新型冠状病毒信息简报

第 86 期（2020 年 12 月 26 - 12 月 31 日周报）

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

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1. 2020 年 12 月 30 日疫情

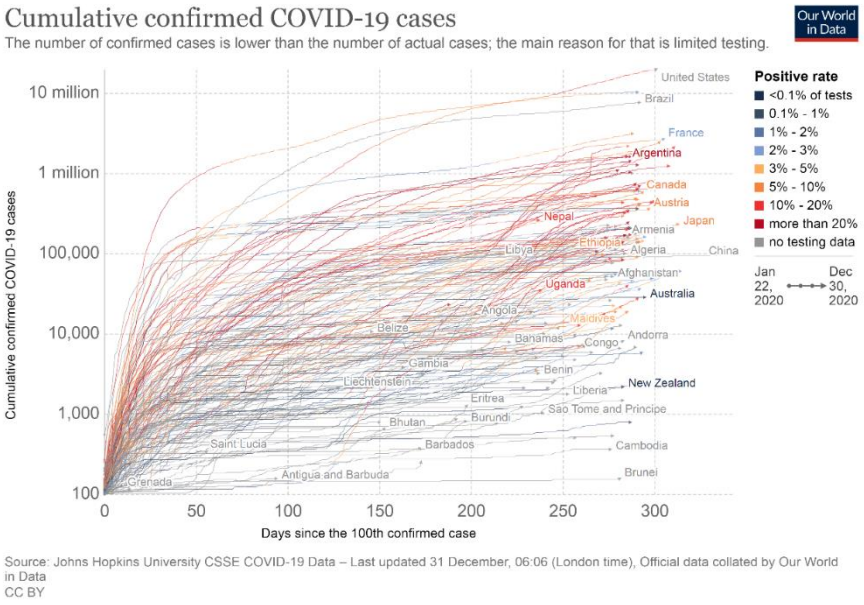
数据来源：WHO

发布时间：2020 年 12 月 30 日北京时间下午 4 点

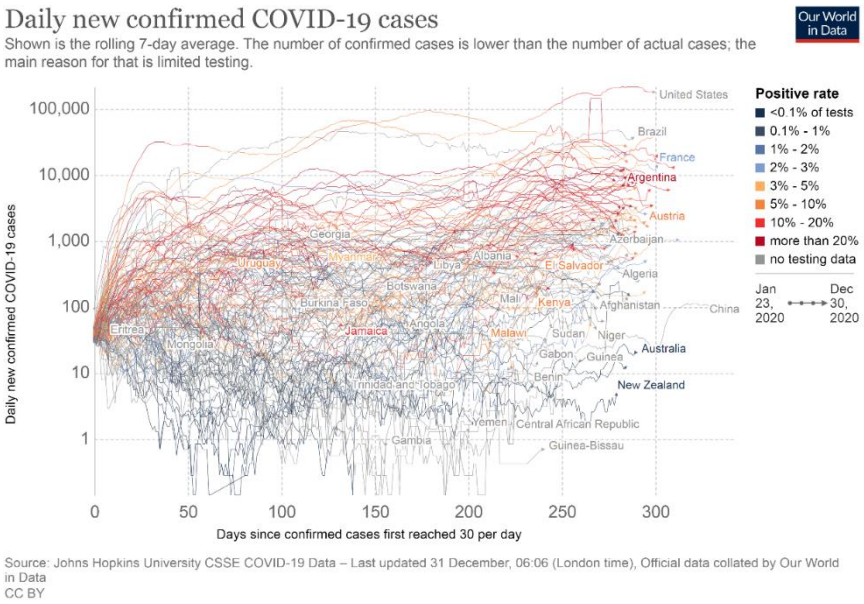
链接：https://covid19.who.int/

根据 WHO 提供的数据，2020 年 12 月 30 日全球累计确诊新型冠状病毒病人 **80,773,033** 例，当日新增确诊 **563,983** 例，累计死亡 **1,783,619** 例，当日新增死亡 **11,784**。

中国累计确诊 **96,592** 例，累计死亡 **4,784** 例，当日新增确诊 **79** 例，新增死亡 **2** 例。



重点国家确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）



重点国家每日新增确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）

全国新型冠状病毒肺炎新增确诊病例分布图（12 月 30 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 对备受关注的 202012/01 于英国出现的 SARS-CoV-2 病毒的新变种的传播能力和严重性的预估

Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England

来源：medRxiv

发布时间：2020-12-26

链接：https://www.medrxiv.org/content/10.1101/2020.12.24.20248822v1

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中文摘要：

2020 年 11 月在英格兰东南部发现了一种 SARS-CoV-2 病毒的新变种，VOC 202012/01，并似乎正迅速发展成为稳定的变种。作者通过观察到的 COVID-19 的住院人数，医院和 ICU 的床位占用率，以及死亡情况；SARS-CoV-2 PCR 的患病率和血清感染率；以及 VOC 202012/01 在受影响最严重的三个 NHS 英格兰地区（东南，英格兰东部和伦敦）的出现相对频率，利用双病毒株数学模型拟合了 SARS-CoV-2 病毒的传播情况。作者估计，VOC 202012/01 的传播率比 SARS-CoV-2 的现有变种高 56%（三个区域的 95%置信区间为 50-74%）。但是，作者未找到明确的证据证明 VOC 202012/01 造成的疾病严重程度比现有变种更高或低。然而，传播能力的提高很可能导致发病率的大幅增加。即使保持 12 月 19 日之前实施的区域分层限制政策，2021 年预计的 COVID-19 的住院和死亡人数将比 2020 年的水平更高。作者的估计表

明，采取与 2020 年 11 月在英格兰实施的全国封锁类似的严格控制措施也不可能将有效繁殖数 R_t降低到 1 以下，除非同时关闭小学，中学和大学。作者预计，放松管控措施可能会造成病毒的大量复活。因此可能有必要大力加快疫苗的推出，以便在抑制由此造成的流行病负担方面产生显著的影响。

Abstract:
A novel SARS-CoV-2 variant, VOC 202012/01, emerged in southeast England in November 2020 and appears to be rapidly spreading towards fixation. We fitted a two-strain mathematical model of SARS-CoV-2 transmission to observed COVID-19 hospital admissions, hospital and ICU bed occupancy, and deaths; SARS-CoV-2 PCR prevalence and seroprevalence; and the relative frequency of VOC 202012/01 in the three most heavily affected NHS England regions (South East, East of England, and London). We estimate that VOC 202012/01 is 56% more transmissible (95% credible interval across three regions 50-74%) than preexisting variants of SARS-CoV-2. We were unable to find clear evidence that VOC 202012/01 results in greater or lesser severity of disease than preexisting variants. Nevertheless, the increase in transmissibility is likely to lead to a large increase in incidence, with COVID-19 hospitalisations and deaths projected to reach higher levels in 2021 than were observed in 2020, even if regional tiered restrictions implemented before 19 December are maintained. Our estimates suggest that control measures of a similar stringency to the national lockdown implemented in England in November 2020 are unlikely to reduce the effective reproduction number Rt to less than 1, unless primary schools, secondary schools, and universities are also closed. We project that large resurgences of the virus are likely to occur following easing of control measures. It may be necessary to greatly accelerate vaccine roll-out to have an appreciable impact in suppressing the resulting disease burden.

3. 科学认识人群新冠病毒抗体流行率——全国新冠肺炎血清流行病学调查结果问答

来源：中国疾控动态
发布时间：2020-12-28
链接：https://mp.weixin.qq.com/s/LXTfDmsQLf3qZnu_S_MxcA
编译者：孔娟
中文摘要：

近期，中国疾控中心组织完成全国新冠肺炎血清流行病学调查和分析。调查涵盖三类地区，包括武汉市、湖北武汉之外市州、以及湖北之外六个省份（北京、辽宁、上海、江苏、广东和四川），采用抽样调查社区人群 3.4 万余人，通过检测调查对象的血清新冠病毒抗体，估计人群中新冠病毒的感染水平。调查时点选取我国遏制第一波新冠肺炎疫情的一个月后开展。结果显示武汉地区的人群新冠抗体阳性率 4.43%，湖北武汉外市州抗体阳性率 0.44%，而湖北之外六省份的 1.2 万余人中仅检测到 2 例抗体阳性，阳性率极低。曾接触过新冠肺炎确诊病例的人群抗体阳性率明显高于其他人群，中老年人群抗体阳性率高于其他年龄段人群。

调查结果显示，我国人群总体处于低感染水平，表明以武汉为主战场的疫情控制取得成功，有效防止了疫情大规模扩散。

4. 肺间质扩张和肺泡内凝血是 Covid-19 死亡的主要原因

Pulmonary stromal expansion and intra-alveolar coagulation are primary causes of Covid-19 death

来源：bioRxiv

发布时间：2020-12-26

链接：https://www.biorxiv.org/content/10.1101/2020.12.23.424172v1

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中文摘要：

大多数 Covid-19 的受害者都是老年人，死于不相关的原因。在这里，我们提供了十二份完整的尸检资料，包括对年轻患者进行的两份快速尸检，死因是 Covid-19 ARDS。病毒引起的主要病理是在肺实质中，而不是在气道中。凝血事件多数发生在肺泡内，而不发生在血管内，少数血栓主要由聚集的血小板细胞组成。主要的炎症反应是 CD163 +巨噬细胞的大量积累和 T 杀手，NK 和 B 细胞的消失。该病毒在肺细胞和巨噬细胞中复制，但不在支气管上皮，内皮，周细胞或基质细胞中复制。大量的再生反应，基质和上皮细胞增殖以及新血管形成产生了肺部固结。我们建议，在晚期 Covid-19 ARDS 的治疗中，血小板聚集抑制、血管生成抑制和一般增殖抑制可能会有所进展。

Abstract:

Most Covid-19 victims are old and die from unrelated causes. Here we present twelve complete autopsies, including two rapid autopsies of young patients where the cause of death was Covid-19 ARDS. The main virus induced pathology was in the lung parenchyma and not in the airways. Most coagulation events occurred in the intra-alveolar and not in the intra-vascular space and the few thrombi were mainly composed of aggregated thrombocytes. The dominant inflammatory response was the massive accumulation of CD163+ macrophages and the disappearance of T killer, NK and B-cells. The virus was replicating in the pneumocytes and macrophages but not in bronchial epithelium, endothel, pericytes or stromal cells. The lung consolidations were produced by a massive regenerative response, stromal and epithelial proliferation and neovascularization. We suggest that thrombocyte aggregation inhibition, angiogenesis inhibition and general proliferation inhibition may have a roll in the treatment of advanced Covid-19 ARDS.

5. NETs 清除缺陷导致 COVID-19 相关肺血栓炎症中 FXII 的持续激活

Defective NETs Clearance contributes to sustained FXII Activation in COVID-19-associated Pulmonary Thrombo-Inflammation

来源：bioRxiv

发布时间：2020-12-29

链接：https://www.biorxiv.org/content/10.1101/2020.12.29.424644v1

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中文摘要：

凝血和炎症是 COVID-19 的特征，与死亡率增加有关。COVID-19 导致血栓炎症的机制尚不清楚。该研究报告了 NETs/因子 XII（FXII）轴在 COVID-19 促凝血和促炎症反应中的作用。蛋白质组学分析显示 COVID-19 患者死后肺组织中 FXII 富集。COVID-19 肺组织的免疫荧光分析显示 FXII 在肺实质、肺血管壁和富含纤维蛋白的肺泡腔中被激活。尤其是活化的 FXII（FXIIa）与 COVID-19 肺组织中的 NETs 共定位，表明 NETs 的积聚导致了 COVID-19 中 FXII 的接触活化。我们进一步证明，NETs 的积累部分是由通过细胞外 DNA 酶的 NETs 清除受损引起的。相反，DNA 酶 I 的加入提高了 NETs 的清除率，降低了 FXII 在体外的活性。该研究认为靶向 FXIIa 和 FXII 激活剂网在减轻 COVID-19 血栓炎症方面是有效的。

Abstract:

Coagulopathy and inflammation are hallmarks of Coronavirus disease 2019 (COVID-19) and are associated with increased mortality. The mechanisms that drive thrombo-inflammation in COVID-19 are poorly understood. Here, we report a role of the NETs/ Factor XII (FXII) axis for initiating procoagulant and proinflammatory reactions in COVID-19. Proteomic analysis revealed enrichment of FXII in postmortem lung tissue from COVID-19 patients. Immunofluorescence analysis of COVID-19 lung tissue showed that FXII is activated in the lung parenchyma, within the pulmonary vessel walls and in fibrin-rich alveolar spaces. In particular, activated FXII (FXIIa) colocalized with NETs in COVID-19 lung tissue, indicating that NETs accumulation leads to FXII contact activation in COVID-19. We further showed that an accumulation of NETs is partially caused by impaired NETs clearance via extracellular DNases. In contrast, addition of DNase I improved NETs clearance and reduced FXII activation in vitro. We propose that targeting both, FXIIa and the FXII activator NETs, is therapeutically effective in mitigating thrombo-inflammation in COVID-19.

6. 在一个国际队列中表征长 COVID：7 个月的症状及其影响

Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact
来源：medRxiv
发布时间：2020-12-27
链接：https://www.medrxiv.org/content/10.1101/2020.12.24.20248802v2
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通讯作者：Athena Akrami
通讯作者单位：Patient-Led Research for COVID-19
DOI 或 PUBMED ID：
编译者：宋张悦
中文摘要：

目标：表征长 COVID 患者的症状特点和病程，以及对日常生活、工作和恢复基线健康的影响。
设计：COVID-19 疑似病例和确诊病例的国际网络调查(持续时间超过 28 天，并于 2020 年 6 月前发病)。
设置：通过 COVID-19 在线支持团体和社交媒体分发调查报告
参与者：来自 56 个国家/地区的 3762 名受访者完成了调查。40-49 岁 1166 人(33.7%)，50-59 岁 937 人(27.1%)，30-39 岁 905 人(26.1%)。女性 2961 例(78.9%)，男性 718 例(19.1%)，非二进制者 63 例(1.7%)。8.4%报告住院。27%报告获得 COVID-19 实验室确诊。96%报告症状超过 90 天。
结果：在该队列中，10 个器官系统估计有 205 种症状，其中 66 种症状追踪时间超过 7 个月。参与者在平均 9.08(95%置信区间 9.04 至 9.13)器官系统中出现症状。第 6 个月后报告的最常见症状是：疲劳(77.7%，74.9%至 80.3%)、运动后不适(72.2%，69.3%至 75.0%)和认知功能障碍(55.4%，52.4%至 58.8%)。这三种症状也是总体上最常见的三种症状。在那些在 90 天内康复的患者中，症状的平均数量在第 2 周达到峰值(11.4,9.4 到 13.6)，而在那些 90 天内没有康复的患者中，症状的平均数量在第 2 个月达到峰值(17.2,16.5 到 17.8)。有症状超过 6 个月的受访者在第 7 个月平均经历了 13.8(12.7 到 14.9)个症状。85.9%(84.8%至 87.0%)有复发，主要诱因为运动、体力或脑力活动和压力。86.7%(85.6%至 92.5%)未恢复的受访者在调查时感到疲劳，而恢复的受访者有 44.7%(38.5%至 50.5%)感到疲劳。45.2%(42.9%至 47.2%)报告说，与患病前相比，需要减少工作时间，22.3%(20.5%至 24.3%)由于健康状况在调查时没有工作。
结论：长 COVID-19 患者报告多系统受累和严重残疾。大多数人在 6 个月前还没有恢复到以前的工作水平。许多患者在 7 个月后仍未恢复，并继续经历显著的症状负担。

Abstract:

Objective. To characterize the symptom profile and time course in patients with Long COVID, along with the impact on daily life, work, and return to baseline health.

Design. International web-based survey of suspected and confirmed COVID-19 cases with illness lasting over 28 days and onset prior to June 2020.

Setting. Survey distribution via online COVID-19 support groups and social media

Participants. 3,762 respondents from 56 countries completed the survey. 1166 (33.7%) were 40-49 years old, 937 (27.1%) were 50-59 years old, and 905 (26.1%) were 30-39 years old. 2961 (78.9%) were women, 718 (19.1%) were men, and 63 (1.7%) were nonbinary. 8.4% reported being hospitalized. 27% reported receiving a laboratory-confirmed diagnosis of COVID-19. 96% reported symptoms beyond 90 days.

Results. Prevalence of 205 symptoms in 10 organ systems was estimated in this cohort, with 66 symptoms traced over seven months. Respondents experienced symptoms in an average of 9.08 (95% confidence interval 9.04 to 9.13) organ systems. The most frequent symptoms reported after month 6 were: **fatigue** (77.7%, 74.9% to 80.3%), **post-exertional malaise** (72.2%, 69.3% to 75.0%), and **cognitive dysfunction** (55.4%, 52.4% to 58.8%). These three symptoms were also the three most commonly reported overall. In those who recovered in less than 90 days, the average number of symptoms peaked at week 2 (11.4, 9.4 to 13.6), and in those who did not recover in 90 days, the average number of symptoms

peaked at month 2 (17.2, 16.5 to 17.8). Respondents with symptoms over 6 months experienced an average of 13.8 (12.7 to 14.9) symptoms in month 7. 85.9% (84.8% to 87.0%) experienced relapses, with exercise, physical or mental activity, and stress as the main triggers. 86.7% (85.6% to 92.5%) of unrecovered respondents were experiencing fatigue at the time of survey, compared to 44.7% (38.5% to 50.5%) of recovered respondents. 45.2% (42.9% to 47.2%) reported requiring a reduced work schedule compared to pre-illness and 22.3% (20.5% to 24.3%) were not working at the time of survey due to their health conditions.

Conclusions. Patients with Long COVID report prolonged multisystem involvement and significant disability. Most had not returned to previous levels of work by 6 months. Many patients are not recovered by 7 months, and continue to experience significant symptom burden.

7. SARS-CoV-2 特异性胎盘抗体转移受损

Compromised SARS-CoV-2-specific placental antibody transfer

来源：cell

发布时间：2020-12-22

链接：https://www.cell.com/cell/fulltext/S0092-8674(20)31749-9

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DOI 或 PUBMED ID：https://doi.org/10.1016/j.cell.2020.12.027

编译者：孔娟

中文摘要：

与未妊娠妇女相比，SARS-CoV-2 感染在妊娠妇女中引起更严重的疾病。产妇感染是否引起婴儿免疫力转移的改变尚不清楚。孕产妇感染以前曾与胎盘抗体转移受损有关，但这种受损转移的潜在机制尚未确定。在此，研究者使用系统血清学表征了通过胎盘转移的流感、百日咳和 SARS-CoV-2 特异性抗体的 Fc-谱。流感和百日咳特异性抗体被主动转移。然而，与流感和百日咳特异性抗体相比，SARS-CoV-2 特异性抗体转移显著减少，脐带滴度和功能活性低于母体血浆，这种效应仅在妊娠晚期感染中观察到。SARS-CoV-2 特异性转移与改变的 SARS-CoV-2 抗体糖基化特征相关，并通过感染诱导的 IgG 增加和 FCGR3A 胎盘表达增加而部分挽救。这些结果表明，意想不到的补偿机制可增强新生儿的免疫力，为母体疫苗设计提供了见解。

Abstract:

SARS-CoV-2 infection causes more severe disease in pregnant women compared to agematched non-pregnant women. Whether maternal infection causes changes in the transfer of immunity to infants remains unclear. Maternal infections have previously been associated with compromised placental antibody transfer, but the mechanism underlying this compromised transfer is not established. Here, we used systems serology to characterize the Fc-profile of influenza-, pertussis-, and SARS-CoV-2-specific antibodies transferred across the placenta. Influenza- and pertussis-specific antibodies were actively transferred. However, SARS-CoV-2specific antibody transfer was significantly reduced

compared to influenza- and pertussis specific antibodies, and cord titers and functional activity were lower than in maternal plasma. This effect was only observed in third trimester infection. SARS-CoV-2-specific transfer was linked to altered SARS-CoV-2-antibody glycosylation profiles and was partially rescued by infection-induced increases in IgG and increased FCGR3A placental expression. These results point to unexpected compensatory mechanisms to boost immunity in neonates, providing insights for maternal vaccine design.

8. 用 tcrdist3 从 TCR 宏克隆型中发现生物标志物：定量分析关于 SARS-CoV-2 感染的共有的 HLA 限制性 TCR 生物标志物

TCR meta-clonotypes for biomarker discovery with tcrdist3: quantification of public, HLA-restricted TCR biomarkers of SARS-CoV-2 infection

来源：biorxiv

发布时间：2020-12-26

链接：https://www.biorxiv.org/content/10.1101/2020.12.24.424260v1

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通讯作者：Andrew Fiore-Gartland

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DOI 或 PUBMED ID：

编译者：蒋立春

中文摘要：

T 细胞受体是后天免疫细胞对抗原进行识别的基础，它们可以反映宿主以前的抗原接触史以及未来的免疫反应，编码了具有重要临床价值的信息。但是，尽管深度免疫谱测序得到了发展，巨大的 TCR 多样性使得利用 TCR 克隆型作为临床生物标记物仍然相当复杂。作者们建议了一个新的工作框架：利用抗原富集的免疫库来形成宏克隆型——群生化上相似的 TCRs——可以用来稳定地混合免疫谱测序中功能相似的 TCRs 进行定量. 作者们采用这个工作框架对来自于 COVID-19 病人的 TCR 数据进行了分析，从针对 18 个 SARS-CoV-2 的抗原富集的具有最强 HLA 限制性的免疫谱，生成了 1915 个共有的 TCR 宏克隆型。将这个方法应用于独立的病人群体，针对这些特定表位的宏克隆型相比氨基酸的完美匹配在混合 TCR 谱数据能更多次的被检出。44% (845/1915)的宏克隆型在表达特定限制性 HLA 位点的 COVID-19 病人中显著富集。这表明我们可能可以将宏克隆型作为抗原特异性的特征来开发生物标记物。为了更好促进相关的应用，作者们开发了开源软件包，tcrdist3,应用这个工作框架来助力基于距离的 TCR 谱分析。

Abstract:

As the mechanistic basis of adaptive cellular antigen recognition, T cell receptors (TCRs) encode clinically valuable information that reflects prior antigen exposure and potential future response. However, despite advances in deep repertoire sequencing, enormous TCR diversity complicates the use of TCR clonotypes as clinical biomarkers. We propose a new framework that leverages antigen-enriched repertoires to form meta-clonotypes – groups of biochemically similar TCRs – that can be used to robustly quantify functionally similar TCRs in bulk repertoires. We apply the framework to TCR data from COVID-19 patients, generating 1,915 public TCR meta-clonotypes from the 18 SARS-CoV-2 antigen-enriched repertoires with the strongest evidence of HLA-restriction. Applied to

independent cohorts, meta-clonotypes targeting these specific epitopes were more frequently detected in bulk repertoires compared to exact amino acid matches, and 44% (845/1915) were significantly enriched among COVID-19 patients that expressed the putative restricting HLA allele, demonstrating the potential utility of meta-clonotypes as antigen-specific features for biomarker development. To enable further applications, we developed an open-source software package, *tcrdist3*, that implements this framework and facilitates workflows for distance-based TCR repertoire analysis.

9. COVID-19 病人中 B 细胞受体谱的图景及其动态多样性

Landscapes and dynamic diversifications of B-cell receptor repertoires in COVID-19 patients

来源：biorxiv

发布时间：2020-12-29

链接：https://www.biorxiv.org/content/10.1101/2020.12.28.424622v1

第一作者：Haitao Xiang

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DOI 或 PUBMED ID：

编译者：蒋立春

中文摘要：

SARS-CoV-2 病毒造成了 COVID-19 大流行。全世界各地投入了巨大的人力物力来开发预防性疫苗以及中和抗体。但是我们对 SARS-CoV-2 病毒引起的 B 细胞免疫反应了解还有限。这篇文章报道了一个详尽的关于 COVID-19 病人中免疫球蛋白重链的动态变化谱。

采用二代测序技术，作者们研究了病人中免疫球蛋的分布图景，发现在 COVID-19 症状发生之后病人们免疫系统中免疫球蛋白重链发生了剧烈变化。虽然不同病人对 SARS-CoV-2 感染存在迥异的免疫反应。用克隆型的重叠，谱系扩增以及克隆型网络分析，作者们观察到在发病 2-3 周内克隆型的重叠更高，B 细胞克隆的谱系扩增也变得显著。于此同时，关于 SARS-CoV-2 感染中 V 基因使用的趋向性，IGHV3-74、IGHV4-34 以及 IGHV4-39 在 COVID-19 病人中比正常人中的含量高。这篇文章为 SARS-CoV-2 对机制研究以及开发治疗方案都有一定促进意义。

Abstract:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the pandemic of coronavirus disease 2019 (COVID-19). Great international efforts have been put into the development of prophylactic vaccines and neutralizing antibodies. However, the knowledge about the B cell immune response induced by the SARS-CoV-2 virus is still limited. Here, we report a comprehensive characterization of the dynamics of immunoglobin heavy chain (IGH) repertoire in COVID-19 patients. By using next-generation sequencing technology, we examined the temporal changes in the landscape of the patient's immunological status, and found dramatic changes in the IGH within the patient's immune system after the onset of COVID-19 symptoms. Although different patients have distinct immune responses to SARS-CoV-2 infection, by employing clonotype

overlap, lineage expansion and clonotype network analyses, we observed a higher clonotype overlap and substantial lineage expansion of B cell clones during 2-3 weeks of illness, which is of great importance to B-cell immune responses. Meanwhile, for preferences of V gene usage during SARS-CoV-2 infection, IGHV3-74 and IGHV4-34 and IGHV4-39 in COVID-19 patients were more abundant than that of healthy controls. Overall, we present an immunological resource for SARS-CoV-2 that could promote both therapeutic development as well as mechanistic research.

10. 新型冠状病毒肺炎灭活疫苗（Vero 细胞）上市获批

来源：国家药品监督管理局

发布时间：2020-12-31

链接：https://www.nmpa.gov.cn/zwfw/sdxx/sdxxyp/yppjfb/20201231102922128.html

编译者：宋张悦

中文摘要：

序号	受理号	批件号	品名	申请单位	批准文号	签发日期
1	CXSS2000061国	2020S00947	新型冠状病毒肺炎灭活疫苗（Vero细胞）	北京生物制品研究所有限责任公司	（1）国药准字S20200029（2）国药准字S20200030	2020年12月30日

11. 保护效力 79.34%，国药中国生物公布新冠疫苗 III 期临床试验中期数据

发布时间：2020.12.30

文章链接：https://mp.weixin.qq.com/s/SiNnuOLljTdgrs_kZ_WuRA

撰文：汤佩兰　戴威

编译者：张怡

中文摘要：

12 月 30 日，北京生物制品研究所有限责任公司在官网公布了新冠病毒灭活疫苗 III 期临床试验中期分析数据结果。目前，国药北生所已正式向国家药监局提交附条件上市申请。12 月 24 日，国家药监局官网显示，国药北生所研发的新冠灭活疫苗上市申请已获受理，也是国内首个获得上市受理的新冠疫苗。

经统计分析，国药集团中国生物北京公司新冠病毒灭活疫苗接种后安全性良好，免疫程序两针接种后，疫苗组接种者均产生高滴度抗体，中和抗体阳转率为 99.52%，疫苗针对由新冠病毒感染引起的疾病（COVID-19）的保护效力为 79.34%。

12. 阿斯利康新冠疫苗获准在英国紧急供应

来源：即刻药闻

发布时间：2020-12-30

链接：

https://www.wuximediatech.com/content/post/detail.html?sn=27987619c9cc495e85f05e1d423663f9&from=wechat

作者：药明康德内容团队编辑

编译者：张鹏伟

中文摘要：

12 月 30 日，阿斯利康（AstraZeneca）宣布英国药品与健康产品管理局（MHRA）已授权紧急供应其新冠疫苗 AZD1222 用于 18 岁或以上个体的主动免疫。MHRA 的授权建议该疫苗接种两次，间隔为 4-12 周。该方案在临床试验中显示可安全有效地预防症状性 COVID-19，在第 2 次给药后超过 14 天无住院和重症病例。

阿斯利康表示计划在 2021 年第一季度供应数百万剂，在英国的供应总量将高达 1 亿剂。公司将继续与世界各地的监管机构合作，以支持他们在健康危机期间对这一疫苗的紧急供应或有条件上市许可进行的滚动审评。阿斯利康还在寻求这一疫苗列入世界卫生组织（WHO）的紧急使用清单，以加速中低收入国家疫苗的供应，以确保在大流行期间以无利可图的方式广泛和公平地获得疫苗。

阿斯利康表示正与其全球合作伙伴合作，在等待监管机构批准之前，继续滚动建设生产高达 30 亿剂疫苗的制造能力。该疫苗可在正常冷藏条件（2-8℃/36-46 华氏度）下储存、运输和处理至少 6 个月，并在现有医疗保健环境中接种。

AZD1222 由牛津大学及其衍生公司 Vaccitech 共同开发。今年 4 月底，阿斯利康与英国牛津大学联合宣布，双方达成协议，共同开发、大规模生产、以及分配该新冠病毒候选疫苗。

AZD1222 使用一种基于普通感冒病毒（腺病毒）弱化版本的复制缺陷型黑猩猩病毒载体，该病毒会引起黑猩猩的感染，并含有 SARS-CoV-2 病毒刺突蛋白的遗传物质。接种该疫苗后，会产生表面刺突蛋白，引发免疫系统产生针对新冠病毒的抗体。

AZD1222 疗效期中分析基于 11636 名受试者，这些受试者来自牛津大学在英国和巴西领导进行的 3 期临床试验，试验期间积累出现的 131 例出现症状的 COVID-19 患者数据的分析。如今年 11 月 23 日宣布，基于汇总分析的主要有效性终点显示，在接受两剂疫苗后超过 14 天预防症状性 COVID-19 发生的有效率为 70.4%（置信区间：54.8%-80.6%）。预防重度疾病的次要疗效终点证明，疫苗组无重症或住院病例。

13. 英国为 AZ-牛津疫苗开绿灯以拯救更多生命

U.K. pairs green light for AZ-Oxford vaccine with aggressive distribution scheme to prioritize saving more lives

来源：biocentury

发布时间：2020-12-30

链接：https://www.biocentury.com/article/633087

第一作者：STEPHEN HANSEN, ASSOCIATE EDITOR

编译者：刘焕珍

中文摘要：

英国急诊科授权广泛接种阿斯利康和牛津大学的 CVID-19 疫苗。MHRA（英国药品和保健品管理机构）批准两次全剂量给药方案，第二次给药在第一次给药后 4-12 周。灵活的剂量安排使委员会可以建议国民保健系统优先让尽可能多的高危人群接种第一剂疫苗，MHRA 表示单剂量 AZD1222 从给药后 21 天到第二次给药期间的疗效高达 70%。MHRA 关于灵活给药间隔的建议可能增加了安慰，因为观察到标准给药间隔越长，疗效越好。英国希望在 1 月 4 日开始接种 AZ 疫苗。

Abstract:

The U.K.’s emergency authorization of the COVID-19 vaccine from AstraZeneca and the University of Oxford prioritizes widespread vaccination. MHRA authorized a regimen of two full doses with the second dose administered 4-12 weeks after the first dose. The flexible dosing schedule allows the committee

to recommend that the NHS prioritize getting as many at-risk individuals vaccinated with the first dose. MHRA showed that a single dose of AZD1222 provided up to 70% efficacy from 21 days after administration until the second dose was received. What may have added comfort to MHRA's recommendation for the flexible dosing interval was the observation that a longer interval between standard doses led to greater efficacy. The U.K. expects to begin vaccinations with the AZ vaccine on Jan. 4.

14. 英国将为阿斯利康开发的疫苗开绿灯以及其他 COVID-19 疫苗新闻

AstraZeneca Could Get Green Light in UK and Other COVID-19 Vaccine News

来源：BioSpace

发布时间：2020-12-28

链接：https://www.biospace.com/article/u-k-could-authorize-astrazeneca-vaccine-this-week-sinovac-vaccine-studies-yield-different-results/

第一作者：Alex Keown

编译者：刘焕珍

中文摘要：

英国预计本周将为阿斯利康和牛津大学开发的疫苗开绿灯。阿斯利康开发的疫苗有望提高该国对抗 COVID-19 的能力并接种更多的公民。在土耳其，卫生官员报告了另一种由中国的 SinoVac 开发的疫苗，其有效率为 91.25%。韩国政府已与辉瑞公司和强生公司签署协议，提供足够剂量的疫苗以保护其 1600 万居民。韩国还与阿斯利康和摩登纳签署了协议。伊朗政府预计将有少量辉瑞和 BioNTech 疫苗.

Abstract:

The United Kingdom is expected to give the green light to the vaccine developed by AstraZeneca and Oxford University this week. The AstraZeneca-developed vaccine is expected to ramp up that nation's ability to fight COVID-19 and inoculate a greater number of citizens. In Turkey, health officials are reporting another vaccine, one developed by China-based SinoVac, has an efficacy rate of 91.25%. The government of South Korea has signed agreements with both Pfizer and Johnson & Johnson for enough vaccine doses to protect 16 million of its residents. South Korea has also signed agreements with AstraZeneca and Moderna. The government of Iran is expecting a small shipment of the Pfizer and BioNTech vaccine.

15. mRNA-1273 新冠疫苗的有效性和安全性

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

来源：NEMJ

发布时间：2020-12-30

链接：https://www.nejm.org/doi/full/10.1056/NEJMoa2035389?query=featured_home

第一作者：Lindsey R. Baden and H.M. El Sahly

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通讯作者单位：Brigham and Women's Hospital, Boston and baylor college of medicine, Houston

DOI 或 PUBMED ID：10.1056/NEJMoa2035389

编译者：蒋立春

中文摘要：

mRNA-1273 疫苗对发生 Covid-19（包括重症在内）表现出 94.1%的有效性。除了短时间的局部性系统反应，没有其他安全问题。

Abstract:

BACKGROUND Vaccines are needed to prevent coronavirus disease 2019 (Covid-19) and to protect persons who are at high risk for complications. The mRNA-1273 vaccine is a lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19. METHODS This phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 μg) or placebo 28 days apart. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2.

RESULTS

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.

CONCLUSIONS

The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE ClinicalTrials.gov number, NCT04470427. opens in new tab)

16. Inovio 新冠疫苗易诱导 T 细胞应答：数据信息

Inovio COVID vaccine leans toward T cell responses: Data Byte

来源：BIOCENTURY

发布时间：2020-12-29
链接： https://www.biocentury.com/article/633044
作者：SANDI WONG
编译者：姜连连
中文摘要：
Invovio 新冠疫苗Ⅰ期临床结果显示新冠 DNA 疫苗 INO-4800 诱导的 T 细胞免疫应答可能强于所诱导的抗体免疫应答。初步数据显示疫苗诱导 CD4+ 和 CD8+记忆性 T 细胞免疫应答。上周在《柳叶刀》子刊上发表的数据显示：2ug 的 INO-4800 疫苗在两次免疫的 8 周内，19 个受试者体内均出现针对新冠病毒 Spike 蛋白高水平的细胞免疫应答，其中 16 名受试者(84%)体内产生特异性中和性抗体。同期进行的 1ug 低剂量免疫组受试者产生体液和细胞免疫应答比例略有降低（74%），但中和抗体水平却高于 2 ug 剂量免疫组。尽管 T 细胞在抗新冠感染的作用还需要进一步研究，但至少灵长动物体内实验结果表明 Inovio 新冠疫苗所诱导的 CD8+T 细胞免疫反应可以补偿低水平的体液免疫，从而保护不能产生高效价抗体的群体。与其他新冠疫苗相比，INO-4800 的优势是可以室温保存一年以上，37℃保存一个月以上，在正常冷藏温度（即 2-8oC）下的保质期为五年。另一种可在 2-8℃稳定保存的疫苗来自 Novavax 公司。该公司本周在美国和墨西哥启动Ⅲ期临床实验，接种人群超过 3 万人，检测 NVX-CoV2373 疫苗肌肉免疫两次后免疫保护效果。
Abstract:
Phase I data for Inovio’s COVID-19 vaccine suggest INO-4800 may stimulate T cell responses more potently than neutralizing responses. The preliminary readout also provided evidence the DNA vaccine induces both CD4+ and CD8+ memory T cell responses. The data in EClinical Medicine, show prime-boost administration of 2 μg INO-4800 led to strong T cell responses against the SARS-CoV-2 spike protein at week eight vs. baseline in all 19 evaluable subjects, and induced neutralizing antibodies in 16 (84%) of them. The study also evaluated prime-boost administration of 1 μg INO-4800. The lower dose led to lower humoral and cellular response rates but higher neutralization titers than the 2μg dose. Although the role of T cells in protecting against COVID-19 has been studied far less, at least one non-human primate study has shown that robust antiviral CD8+ T cell responses can compensate for weak humoral immunity, indicating the T cell responses induced by Inovio’s vaccine may protect individuals who failed to mount a strong antibody response. INO-4800 does have an advantage over COVID-19 vaccines that require storage at very cold temperatures: the intradermal vaccine is stable at 37° C for over a month and at room temperature for over a year. It has an expected 5-year shelf-life at normal refrigeration temperatures of 2-8° C. Another candidate that is stable at 2-8° C is NVX-CoV2373 from Novavax. The biotech announced Monday the start of the U.S. and Mexican Phase III PREVENT-19 trial testing intramuscular prime-boost administration of NVX-CoV2373 in up to 30,000 subjects.

17. 美国 CDC 公布各州新冠疫苗接种配额：数据信息

CDC’s COVID-19 vaccine allocation across the U.S.: Data Byte
来源：BIOCENTURY

发布时间：2020-12-31
链接：https://www.biocentury.com/article/633092
第一作者：GUNJAN OHRI
编译者：姜连连
中文摘要：
美国 CDC 公布首个新冠疫苗接种计划配额，将覆盖每个州近 5%群体，首先接种疫苗的是高感染风险人群，包括 CDC 推荐接种疫苗项目中第一梯队群体：卫生保健人员和护理机构的相关人员。整个第一针疫苗接种配额中，本月 BioNTech-辉瑞的 mRMA 疫苗为 800 万份，Moderna 疫苗为 760 万份。BioCentury 根据 CDC 提供的疫苗数量和 2019 年人口普查结果计算出各州所分配到的疫苗配额比例。新冠疫苗分配数量最多州为：加利福尼亚、佛罗里达、纽约和德克萨斯州。阿拉斯加和特拉华州的新冠疫苗分配比例最高，分别为 8%和 6%。疫苗分配比例最低的是哥伦比亚特区和犹他州，都大约为 4%。2021 年时，各州将开始重点免疫接种基层工作人员、65 岁以人老年人和免疫功能低下并发症患者。
Abstract:
The first planned allocation of COVID-19 vaccines covers an average of nearly 5% of the population in each state, beginning to bring relief to the high-risk healthcare personnel included in the first phase of the CDC-recommended vaccination program.Of the total first doses allocated, the vaccine from BioNTech and Pfizer amounts to around 8 million, and Moderna can provide 7.6 million vaccine doses this month.BioCentury calculated the percentages allocated to each state from data provided by the CDC and 2019 population census data.The highest numbers of vaccines were allocated to the state of California, Florida, New York and Texas.Allocation as a percentage of population was highest in Alaska and Delaware at 8% and 6%, respectively. The lowest allocation was seen in the District of Columbia and Utah, with both approaching 4%.Entering 2021, states will begin to focus on immunization of essential workers, people over the age of 65 and immunocompromised individuals with co-morbidities

18. Arcturus 疫苗临床研究不会被临床 I 期结果疫苗产生较低的中和抗体滴度所影响
Arcturus undeterred by low neutralizing titers from COVID vaccine in Phase I
来源：BioCentury
发布时间：2020-12-30
链接：https://www.biocentury.com/article/633056
作者：Sandi Wong, Assistant Editor
编译者：孔娟
中文摘要：
Arcturus 公司表示由其新冠肺炎候选疫苗 ARCT-021 (mRNA 方法)诱导的细胞应答将弥补其 I/II 期中期数据中和抗体水平低的不足。周一数小时后，该公司股价下跌 39%，周二下跌 54%。所有接受 5 g ARCT-021 强化给药的受试者均有可检测到的中和抗体。然而，与其他制药商竞争的候选疫苗相比 ARCT-021 没有产生尽可能多的中和抗体。数据显示 Arcturus 自我复制 mRNA 疫苗的单次和预增强疫苗接种刺激了 CD4+和 CD8+ T 细胞应答。科学家推测稳健的 T 细胞应答是第二次 5 g ARCT-021 给药后低抗体产生的原因。也有表示认为受试者的 T 细胞反应可能太快，无法增强体液反应。研究者表示，针对 S 蛋白的非中和抗体可以

通过刺激补体和吞噬作用等其他免疫反应来介导保护作用。 他还引用了最近批准的两种mRNA 疫苗的关键试验的疗效数据，表明疾病预防在单次疫苗接种后约两周显现。I 期研究中共纳入 106 名志愿者，Arcturus 将继续收集数据，正在进行 600 人的 II 期试验,III 期测试将于 2021 年第 2 季度开始。

Abstract：

Arcturus believes cellular responses induced by its COVID-19 vaccine candidate will compensate for the underwhelming neutralizing antibody levels in its interim Phase I/II data.

The RNA company’s shares fell 39% after hours Monday, and on Tuesday sank by 54% to $42.36 as investors further digested the data and Wall Street analysts downgraded the stock.

Arcturus Therapeutics Holdings Inc. (NASDAQ:ARCT) reported late Monday that all subjects receiving prime-boost administration of 5 μg ARCT-021 had detectable neutralizing antibodies. But the mean peak titer after boost (46) was not markedly higher than the titer in volunteers who received only one 5 μg injection (32). The mean peak titer in individuals who received a single dose of 7.5 μg vaccine was 33.

The titers fell on the low end of the range of 12 to 1818 in convalescent sera from patients asymptomatic to severe COVID-19.

On a conference call to discuss the readout, Arcturus Chief Development Officer Steve Hughes presented data showing that single and prime-boost vaccinations of the company’s self-replicating mRNA vaccine stimulated CD4+ and CD8+ T cell responses in the study.

Eng Eong Ooi, a member of Arcturus’ vaccine platform SAB, hypothesized the robust T cell responses were behind the low antibody production following the second 5 μg ARCT-021 administration. Speaking on the call, Ooi, a Duke-NUS Medical School professor, said the T cell responses may have been too fast for the candidate to boost the humoral response.

The study enrolled a total of 106 volunteers, including 37 adults ages ≤ 55 years and 29 over 55 whose immunogenicity responses were reported in Monday’s presentation.

The company plans to test single and prime-boost administration of the candidate at the 7.5 μg dose and prime-boost immunization at the lower dose in a Phase II study in about 600 people. The Phase I/II trial does not have a 7.5 μg prime-boost cohort.

Interim Phase II data are expected early next year, with Phase III testing to begin in 2Q21.

Also on the call, President and CEO Joseph Payne noted the company’s data demonstrating protection in animals models, including non-human primates with deficient humoral immunity. He said, “I think that there’s a reasonable sense of optimism that our single administration could be efficacious based on the data that we’ve collected.”

After Hughes’ presentation, Ooi showed animal data that he said suggested that antibodies were not necessary for protection against SARS-CoV-2. He also cited

anecdotal reports of recovery in COVID-19 patients with genetic B cell deficiencies.
Ooi added that non-neutralizing antibodies against the spike could mediate protection by stimulating other immune responses such as complement and phagocytosis.
He also cited efficacy data from pivotal trials of two recently authorized mRNA vaccines that showed disease prevention manifested about two weeks after a single vaccination.
Phase I data for mRNA-1273 from Moderna Inc. (NASDAQ:MRNA) and NIH and Comirnaty (BNT162b2) from BioNTech SE (NASDAQ:BNTX) and Pfizer Inc. (NYSE:PFE) showed that neutralizing antibody levels were undetectable in a large proportion of participants before vaccine boost at weeks four and three, respectively. Mean titers in both trials' subjects rose over 10-fold after a second shot.

19. 在一项随机对照试验中，接受托珠单抗治疗的 COVID-19 患者的预后和预测性生物标志物

Prognostic and predictive biomarkers in patients with COVID-19 treated with tocilizumab in a randomised controlled trial

来源：medrxiv
发布时间：2020.12.26
文章链接：https://www.medrxiv.org/content/10.1101/2020.12.23.20247379v1
第一作者：Jennifer Tom
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doi: https://doi.org/10.1101/2020.12.23.20247379
编译者：张怡
中文摘要：
背景 回顾性观察研究表明在 COVID-19 肺炎患者中，白细胞介素-6 （IL-6），C 反应蛋白（CRP），乳酸脱氢酶（LDH），铁蛋白，淋巴细胞，单核细胞，中性粒细胞，D-二聚体，血小板、与疾病进程，治疗效果或与两者都相关。研究者们探讨了这些候选的预后和预测的生物标志物在使用托珠单抗治疗后的疗效效果，一种抗 IL-6 受体抗体，采用了来自 COVACTA 的数据，用于因严重 COVID-19 肺炎住院的患者。
方法 分别检测用托珠单抗治疗的 295 名患者和安慰剂组 142 名患者的候选生物标志物。疗效结果评估的临床状态在 7 类序级量表(1，出院；7，死亡)、死亡率、出院时间、机械通气(如果没有随机选择)，直到第 28 天。通过比例优势、二项或 Fine-Gray 模型和额外的敏感性分析，对生物标志物进行持续评估。
结果 安慰剂组显示除了 LDH 和 D-二聚体外的所有候选生物标志物对第 28 天死亡率、机械通气、临床状态和出院时间具有很强的预后作用。托珠单抗组显示铁蛋白对第 28 天死亡率、机械通气、临床状态有预测作用。
解释 在 COVACTA 患者中多个生物标志物预后的临床结果得到证实。铁蛋白被确定为托珠单抗在 COVACTA 患者人群中作用的预测生物标志物；与第 28 天的安慰剂相比，高铁蛋白水平与托珠单抗更好的临床结果有关。
Abstract

Background Retrospective observational studies suggest that interleukin-6 (IL-6), C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, lymphocytes, monocytes, neutrophils, D-dimer, and platelets are associated with disease progression, treatment outcomes, or both, in patients with COVID-19 pneumonia. We explored these candidate prognostic and predictive biomarkers with efficacy outcomes after treatment with tocilizumab, an anti‐IL-6 receptor antibody using data from the COVACTA trial for patients hospitalised with severe COVID-19 pneumonia.
Methods Candidate biomarkers were measured in 295 patients in the tocilizumab arm and 142 patients in the placebo arm. Efficacy outcomes assessed were clinical status on a seven-category ordinal scale (1, discharge; 7, death), mortality, time to hospital discharge, and mechanical ventilation (if not receiving it at randomisation) through day 28. Prognostic and predictive biomarkers were evaluated continuously with proportional odds, binomial or Fine-Gray models, and additional sensitivity analyses.
Findings Modelling in the placebo arm showed all candidate biomarkers except LDH and D-dimer were strongly prognostic for day 28 clinical outcomes of mortality, mechanical ventilation, clinical status, and time to hospital discharge. Modelling in the tocilizumab arm showed a predictive value of ferritin for day 28 clinical outcomes of mortality (predictive interaction p=0.03), mechanical ventilation (predictive interaction p=0.01), and clinical status (predictive interaction p=0.02) compared with placebo.
Interpretation Multiple biomarkers prognostic for clinical outcomes were confirmed in COVACTA. Ferritin was identified as a predictive biomarker for the effects of tocilizumab in the COVACTA patient population; high ferritin levels were associated with better clinical outcomes for tocilizumab compared with placebo at day 28.

20. HLA-C*04:01 是 COVID-19 重症的遗传风险等位基因

HLA-C* 04:01 is a Genetic Risk Allele for Severe Course of COVID-19
来源：medRxiv
发布时间：2020-12-24
链接：https://www.medrxiv.org/content/10.1101/2020.12.21.20248121v1
第一作者：Weiner January
通讯作者：Heidecker Bettina
通讯作者单位：Department of Cardiology, Charite University Hospital Berlin
DOI 或 PUBMED ID：
编译者：王玮
中文摘要：

背景 自 2019 年 COVID-19 大流行以来，对 SARS-CoV-2 感染患者发展到重症的预测因子的需求日益增加。人类白细胞抗原等位基因（HLA）被认为是潜在的遗传宿主因素。该研究试图通过使用 HLA 测序和随后的独立验证进行一项国际多中心研究来评估这一假设。
方法 对 332 份标本进行分析。首先，在德国、西班牙和瑞士招募了 233 名患者进行 HLA 和全外显子组测序。此外，在一个公共数据集（美国，n=99）上验证结果。选择年龄超过 18 岁

的患者，代表疾病的全谱。HLA 候选等位基因在衍生队列（n=92）中鉴定，并在两个独立验证队列（n=240）中检测。

结果 研究发现HLA-C*04:01是COVID-19发展成重症的一个新的基因预测因子。HLA-C*04:01携带者感染 SARS-CoV-2 时气管插管的风险增加 2 倍（hazard ratio 2.1, adjusted p-value=0.0036）。重要的是，这些发现在一个独立的数据集中得到了验证。此外，该发现在生物学上是可信的，因为与其他 HLA 等位基因相比，HLA-C*04:01 与相关 SARS-CoV-2 多肽的预测结合位点较少。外显子组测序证实了 HLA 分析的结果。

结论 HLA-C*04:01 携带与 SARS-CoV-2 感染患者气管插管风险增加 2 倍有关。HLA-C*04:01检测对鉴别高危患者和个体化治疗具有临床意义。

Abstract:

Background Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, there has been increasing demand to identify predictors of severe clinical course in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Human leukocyte antigen alleles (HLA) have been suggested as potential genetic host factors. We sought to evaluate this hypothesis by conducting an international multicenter study using HLA sequencing with subsequent independent validation.

Methods We analyzed a total of 332 samples. First, we enrolled 233 patients in Germany, Spain, and Switzerland for HLA and whole exome sequencing. Furthermore, we validated our results in a public data set (United States, n=99). Patients older than 18 years presenting with COVID-19 were included, representing the full spectrum of the disease. HLA candidate alleles were identified in the derivation cohort (n=92) and tested in two independent validation cohorts (n=240).

Results We identified HLA-C* 04:01 as a novel genetic predictor for severe clinical course in COVID-19. Carriers of HLA-C* 04:01 had twice the risk of intubation when infected with SARS-CoV-2 (hazard ratio 2.1, adjusted p-value=0.0036). Importantly, these findings were successfully replicated in an independent data set. Furthermore, our findings are biologically plausible, as HLA-C* 04:01 has fewer predicted bindings sites with relevant SARS-CoV-2 peptides as compared to other HLA alleles. Exome sequencing confirmed findings from HLA analysis.

Conclusions HLA-C* 04:01 carriage is associated with a twofold increased risk of intubation in patients infected with SARS-CoV-2. Testing for HLA-C* 04:01 could have clinical implications to identify high-risk patients and individualize management.

21. SARS-CoV-2 spike 糖蛋白的 S1 能够诱导 BV-2 小胶质细胞中的神经炎症

SARS-CoV-2 spike glycoprotein S1 induces neuroinflammation in BV-2 microglia

来源：bioRxiv

发布时间：2020-12-29

链接：https://www.biorxiv.org/content/10.1101/2020.12.29.424619v1

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编译者：宋珂
中文摘要：

SARS-CoV-2 病毒造成了全球性的疫情。除了由 SARS-CoV-2 造成的呼吸道并发症以外，越来越多的证据表明，患者的神经系统症状和神经精神症状也与病毒引起的疾病有关。在本研究中，作者考察了 SARS-CoV-2 spike 糖蛋白 S1 的刺激对 BV-2 小胶质细胞中神经炎症的影响。对培养物上清液的分析表明，TNFα，IL-6，IL-1β 和 iNOS/NO 的含量增加。SARS-CoV-2 spike 糖蛋白 S1 提高了磷酸化 p65 和磷酸化 IκB 蛋白的表达，并增强了 NF-κB 与 DNA 的结合能力和转录活性。在 BAY11-7082（1 μM）存在的条件下，糖蛋白的促炎作用受到了抑制。在 BV-2 小胶质细胞中，SARS-CoV-2 spike 糖蛋白 S1 的存在提高了 NLRP3 蛋白的表达，以及 caspase-1 活性。但是，用 CRID3（1 μM）或 BAY11-7082（1 μM）进行预处理会导致 NLRP3 炎性小体/caspase-1 被抑制。作者还观察到，CRID3 削弱了 SARS-CoV-2 spike 糖蛋白 S1 诱导的 IL-1β 产量的提高。在被 spike 糖蛋白 S1 刺激的 BV-2 小胶质细胞中，作者观察到 p38 MAPK 蛋白表达的提高，而当 SKF 86002 存在时，蛋白的表达降低。作者推测，spike 糖蛋白 S1 通过激活 NF-κB，NLRP3 炎性小体和 p38 MAPK 介导了神经炎症发生的提高。目前结果的意义在于，有助于我们理解感染 SARS-CoV-2 的患者中观察到的神经和神经精神症状的机制。

Abstract:

The emergence of SARS‐CoV‐2 has resulted in a global pandemic. In addition to respiratory complications as a result of SARS-CoV-2 illness, accumulating evidence suggests that neurological and neuropsychiatric symptoms are associated with the disease caused by the virus. In this study, we investigated the effects of the SARS-CoV-2 spike glycoprotein S1 stimulation on neuroinflammation in BV-2 microglia. Analyses of culture supernatants revealed an increase in the production of TNFα, IL-6, IL-1β and iNOS/NO. SARS‐CoV‐2 spike glycoprotein S1 increased protein expressions of phospho-p65 and phospho-IκB, as well as enhancing DNA binding and transcriptional activity of NF-κB. Pro-inflammatory effects of the glycoprotein effects were reduced in the presence of BAY11-7082 (1 μM). The presence of SARS-CoV-2 spike glycoprotein S1 in BV-2 microglia increased the protein expression of NLRP3, as well as caspase-1 activity. However, pre-treatment with CRID3 (1 μM) or BAY11-7082 (1 μM) resulted in the inhibition of NLRP3 inflammasome/caspase-1. It was also observed that CRID3 attenuated SARS-CoV-2 spike glycoprotein S1-induced increase in IL-1β production. Increased protein expression of p38 MAPK was observed in BV-2 microglia stimulated with the spike glycoprotein S1, and was reduced in the presence of SKF 86002. These results have provided the first evidence demonstrating SARS-CoV-2 spike S1 glycoprotein-induced neuroinflammation in BV-2 microglia. We propose that promotion of neuroinflammation by this glycoprotein is mediated through activation of NF-κB, NLRP3 inflammasome and p38 MAPK. These results are significant because of their relevance to our understanding of neurological and neuropsychiatric symptoms observed in patients infected with SARS-CoV-2.

22. SARS-CoV-2 宿主内遗传多样性的模式

Patterns of within-host genetic diversity in SARS-CoV-2

来源：bioRxiv
发布时间：2020-12-25
链接：https://www.biorxiv.org/content/10.1101/2020.12.23.424229v1

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中文摘要：

监测 SARS-CoV-2 的传播并重建传播链已成为世界各国政府关注的重大公共卫生问题。SARS-CoV-2 的适度突变率和快速传播阻碍了从共有的基因组序列重建传播链，但宿主内遗传多样性理论上有助于识别密切接触者。本文描述了 1181 份重复深度测序的 SARS-CoV-2 样本的宿主内多样性模式。95%的样本在可检测的等位基因频率上显示宿主内突变。对突变谱的分析显示，在 SARS-CoV-2 大流行期间，突变的积累主要是由于正链的损伤或 RNA 编辑，而不是复制错误。宿主内部和宿主之间的多样性表现出强大的净化选择，特别是针对无义突变。反复发生的宿主内突变，其中许多与已知的系统发育同源性相一致，显示出净化选择的频谱和模式，比重组或趋同进化更能说明突变热点。虽然等位基因频率表明大多数样本是由单一谱系感染的结果，但我们确定了多个假定的合并感染的例子。将这些结果整合到流行病学推断框架中，我们发现，虽然样本之间共享宿主内变异有助于重建传播链，但突变热点和罕见的重复感染病例可能会混淆这些分析。

Abstract:

Monitoring the spread of SARS-CoV-2 and reconstructing transmission chains has become a major public health focus for many governments around the world. The modest mutation rate and rapid transmission of SARS-CoV-2 prevents the reconstruction of transmission chains from consensus genome sequences, but within-host genetic diversity could theoretically help identify close contacts. Here we describe the patterns of within-host diversity in 1,181 SARS-CoV-2 samples sequenced to high depth in duplicate. 95% of samples show within-host mutations at detectable allele frequencies. Analyses of the mutational spectra revealed strong strand asymmetries suggestive of damage or RNA editing of the plus strand, rather than replication errors, dominating the accumulation of mutations during the SARS-CoV-2 pandemic. Within and between host diversity show strong purifying selection, particularly against nonsense mutations. Recurrent within-host mutations, many of which coincide with known phylogenetic homoplasies, display a spectrum and patterns of purifying selection more suggestive of mutational hotspots than recombination or convergent evolution. While allele frequencies suggest that most samples result from infection by a single lineage, we identify multiple putative examples of co-infection. Integrating these results into an epidemiological inference framework, we find that while sharing of within-host variants between samples could help the reconstruction of transmission chains, mutational hotspots and rare cases of superinfection can confound these analyses.