冠肺炎的主要后果是呼吸衰竭。然而，目前用于新冠病毒研究的主要模型是非洲绿猴肾来源的 Vero 细胞，Vero 细胞在模拟复杂的人类肺或其他器官系统方面有明显的局限性。因此，开发生理相关的人类细胞模型来研究新冠病毒的感染至关重要。在这里，作者开发了一个能表达 ACE2 和 TMPRSS2 的人多能干细胞来源的肺类器官平台，ACE2 和 TMPRSS2 是与 SARS-CoV-2 感染有关的两个关键因素。被感染的肺类器官的 RNA-seq 显示出细胞因子/趋化因子信号转导的上调，这些变化和在人类原发性新冠肺炎的肺部感染中观察到的细胞因子和趋化因子的变化相似。最后，对 FDA 批准的药物进行高通量筛选来找出对多能干细胞来源的肺类器官有效的候选药物。作者筛选出几种在体外和体内均可降低新冠病毒假病毒的荧光素酶活性的药物，包括 imatinib，MPA 和 QNHC。

Abstract:

The lung is the most vulnerable target organ for the SARS-CoV-2 virus, and

respiratory failure is the primary disease outcome for COVID-19. Yet the primary model currently used for SARS-CoV-2 studies are African green monkey kidney derived Vero cells, which have clear limitations for modeling complex human pulmonary or other organ systems. Therefore, the development of physiologically relevant human cell models to study SARS-CoV-2 infection is critically important. Here, we present an hPSC-derived lung organoid platform that express ACE2 and TMPRSS2, two key factors involved in SARS-CoV-2 infection. RNA-seq of infected organoids revealed upregulation of cytokine/chemokine signaling, which phenocopies the cytokine and chemokine changes observed in primary human COVID-19 pulmonary infection. Finally, we used the hPSC-derived lung organoids in a high throughput screen for FDA-approved drugs. We identified several drugs that decreased the luciferase activity of SARS-CoV-2 pseudo-entry virus including imatinib, MPA and QNHC, both in vitro and in vivo.

9. COVID-19 恢复期患者的 SARS-CoV-2 特异性体液和细胞免疫检测

Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals

来源：Immunity

发布时间：2020-05-03

链接：https://www.cell.com/immunity/fulltext/S1074-7613(20)30181-3

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DOI 或 PUBMED ID：10.1016/j.immuni.2020.04.023

编译者：雷颖

中文摘要：

人们对 SARS-CoV-2 感染的免疫反应，特别是适应性免疫反应的理解非常有限。文中作者收集了近期病毒转阴而出院的 COVID-19 患者的血液，并在 8 名新出院的患者中检测到了 SARS-CoV-2 特异性的体液和细胞免疫。对出院 2 周的 6 例患者的随访分析也显示出 IgG 抗体的高滴度。在所有 14 例被测患者中，13 例在假型病毒侵入试验中显示出血清中和活性。值得注意的是，中和抗体滴度与病毒特异性 T 细胞数量之间存在很强的相关性。作者的工作为进一步分析 SARS-CoV-2 的保护性免疫和理解 COVID-19 的发病机制提供了依据，特别是对重症病例。这对开发有效的 SARS-CoV-2 疫苗也有影响。

Abstract:

The World Health Organization has declared SARS-CoV-2 virus outbreak a world-wide pandemic. However, there is very limited understanding on the immune responses, especially adaptive immune responses to SARS-CoV-2 infection. Here, we collected blood from COVID-19 patients who have recently become virus-free and therefore were discharged, and detected SARS-CoV-2-specific humoral and cellular immunity in 8 newly discharged patients. Follow-up analysis on another cohort of 6 patients 2 weeks post discharge also revealed high titers of IgG

antibodies. In all 14 patients tested, 13 displayed serum neutralizing activities in a pseudotype entry assay. Notably, there was a strong correlation between neutralization antibody titers and the numbers of virus-specific T cells. Our work provides a basis for further analysis of protective immunity to SARS-CoV-2, and understanding the pathogenesis of COVID-19, especially in the severe cases. It has also implications in developing an effective vaccine to SARS-CoV-2 infection.

10. 在危重症 COVID-19 中阻断 CCL5/RANTES-CCR5 通路可恢复免疫稳态并降低血浆病毒载量

Disruption of the CCL5/RANTES-CCR5 Pathway Restores Immune Homeostasis and Reduces Plasma Viral Load in Critical COVID-19

来源：medRxiv

发布时间：2020-05-05

链接：https://www.medrxiv.org/content/10.1101/2020.05.02.20084673v1

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DOI 或 PUBMED ID：Preprint

编译者：孔娟

中文摘要：

临床研究显示重症患者中过度的免疫炎症反应，包括细胞因子释放综合征(CRS)，是严重 COVID-19 的主要病理驱动因素。因此迫切需要开发预防或治疗 SRARS-CoV-2 感染引起的过度炎症的治疗方法。CCR5 受体在调制免疫细胞向炎症部位的转移中发挥着核心作用。这篇文章利用 CCR5 拮抗剂 leronlimab 治疗重症高炎性的 COVID-19 患者，并对相关免疫指标进行了检测。研究中纳入了 10 名晚期危重患者，患者血浆 IL-6 和 CCL5 (RANTES)水平显著升高,CD8+ T 细胞水平降低,以及 SARS-CoV-2 血浆病毒血症。在使用 CCR5 阻断抗体 leronlimab 进行同情治疗后，结果显示巨噬细胞和 T 细胞上的 CCR5 受体被完全阻断，血浆 IL-6 迅速降低，CD4/CD8 比率恢复，以及 SARS-CoV-2 型血浆病毒血症显著降低。单细胞测序显示表达 IL-6 和干扰素相关基因的转录组髓样细胞群减少,这与 IL-6 的减少结果相一致。研究结果显示了在 leronlimab 介导的 CCR5 阻断后炎症减轻、T 细胞淋巴细胞减少症恢复和 SARS-CoV-2 型血浆病毒血症减少。总之这些结果为临床治疗 SARS-CoV-2 重症患者提供了一种新的方法。

（注：事实上，CytoDyn 公司正在进行相关随机、双盲、安慰剂对照临床试验，以评估 leronlimab 治疗轻度至中度(NCT04343651)和重度至重度(NCT04347239) COVID-19 患者的疗效。）

Abstract:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), is now pandemic with nearly three million cases reported to date. Although the majority of COVID-19 patients experience only mild or moderate symptoms, a subset will progress to severe disease with pneumonia and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Emerging results indicate a dysregulated immune response

characterized by runaway inflammation, including cytokine release syndrome (CRS), as the major driver of pathology in severe COVID-19. With no treatments currently approved for COVID-19, therapeutics to prevent or treat the excessive inflammation in severe disease caused by SARS-CoV-2 infection are urgently needed. Here, in 10 terminally-ill, critical COVID-19 patients we report profound elevation of plasma IL-6 and CCL5 (RANTES), decreased CD8+ T cell levels, and SARS-CoV-2 plasma viremia. Following compassionate care treatment with the CCR5 blocking antibody leronlimab, we observed complete CCR5 receptor occupancy on macrophage and T cells, rapid reduction of plasma IL-6, restoration of the CD4/CD8 ratio, and a significant decrease in SARS-CoV-2 plasma viremia. Consistent with reduction of plasma IL-6, single-cell RNA-sequencing revealed declines in transcriptomic myeloid cell clusters expressing IL-6 and interferon-related genes. These results demonstrate a novel approach to resolving unchecked inflammation, restoring immunologic deficiencies, and reducing SARS-CoV-2 plasma viral load via disruption of the CCL5-CCR5 axis, and support randomized clinical trials to assess clinical efficacy of leronlimab-mediated inhibition of CCR5 for COVID-19.

11. 气道上皮和激活的免疫细胞的相互作用决定了 COVID-19 的严重程度

Cross-talk between the airway epithelium and activated immune cells defines severity in COVID-19

来源：bioRxiv

发布时间：2020-05-06

链接：https://www.medrxiv.org/content/10.1101/2020.04.29.20084327v1

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DOI：preprint

编译者：蒋立春

中文摘要：

COVID-19 的临床进程呈现高度异质性，但是背后的宿主因子和决定病人会发展成为重症的因素仍然未知。

研究者们对 10 个有详细临床资料的中度和危重症 COVID-19 病人的鼻咽和支气管样品进行了单细胞转录组测序(数据展示链接：https://digital.bihealth.org/)。该研究揭示了对 SARS-CoV-2 感染敏感的不同类型和状态的气道上皮细胞。在 COVID-19 病人中，作者们发现气道上皮中表达 ACE2 的细胞数量升高了 2-3 倍。

ACE2 在上皮细胞中是通过免疫细胞的感染素信号上调，这提示宿主的病毒防御系统可能会导致呼吸上皮中的易感细胞数目增多。

感染的上皮细胞通过趋化因子通路招募并激活免疫细胞。招募到的 T 淋巴细胞以及炎性巨噬细胞被超激活，这些细胞表现出和和上皮细胞的强相互作用。在危重病人中，巨噬细胞 CCL2, CCL3, CCL5, CXCL9, CXCL10, IL8, IL1B 和 TNF 等基因表达升高可能是肺部炎症过激病变有关。作者们还观察到了上皮细胞坏死的恶化情况，可能和死亡病例里肺部损伤以及呼吸衰竭得有关系。我们的研究为 COVID-19 的病理提供了全新的视角，提示免疫调节 CCL2, CCL3/CCR1 轴可能是一个很有潜力用来治疗 COVID-19 的选择。

Abstract:
The clinical course of COVID-19 is highly variable, however, underlying host factors and determinants of severe disease are still unknown. Based on single-cell transcriptomes of nasopharyngeal and bronchial samples from clinically well-characterized patients presenting with moderate and critical severities, we reveal the different types and states of airway epithelial cells that are vulnerable for SARS-CoV-2 infection. In COVID-19 patients, we observed a two- to threefold increase of cells expressing the SARS-CoV-2 entry receptor ACE2 within the airway epithelial cell compartment. ACE2 is upregulated in epithelial cells through Interferon signals by immune cells suggesting that the viral defense system may increase the number of potentially susceptible cells in the respiratory epithelium. Infected epithelial cells recruit and activate immune cells by chemokine signaling. Recruited T lymphocytes and inflammatory macrophages were hyperactivated and showed a strong interaction with epithelial cells. In critical patients, increased expression of CCL2, CCL3, CCL5, CXCL9, CXCL10, IL8, IL1B and TNF in macrophages was identified as a likely cause of a hyperinflammatory lung pathology. Moreover, we observed exacerbated epithelial cell death, likely leading to lung injury and respiratory failure in fatal cases. Our study provides novel insights into the pathophysiology of COVID-19 and suggests an immunomodulatory therapy along the CCL2, CCL3/CCR1 axis as promising option to prevent and treat critical course of COVID-19.

12. SARS-CoV-2 主蛋白酶催化分解 HEAT 分子并通过共价键与分解后的部分产物-四氢萘酮结合

Catalytic cleavage of HEAT and subsequent covalent binding of the tetralone moiety by the SARS-CoV-2 main protease

来源：bioRxiv

发布时间：2020-05-04

链接：https://www.biorxiv.org/content/10.1101/2020.05.02.043554v1

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中文摘要：

本文中，作者解析了 SARS-CoV-2 病毒的主蛋白酶(Mpro)与 2-甲基-1-四氢萘酮(2-Methyl-1-tetralon)分子通过共价键结合的复合物结构。通过一项大规模的 X 射线晶体学筛选项目，在包含 5632 个已获批的药物或处于临床试验阶段的化合物的小分子库中，针对 Mpro 进行了老药新用筛选。将 Mpro 与 HEAT (2-(((4-hydroxyphenethyl)amino)methyl)-3,4-dihydronaphthalen-1(2H)-one)分子共结晶后，作者最终发现了该复合物。进一步的研究表明，Mpro 通过类似单分子共轭碱消除(E1cB)的反应机理，将 HEAT 分解为 2-亚甲基-1-四氢萘酮(2-Methylene-1-tetralon)和酪胺(Tyramine)。随后，催化中心的 Cys145 以 Michael 加成的方式，与 2-亚甲基-1-四氢萘酮(2-Methylene-1-tetralon)上的亚甲基碳原子共价结合。根据此推测的机理，HEAT 以类似前药的方式发挥作用。通过被 Mpro 代谢，其一种代谢产物与活性位点形成共价键。此研究中发现的共价复合物的结构，为开发非肽类病毒抑制剂

开辟了新的途径。

注：复合物 RCSB PDB ID：6YNQ

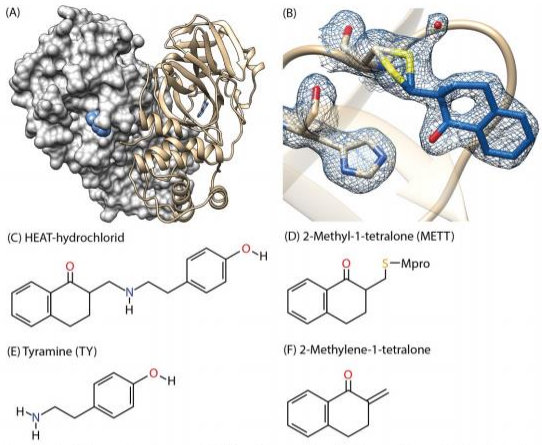

Figure 1: *X-ray structure of M^{pro} with covalently bound 2-methyl-1-tetralone.* (A) The biologically active form of M^{pro} is a homodimer found in the crystal structure. Here one monomer is depicted as surface representation, while the second monomer is shown as cartoon model. The ligand is highlighted as sphere and stick model (blue). (B) A simulated annealing omit 2Fo-Fc-map of the active site of M^{pro} reveals clear electron-density for a ligand covalently bound to Cys145 that can be modeled as METT. Coordinates of the ligand were removed before calculating the map (1 rmsd and carved at 1.4 Å around the atoms). Diffraction data together with coordinates were deposited in the Protein Data Bank with PDB accession code 6YNQ. (C-F) Chemical structures of the parent compound HEAT (C), 2-methyl-1-tetralone (METT) bound to M^{pro} (D), the proposed degradation products tyramine (TY, E) and the potential reaction intermediate 2-methylene-1-tetralone (F).

Abstract:

Here we present the crystal structure of SARS-CoV-2 main protease (Mpro) covalently bound to 2-methyl-1-tetralone. This complex was obtained by co-crystallization of Mpro with HEAT (2-(((4-hydroxyphenethyl)amino)methyl)-3,4-dihydronaphthalen-1(2H)-one) in the framework of a large X-ray crystallographic screening project of Mpro against a drug repurposing library, consisting of 5632 approved drugs or compounds in clinical phase trials. Further investigations showed that HEAT is cleaved by Mpro in an E1cB-like reaction mechanism into 2-methylene-1-tetralone and tyramine. The catalytic Cys145 subsequently binds covalently in a Michael addition to the methylene carbon atom of 2-methylene-1-tetralone. According to this postulated model HEAT is acting in a pro-drug-like fashion. It is metabolized by Mpro, followed by covalent binding of one metabolite to the active site. The structure of the covalent adduct elucidated in this study opens up a new path for developing non-peptidic inhibitors.

13. 单细胞转录组研究提示了在感染 SARS-CoV-2 发生心衰的病人中 ACE2 和利钠肽信号通路的调控机制

Single-cell Transcriptome Analysis Indicates New Potential Regulation Mechanism of ACE2 and NPs signaling among heart failure patients infected with SARS-CoV-2

主要结论中文摘要：

通过比较正常人和心脏病病人的心脏单细胞测序数据，作者们发现 ACE2 和利钠肽可能相互形成一个负反馈调控。在心脏病病人中，ACE2 的表达以及和病毒进入，复制等相关信号通路都增强了。这些病人样品中同时存在着 IFN-γ 信号的抑制。作者认为心脏病人中升高的 ACE2，利钠肽等是病人对 SARS-CoV-2 病毒易染以及预后不好的原因。

链接：https://www.medrxiv.org/content/10.1101/2020.04.30.20081257v1

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