新型冠状病毒信息简报

第 31 期（2020 年 4 月 18 日报）

上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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1. 2020 年 4 月 17 日疫情

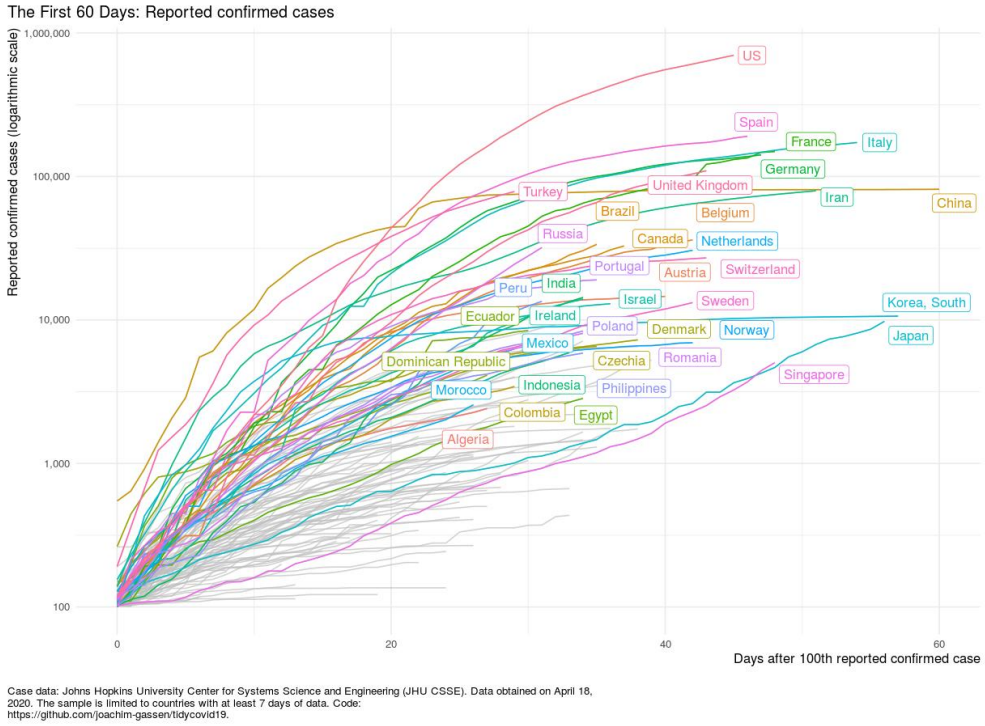
数据来源：WHO

发布时间：2020 年 4 月 17 日北京时间下午 4 点

链接：https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

根据 WHO 提供的数据，2020 年 4 月 17 日全球累计确诊新型冠状病毒病人 2074529 例，当日新增确诊 82967 例，累计死亡 139378 例，当日新增死亡 8493。

中国累计确诊 84149 例，累计死亡 4642 例，当日新增确诊 352 例，新增死亡 1290 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 4 月 18 日北京时间下午 4 点）

全国新型冠状病毒肺炎新增确诊病例分布图（4 月 17 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 巴黎废水中 SARS-CoV-2 的时间进程定量检测与 COVID-19 确诊病例相关

Time course quantitative detection of SARS-CoV-2 in Parisian wastewaters correlates with COVID-19 confirmed cases

来源：medRxiv
发布时间：2020-04-17
链接：https://www.medrxiv.org/content/10.1101/2020.04.12.20062679v1
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DOI 或 PUBMED ID：10.1101/2020.04.12.20062679
编译者：宋张悦

中文摘要：
由于许多 SARS-CoV-2 携带者没有或很少表现出非特异性症状，因此在人群中检测到 SARS-CoV-2 传播的时间可能太晚了，只有可以进行大规模人体检测或有临床 COVID-19 病例被报道时才能被检测到。这显然是评估和可能控制当前流行病的一个重大陷阱。由于粪便样本中存在 SARS-CoV-2，最近有人提出在废水中定性检测 SARS-CoV-2，作为研究人类体内病毒循环的补充工具。如果这一假设是正确的，那么废水中 SARS-CoV-2 的相对含量应该与确诊的 COVID-19 病例数相关。为了验证这一假设，我们对巴黎地区 3 个主要污水处理厂（WWTP）收集的 23 个未经处理和 8 个处理过的废水样本（来自 300-400 万居民的废弃物）进行了 SARS-CoV-2 的 RT-qPCR 定量分析。本研究于 2020 年 3 月 5 日至 4 月 7 日进行。所有未经处理的废水样本的 SARS-CoV2 均为阳性。另外，8 个处理过的废水样本中有 6 个被 RT-qPCR 检测为阳性。与相应的未处理废水样本相比，处理后废水的病毒载量减少了 100 倍，这与之前对肠道病毒的研究一致。紧接着，研究人员将废水样本中 SARS-CoV2 基因组的平均水平与巴黎地区和法国的 COVID-19 确诊致死病例数量进行了比较，正如预期的那样，证实在原始废水中基因组单位的增加与区域和国家层面统计到的致死病例数量的增加是完全一致的。本研究表明，废水污染和病毒基因组检测发生在流行病指数增长开始之前。这项工作表明，对废水中 SARS-CoV2 基因组进行定量监测，可以为更好地在本地或区域范围内调查 SARS-CoV-2 的传播提供重要的信息。此外，当由于逻辑、伦理或经济原因难以对人类进行调查时，废水调查可能提供另一种可能的早期工具来检测人群中的病原体。

Abstract:
Since many SARS-CoV-2 carriers are assumed to exhibit no or few non-specific symptoms, SARS-CoV-2 circulation among human populations may be detected too lately and only when massive human testing is available or when clinal COVID-19 cases are reported. This is obviously a major pitfall for evaluating and possibly controlling the current epidemic. Due to the presence of SARS-CoV-2 in stool samples qualitative detection of SARS-CoV-2 in wastewaters has recently been proposed as a complementary tool to investigate the virus circulation in human populations. If this assumption is correct, SARS-CoV-2 relative amounts in wastewaters should correlate with the number of confirmed COVID-19 cases. To test this hypothesis, we performed a time-course quantitative analysis of SARS-CoV-2 by RT-qPCR in 23 raw and 8 treated wastewater samples collected from 3 major wastewater treatment plant (WWTP) of the Parisian area collecting 3 to 4 million inhabitants reject. This study was conducted from 5 March to 7 April

2020. All raw wastewater samples scored positive for SARS-CoV2. Additionally, 6 out of 8 samples from treated wastewater scored positive by RT-qPCR. Treated wastewater effluents showed a 100 times reduction in the viral load compared to the corresponding raw wastewater samples, which agrees with previous work on enteric viruses. We next compared the average level of SARS-CoV-2 genomes in wastewater samples over time with the number of confirmed fatal cases of COVID-19 in Paris area and in France As expected, we confirmed that the increase of genome units in raw wastewaters accurately followed the increase in the number of fatal cases observed at the regional and national level Therefore, our study demonstrates that the contamination of wastewater and the detection of viral genome occurred before the beginning of the exponential growth of the epidemic. This work demonstrated that a quantitative monitoring of SARS-CoV2 genomes in wastewaters should bring important and additional information for better survey of SARS-CoV2 circulation at the local or regional scale. Additionally, wastewater survey may provide an alternative and possibly early tool to detect pathogens in populations when investigations in humans is difficult for logistic, ethical or economic reasons.

3. 一种基于 Luminex 技术的检测血清中抗 SARS-CoV-2 S 蛋白循环抗体的高通量方法

A high through put assay for circulating antibodies directed against the S protein of SARS-CoV-2

来源：medRxiv

发布时间：2020-04-14

链接：https://www.medrxiv.org/content/10.1101/2020.04.14.20059501v1

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DOI 或 PUBMED ID：Preprint

编译者：孔娟

中文摘要：

背景：严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）在全球大流行，目前检测方法大多基于 RT-PCR 分子诊断，迫切需要开发高通量的血清学方法来检测血清中抗体，并用于鉴定血清转化、潜在的血浆供体、评估人群中感染的流行程度、确定可能对 SARS-CoV-2 免疫的医护人员等。

方法：使用 Luminex 技术对 14 份（3 例健康血清，10 例患者血清，1 例不确定）血清样本中针对 SARS-CoV-2 S 蛋白和受体结合区域 RBD 的特异性抗体进行了检测。

结果：用特定荧光染料标记的珠子用可溶性 S 蛋白三聚体、S 蛋白中心区域或 RBD 包被，与血清、生物素化的抗人总 Ig 抗体和 PE 标记的链霉抗生物素蛋白一起孵育,经 Luminex 分析仪检测后分析患者和正常人血清中抗体含量。结果显示此方法可以识别已发生血清转化的个体及康复者血清中抗 SARS-CoV-2 抗体，所有患者血清均与 SARS-CoV-2 抗原有较强的反应，针对 S 蛋白检测信号强于 RBD 蛋白，三份健康者血清不与任何一种抗原发生反应 。

解释：Luminex 技术在每次测试中使用少至 5ng 的抗原，在 2.5 小时内可同时对多个样本进行有效测试，每天可以产生超过 5,000 个样本的结果。该测试使大规模、经济和有效的抗体测试成为可能。

Abstract

Background. More than one million infections with the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) have been confirmed. While PCR-based assays are used for diagnosis, high through-put serologic methods are needed to detect antibodies for seroserveillance and for identification of seroconversion, potential plasma donors, and the nature of the immune response to this pathogen.

Methods. A Luminex binding assay was used to assess the presence of antibodies in human sera from COVID-19-infected and -uninfected individuals specific for two recombinant proteins of SARS-CoV-2.

Findings. Fluorochrome-labeled beads were coated with a recombinant soluble stabilized trimeric SARS-CoV-2 S protein ectodomain or its central portion, the receptor binding domain (RBD). Coated beads were incubated with sera, followed by incubation with biotinylated anti-human total Ig antibodies and phycoerythrin (PE)-labeled streptavidin. Readout using a Luminex analyzer clearly differentiated between sera of the infected and uninfected subjects, delineating a wide range of serum antibody levels in infected subjects.

Interpretation. Antibody assays of sera can identify individuals who are infected with SARS-CoV-2 and have seroconverted, as well as subjects who have been infected and recovered. The use of the Luminex binding Ab assay has the advantage that it can be run in approximately 2.5 hours, uses very little antigen, and permits a high through-put of samples/day.

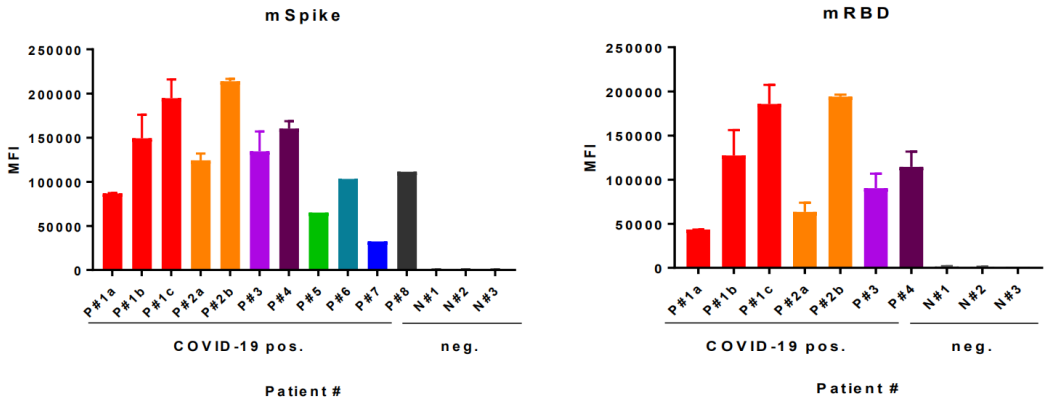

Figure 1. Screening for the presence of SARS-CoV-2 antibodies in specimens from COVID-19-infected and uninfected (neg) humans. Assays were run using the S protein produced in mammalian cells (mSpike, left) with sera from eight infected patients and with sera from four of these patients with mRBD (right). Results are shown using sera tested at a dilution of 1:200. For specimens from four patients (P#1, 2, 3 and 4) run against both antigens, the data shown are the mean + S. D. of two to five experiments. For four patients (P#5-8), the specimens were run only against the mSpike in a single experiment.

4. 独特的早期 IgA 特征可能决定 COVID-19 症状的严重程度：一个免疫病例系列

Distinct early IgA profile may determine severity of COVID-19 symptoms: an immunological case series

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编译：张怡
中文摘要：
SARS-CoV-2 是 COVID-19 的病原体，对全球健康构成严重威胁。感染 SARS-CoV-2 的患者表现出广泛的症状和疾病严重程度，而关于其免疫原性的数据有限。
本文中，作者报告了 SARS-CoV-2 特异性抗体反应的动力学与临床特征和特定 B 细胞群的动态关系。采用流式细胞术对 B 细胞进行免疫分型，纵向采集 PBMCs。同时，使用整个蛋白质组肽微阵列分析血清样本中是否存在 SARS-CoV-2 特异性 IgA、IgG 和 IgM 抗体。在轻度病例发病后不久，作者观察到造浆细胞存活率增加，同时伴有较强的 SARS-CoV-2 特异性 IgA 反应。相比之下，病情进展较严重的病例表现为延迟，但最终非常强烈且广泛的 SARS-CoV-2 特异性 IgA 反应。
本病例研究表明，确定 SARS-CoV-2 特异性抗体表位对监测早期 B 细胞反应的特异性和量级有价值，可以指导候选疫苗的开发。后续研究需要评估 SARS-CoV-2 特异性 IgA 反应的动力学和强度是否可能成为病毒控制的潜在预后标志物。

Abstract
SARS-CoV-2 is the causative agent of COVID-19 and is a severe threat to global health. Patients infected with SARS-CoV-2 show a wide range of symptoms and disease severity, while limited data is available on its immunogenicity.
Here, the kinetics of the development of SARS-CoV-2-specific antibody responses in relation to clinical features and dynamics of specific B-cell populations are reported. Immunophenotyping of B cells was performed by flow cytometry with longitudinally collected PBMCs. In parallel, serum samples were analyzed for the presence of SARS-CoV-2-specific IgA, IgG, and IgM antibodies using whole proteome peptide microarrays. Soon after disease onset in a mild case, we observed an increased frequency of plasmablasts concomitantly with a strong SARS-CoV-2-specific IgA response. In contrast, a case with more severe progression showed a delayed, but eventually very strong and broad SARS-CoV-2-specific IgA response. This case study shows that determining SARS-CoV-2-specific antibody epitopes can be valuable to monitor the specificity and magnitude of the early B-cell response, which could guide the development of vaccine candidates. Follow-up studies are

required to evaluate whether the kinetics and strength of the SARS-CoV-2-specific IgA response could be potential prognostic markers of viral control.

5. 严重新冠肺炎中的细胞因子风暴

Cytokine release syndrome in severe COVID-19

来源：Science
发布时间：2020-04-16
链接：https://science.sciencemag.org/content/early/2020/04/16/science.abb8925
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Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, PA, USA.
DOI 或 PUBMED ID：10.1126/science.abb8925 (2020)
编译者：刘焕珍
中文摘要：
SARS-CoV-2 诱发的新冠肺炎病例高达 20%出现 ARDS，而 SARS-CoV 病例， MERS-CoV 病例及 CAR-T 治疗病例均观察到细胞因子风暴（CRS）诱发了 ARDS 及继发性噬血细胞性淋巴组织增生症（sHLH），这些案例提示抑制 CRS 是治疗新冠肺炎的重要途径。事实上，新冠肺炎已发现 CRS 和 sHLH 特征，文章结合 IL-6 抑制策略对控制 CAR-T 治疗中的 CRS 和 sHLH 的有效性，强调 IL-6 信号通路在超炎性反应中的关键作用，并认为基于 IL-6 通路的治疗可用于超炎性反应的急性控制但可能延缓病毒清除。中国开展的托珠单抗治疗新冠肺炎的开放标签的初步临床实验已得到令人鼓舞的结果，更多的对照临床试验正在进行中。抑制 IL-6 通路可能还可以用于像流感或埃博拉等传染病的治疗。
Abstract
Although the situation is rapidly evolving, severe disease manifested by fever and pneumonia, leading to acute respiratory distress syndrome (ARDS), has been described in up to 20% of COVID-19 cases. This is reminis-cent of cytokine release syndrome (CRS)–induced ARDS and secondary hemophagocytic lymphohistiocytosis (sHLH) ob-served in patients with SARS-CoV and MERS-CoV as well as in leukemia patients receiving engineered T cell therapy. The efficacy of IL-6–IL-6R antagonists for the treatment of CRS as well as sHLH underscores the central role of IL-6 signaling in the pathophysiology of cytokine-driven hyperin-flammatory syndromes. A theoretical possibility is that the suppression of inflamma-tion by IL-6 antagonism might delay viral clearance pre-liminary results from an open-label study in 21 patients with COVID-19 treated with tocilizumab in China are encouraging.

6. 用 QTY 编码设计的水溶性的细胞因子受体和 Fc 的融合蛋白可以结合到它们各自的配体

QTY code-designed water-soluble Fc-fusion cytokine receptors bind to their respective ligands

来源：QRB Discovery （Accepted）
发布时间：2020-04
链接：https://www.cambridge.org/core/services/aop-cambridge-core/content/view/6F70CCA13FD9E6841830A8A8C7D64EE2/S2633289220000046a.pdf/qty_codedesigned_watersoluble_fcfusion_cytokine_receptors_bind_to_their_respective_ligands.pdf
参考：转化医学网公众号
第一作者：Shilei Hao
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通讯作者单位：MIT
DOI：10.1017/qrd.2020.4
编译者：蒋立春
中文摘要：
细胞因子风暴在 COVID-19 也扮演了关键性角色。所以在 COVID-19 治疗中必须有效清除过量的细胞因子。研究者们以前报道过一个创新的叫做 QTY 的蛋白修饰工具。这个工具通过将疏水性氨基酸比如 Leu，Ile，Val 和 Phe 替代为 Gln（Q），Thr（T）以及 Tyr（Y）. 这样研究者就设计出了可溶性的膜蛋白。该研究者中将 QTY 应用于中 6 个细胞因子受体，包括 IL4αR 和 IL10αR，趋化因子受体 CCR9 以及 CXCR2，以及感染素受体 IFNγR1 和 IFNλR1。经过 QTY 工具变异过的细胞因子受体虽然没用原始细胞因子受体的疏水性片段，他们保存着和原始细胞因子受体相似的生理特性。研究者们将这些受体融合到 IgG 的 Fc 上形成一个类抗体的结构。然后研究所们在 E.Coli 中表达和纯化了这些按照 QTY 编码的 Fc 融合受体。这些表达纯化得到的水溶性的融合受体和它们各自的配体结合的亲和常数 Kd 和原始受体相似。作者们认为这些细胞因子受体和 Fc 的融合蛋白有潜力成为像抗体一样的海绵吸收细胞因子从而抑制细胞因子风暴的发生。

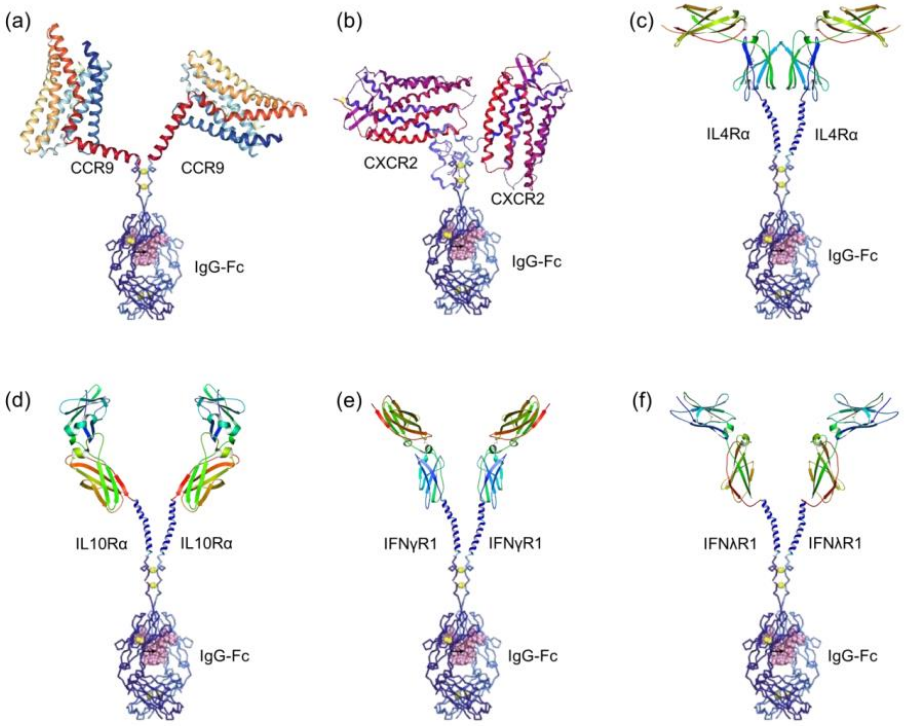

Figure 2. Schematic illustration for Fc fused QTY variant cytokine receptors with antibody-like structure. (a) $CCR9^{QTY}$-Fc; (b) $CXCR2^{QTY}$-Fc; (c) $IL4R\alpha^{QTY}$-Fc; (d) $IL10R\alpha^{QTY}$-Fc; (e) $IFN\gamma R1^{QTY}$-Fc; (f) $IFN\lambda R1^{QTY}$-Fc. These illustrations are not to scale and the receptors parts are significantly emphasized for clarity.

Abstract
Cytokine release syndrome (CRS), or “cytokine storm”, is the leading side effect during CAR-T therapy that is potentially life-threatening. It also plays a critical role in viral infections such as COVID-19. Therefore, efficient removal of excessive cytokines is essential for treatment. We previously reported a novel protein modification tool called the QTY code, through which hydrophobic amino acids Leu, Ile, Val and Phe are replaced by Gln (Q), Thr (T) and Tyr (Y). Thus the functional detergent-free equivalents of membrane proteins can be designed. Here we report the application of the QTY code on six variants of cytokine receptors, including interleukin receptors IL4αR and IL10αR, chemokine receptors CCR9 and CXCR2, as well as interferon receptors IFNγR1 and IFNλR1. QTY variant cytokine receptors exhibit physiological properties similar to those of native receptors without the presence of hydrophobic segments. The receptors were fused to the Fc region of IgG protein to form an antibody-like structure. These QTY code-designed Fc fusion receptors were expressed in E. coli and purified. The resulting water-soluble fusion receptors bind to their respective ligands with Kd values affinity similar to isolated native receptors. Our cytokine receptor-Fc fusion proteins potentially serve as an antibody-like decoy to dampen the excessive cytokine levels associated with CRS and COVID-19 infection.

7. 非人类灵长类动物模型中 COVID-19、MERS 和 SARS 发病机制的比较

Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model
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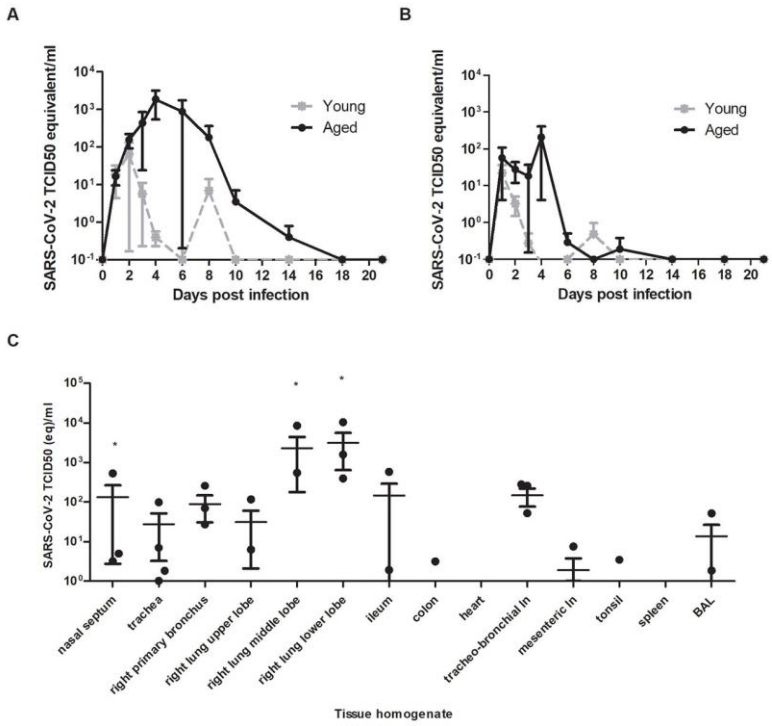
发布时间：2020-04-17
链接：https://science.sciencemag.org/content/early/2020/04/16/science.abb7314
第一作者：Barry Rockx
通讯作者：Barry Rockx，Bart L. Haagmans
通讯作者单位：荷兰鹿特丹伊拉斯姆斯大学
DOI 或 PUBMED ID：10.1126/science.abb7314
编译者：王玮
中文摘要：
为了将 COVID-19 发病机制与以前出现的冠状病毒进行比较，该研究用 SARS-CoV-2 或 MERS-CoV 接种猕猴（cynomolgus macaques），并将其病理学和病毒学与 SARS-CoV 感染的历史报告进行比较。在 SARS-CoV-2 感染的猕猴中（共四只猕猴，两只属于年轻组，两只属于年长组），病毒在没有临床症状的情况下，病毒从鼻子和喉咙排出，在弥漫性肺泡损伤灶的 I 型和 II 型肺泡细胞以及鼻、支气管和细支气管粘膜的纤毛上皮细胞中检测到病毒（图一）。在四分之三的猕猴中，回肠和气管支气管淋巴结中也检测到 SARS-CoV-2 RNA（图一 C）。在 SARS-CoV 感染中，肺部病变通常较严重，而 MERS-CoV 感染则较轻，其病毒主要在 II 型肺细胞中检测到。此外，该研究发现在第 4 天，猕猴鼻粘膜纤毛上皮细胞中检测到 SARS-CoV-2 抗原，这种现状在该研究 SARS-CoV 或 MERS-CoV 感染动物模型中未发现。病毒对鼻粘膜的嗜性与有效的呼吸道传播相吻合，如甲型流感病毒。SARS-CoV-2 的早期病毒脱落高峰与流感病毒脱落相似，这可能解释为什么病例检测和隔离对 SARS-CoV-2 的防控效果不如对 SARS-CoV 的防控控制。这些数据表明 SARS-CoV-2 在猕猴体内引起了 COVID-19 样疾病，为检验防治策略提供了一个新的模型。



图一 SARS-CoV-2 猕猴器官的病毒脱落和病毒检测

Virus shedding and virus detection in organs of SARS-CoV-2 inoculated cynomolgus macaques.

Viral RNA was detected in nasal (A) and throat (B) swabs and tissues (C) of SARS-CoV-2 infected animals by RT-qPCR. Samples from four animals (days 1-4) or two animals (days >4) per group were tested. The error bars represent the standard error of the mean. Virus was detected in tissues from two young, and two aged animals on day 4 by RT-qPCR.* = infectious virus was isolated.

Abstract:

The current pandemic coronavirus, SARS-CoV-2, was recently identified in patients with an acute respiratory syndrome, COVID-19. To compare its pathogenesis with that of previously emerging coronaviruses, we inoculated cynomolgus macaques with SARS-CoV-2 or MERS-CoV and compared the pathology and virology with historical reports of SARS-CoV infections. In SARS-CoV-2-infected macaques, virus was excreted from nose and throat in the absence of clinical signs, and detected in type I and II pneumocytes in foci of diffuse alveolar damage and in ciliated epithelial cells of nasal, bronchial, and bronchiolar mucosae. In SARS-CoV-infection, lung lesions were typically more severe, while they were milder in MERS-CoV infection, where virus was detected mainly in type II pneumocytes. These data show that SARS-CoV-2 causes COVID-19-like disease in macaques, and provides a new model to test preventive and therapeutic strategies.