

COVID-19胃肠道症状机制的研究进展

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摘要

COVID-19自2020年初大流行至今,已然成为长新冠现象,与人类长期存在,目前全球依旧散发。COVID-19常常可累及多个系统,呼吸系统最常见的就是发热、咳嗽等不适,许多患者也经常出现消化道症状,例如腹泻、恶心、呕吐等。目前大量的证据可证实COVID-19已发生多次变异,虽然COVID-19感染的患者症状越来越轻,但探究其致病机制及与呼吸系统的关系仍具有重要意义。COVID-19的治疗应根据患者的年龄、合并症和可用的治疗方案进行个体化治疗,用来预防和治疗并发症和后遗症的出现。本文就COVID-19引起消化道症状的机制及益生菌作为辅助治疗的潜在机制进行论述。

关键词

COVID-19, SARS-CoV-2肠道菌群, 肠肺轴, 免疫系统, ACE2

Research Progress on the Mechanism of COVID-19 Gastrointestinal Symptoms

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Abstract

COVID-19 has been a pandemic since the early 2020's and has become a long new crown phenomenon, persisting in humans and still circulating globally. COVID-19 often involves multiple systems, with the respiratory system most commonly affected by fever and coughing, and many patients often present with gastrointestinal symptoms, such as diarrhoea, nausea, and vomiting. A large body of evidence confirms that COVID-19 has undergone multiple mutations, and although patients with COVID-19 infections are becoming less symptomatic, it is still important to investigate its pathogenesis and relationship with the respiratory system. The treatment of COVID-19

should be individualised according to the age of the patient, comorbidities, and available therapeutic regimens, and should be used to prevent and treat the emergence of complications and sequelae. This article discusses the mechanisms by which COVID-19 causes GI symptoms and the potential mechanisms by which probiotics can be used as adjunctive therapy.

Keywords

COVID-19, SARS-CoV-2, Intestinal Flora, Intestinal-Lung Axis, Immune System, ACE2

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1. 引言

2019 年的 COVID-19 与 2002 年的 SARS-CoV 和 2012 年 MERS-CoV 引起的疾病大流行并列成为三大严重的冠状病毒疫情[1]。而 COVID-19 是由 SARS-CoV-2 引起的呼吸系统疾病,主要通过呼吸道在人与人之间传播,大多数患者表现出典型的呼吸道症状。事实上,COVID-19 可累及多个肺外器官,COVID-19 患者中持续胃肠道症状的报告日益增多,甚至有些患者在感染后长达六个月内可能经历胃灼热、便秘、腹泻和腹痛[2]。目前认为,这些症状可能与病毒在肠道内的复制有关,尽管 COVID 胃肠道症状的确切原因尚未明确,潜在的原因可能包括 SARS-CoV-2 病毒对胃肠道的直接影响,以及伴随的肠道微生物组变化、肠道黏膜屏障损伤和严重的全身性炎症反应。正确认识 COVID-19 与胃肠道的关系具有积极的意义,在管理 COVID-19 患者时,应密切监测他们的胃肠道症状。

2. COVID-19 在胃肠道中的症状

越来越多的证据表明,胃肠道(GIT),包括胃、小肠、大肠、肝脏和胰腺,也可能受到 SARS-CoV-2 的影响。美国确诊的首例 COVID-19 感染病例表现为恶心和呕吐症状,随后出现腹部不适和腹泻[3]。一项研究纳入了 25,210 例患者,其胃肠道特征包括厌食(26.1%)、腹泻(13.5%)、呕吐(6.0%)和恶心(7.5%),发病率为 18.6% [4]。其他消化系统症状,如胃肠道穿孔、上消化道出血、味觉和食欲丧失,也见于部分病例[5]-[7],约 10% 的感染患者实际上仅表现为胃肠道表现,无呼吸道症状[8]。除了非特异性胃肠道症状外,COVID-19 在疾病进展过程中主要导致多种胃肠道相关并发症,包括消化和吸收功能障碍、胃肠道动力障碍、急性肠缺血、胃肠道出血、艰难梭菌(*C. difficile*)感染和胰腺损伤。COVID-19 中的其他胃肠道并发症,如肠梗阻或穿孔,很少见报道[9]。胃肠道症状具有一定的家族性聚集性[10]。孟加拉国的一项研究表明,如果患者有胃肠道症状,他们的家庭成员感染风险增加,更有可能出现胃肠道症状[10]。胃肠道症状的特征比呼吸道症状更隐匿,因此很容易被忽视。感染 SARS-CoV-2 时出现没有呼吸道特征的胃肠道症状。这些患者更有可能延迟诊断,从而给自己和与他们接触的个人带来潜在的问题。并且有大量研究表明 SARS-CoV-2 可以通过粪便传播,因此有胃肠道症状的 COVID-19 患者的临床特征和潜在机制分析对于防止疾病传播具有重要意义。

3. COVID-19 导致胃肠道症状的机制

COVID-19 是由 SARS-CoV-2 引起的呼吸系统疾病,SARS-CoV-2 引起新冠患者胃肠道症状的机制可能与 ACE2 进入细胞直接诱导的细胞病变效应,肠道黏膜屏障损伤以及炎症因子的产生息息相关。

3.1. ACE2 与 SARS-CoV-2 的相互作用

肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)在控制血压和维持电解质平衡方面起着重要作用[11],而肾脏分泌的肾素可以将肝脏产生和分泌的血管紧张素原转化为血管紧张素 I (AngI)。血管紧张素转换酶(ACE)将 AngI 转化为血管紧张素 II (AngII) [12]。血管紧张素 II 具有血管收缩、钠重吸收和肾脏钾排泄、醛固酮合成、血压升高和促炎途径的诱导的作用。ACE2 可以将 AngII 转化为 Ang (1~9),随后在 ACE 的作用下形成 Ang (1~7)。ACE2 被认为是 ACE 的同源物,但它们在体内具有相反的作用。ACE2 参与的通路被认为是抗炎和抗纤维化的,而 ACE 参与的通路是促炎和促纤维化的,可以说,ACE2 具有抗炎和发挥抗重塑作用[13]。血管紧张素转换酶 2 (ACE2)是 SARS-CoV-2 的受体。ACE2 在人肺和肠上皮细胞中表达,其在肠道中的表达是其他组织的 4 倍以上。此外,ACE2 在近端和远端小肠细胞中高表达[14]。已有研究证明,SARS-CoV-2 进入上皮细胞是通过病毒刺突(S)蛋白与细胞上表达的 ACE2 受体的结合介导的。S 蛋白具有 S1 和 S2 功能亚基。S1 促进病毒附着在靶细胞表面,S2 允许病毒和细胞膜融合。S 蛋白由丝氨酸蛋白酶 TMPRSS2 启动,丝氨酸蛋白酶对 SARS-CoV-2 进入细胞至关重要。TMPRSS2 在 S1/S2 和 S2 位点切割 S 蛋白[15],最终导致 ACE2 下调。ACE2 缺失会导致 ANGII 积累[16]。尽管 ACE2 降低会导致小鼠结肠中 ANGII 水平升高,但 ACE2 主要不是通过肠道中的 RAS 系统发挥其功能,而是直接调节肠道氨基酸的稳态、抗菌肽的表达和肠道微生物组的生态[17]。因此,我们推测 SARS-CoV-2 与胃肠道中 ACE2 的结合会降低可用受体的水平,影响色氨酸的吸收,并最终破坏肠道菌群的稳定状态,这是腹泻等胃肠道症状的原因之一。通过表面等离子体共振,Daniel 等人[18]也发现 ACE2 与 SARS-CoV-2 外域的结合亲和力比 SARS-CoV 高 10~20 倍。据报道,COVID-19 患者血管紧张素 II (ANGII)水平的积累显著增加,并且升高程度与疾病的严重程度有关。这可能是因为 SARS-CoV-2 附着在 ACE2 上触发 ACE2 病毒复合物内化到靶细胞中,导致其下调相关。然后将 SARS-CoV-2RNA 释放到细胞质中,并开始病毒复制,引起一系列的胃肠道症状。

3.2. SARS-CoV-2 与肠道屏障功能损伤

Giron 等人[19]证明,严重的 COVID-19 与血浆中较高的连蛋白水平相关,表明紧密连接稳态严重破坏,以及脂多糖(LPS)结合蛋白(LBP)和 β 葡聚糖水平升高,它们分别是细菌和真菌易位的可靠标志物。重要的是,紧密连接通透性和微生物易位的血清标志物与循环促炎介质(如 IL-6)显著相关,表明全身炎症在一定程度上是由肠道屏障破坏引发的。此外,在 283 名因 COVID-19 住院的患者的尿液中测量了肠道脂肪酸结合蛋白(I-FABP),这是一种由负责脂肪酸周转的成熟肠细胞合成的蛋白质,用作肠道损伤的生物标志物[20] [21]。SARS-CoV-2 主要通过 ACE2 受体进入靶细胞,从而通过改变 TJ 相关蛋白的表达和功能对肠道造成原发性损伤,导致细胞旁屏障功能的破坏[22]-[25]。研究还表明,ZO-1 与以下因素相互作用: 1) Occludin、claudins 和 JAM; 2) 细胞内 TJ 斑块的分子成分,如 ZO-2、ZO-3 和扣带蛋白; 3) 肌动蛋白细胞骨架[26]。因此,ZO-1 在细胞旁屏障的结构和功能完整性中起着关键作用[27]。此外,细胞骨架和屏障生物标志物 KRT19 和 ZO1 分别富集在 COVID-19 患者的粪便和血液样本中,表明肠道旁细胞通透性和损伤增加[27]-[29]。此外,COVID-19 患者肠上皮细胞的凋亡是影响胃肠道机械屏障完整性的另一个重要因素。Lehmann 等[26]的一项研究表明,通过使用免疫组化检测裂解的半胱天冬酶-3,COVID-19 患者的凋亡上皮细胞数量显著增加。他们还检查了上皮细胞的组织形态学变化,发现 COVID-19 患者小肠中上皮细胞的凋亡和随后的再生增殖[26]。

3.3. SARS-CoV-2 与免疫系统

宿主能够在病毒感染时产生免疫反应,并控制这些病原体在体内的传播。然而,一些病毒株能够逃

避免免疫攻击并在体内增殖,并引起严重的炎症反应。例如:流感病毒、水疱性口炎病毒等[30]。更重要的是,在易感个体中,病毒会引起强烈的全身炎症反应,称为“细胞因子风暴”,导致严重的病理后果[31]。He 等人[32]对死于 SARS-CoV 的患者进行了尸检。病理结果显示,在表达 ACE2 的细胞中,单核细胞趋化因子-1 (MCP-1)、肿瘤生长因子- β 1 (TGF- β 1)、肿瘤坏死因子- α (TNF- α)、白细胞介素(IL)-1 β 和 IL-6 等促炎细胞因子(PIC)表达高,而不表达 ACE2 的细胞中未发生 PIC 表达。大量的 PIC 会引起细胞因子风暴,进而导致多器官损伤。

干扰素(IFN)是细胞因子的一个子集,对应于对病毒感染的先天免疫反应的核心部分[33],SARS-CoV-2 能够通过破坏干扰素信号传导来逃避先天免疫反应。SARS-CoV-2 膜蛋白介导的,该膜蛋白抑制负责磷酸化和随后激活 IFN 调节因子(IRF) 3 的多蛋白复合体的形成[34]。IRF3 激活是 IFN 转录和合成的先决条件。SARS-CoV-2 辅助蛋白 ORF9b 是阻断 IRF3 激活通路的另一种分子[35]。ORF9b 还通过与 IFN 基因刺激因子(STING)相互作用来抑制 IFN 基因表达;STING 可以募集 TANK 结合激酶 1 (TBK1),TBK1 是 IRF3 磷酸化因子之一[35]。此外,ORF9b 靶向线粒体外膜 70 (TOMM70)的转位酶,该转位酶位于线粒体膜上,可作为线粒体抗病毒信号蛋白(MAVS)的受体发挥作用。MAVS 还参与 IRF3 磷酸化途径。因此,ORF9b 通过干扰 TOMM70 和 MAVS 之间的相互作用来下调 I 型 IFN 的产生[36] [37]。然而,TOMM70 的过表达可以克服 ORF9b 介导的抑制并恢复 IFN- β 表达[36],干扰素反应失调会导致 SARS-CoV-2 侵入肠道细胞导致 I 型和 III 型 IFN 和其他促炎细胞因子(如 IL-8 和 IL-12)的表达增加[38] [39]。所有类型的 IFN 都可以激活 JAK/STAT 通路。I 型 IFN 可由多种细胞类型分泌,尤其是浆细胞样 DC。SARS-CoV-2 已开发出多种策略,通过减弱 I 型和 III 型 IFN 反应来逃避免疫监视[34]。

T 细胞可以通过控制过度的先天免疫反应来拯救器官免受严重损害。COVID-19 患者 T 细胞的减少可能是因为 SARS-CoV-2 蛋白的 C 末端胞质结构域中存在 BH3 样区域,这可以促进病毒蛋白与 T 细胞中的 Bcl-xL 结合并诱导 T 细胞凋亡[40]。最近的一项研究指出,SARS-CoV-2 诱导巨噬细胞和肥大细胞(MC)产生 IL-1,从而诱导基因表达并激活其他促炎细胞因子。由于 IL-1 是有毒的,由无处不在的 MC 和 SARS-CoV-2 激活的巨噬细胞产生的 IL-1 也会导致胃肠道疾病。此外,IL-1 还促进一氧化氮的释放和炎性花生四烯酸产物(如前列腺素和血栓素 A₂)的释放[41]。所有这些影响都会促进细胞因子风暴的产生和发展,并导致继发性肠道损伤。

3.4. SARS-CoV-2 与肠肺轴

肠肺轴是指肠道和肺之间错综复杂的相互作用,由各种免疫、神经和微生物介质调节。肠道微生物组已成为肠肺轴的关键调节因子。特定微生物及其代谢物对肺免疫应答和炎症有深远影响[42],肠肺轴似乎与 COVID-19 的发病机制有关,临床观察表明,出现胃肠道症状的 COVID-19 患者更可能出现严重的呼吸道表现,包括急性呼吸窘迫综合征、肝损伤和休克[43] [44]。一项研究发现,有胃肠道症状的 COVID-19 患者的粪便中并不总是检测到 SARS-CoV-2,因此我们推测某些患者的胃肠道症状可能不是由病毒感染造成的直接损害引起的。进入肠粘膜的效应 CD4⁺ T 细胞是粘膜免疫和慢性肠炎的关键。C-C 趋化因子受体 9 型(CCR9)是 CD4⁺ T 细胞进入小肠的必需趋化因子受体[45]。Jian Wang 等[45]发现病毒感染后肺源性 CCR9 CD4⁺ T 细胞增加。小肠上皮可表达 CCL25 [46],促进 CCR9 CD4⁺ T 细胞募集到小肠[47],导致肠道免疫损伤并破坏肠道菌群的稳态。肠道菌群的紊乱会促进小肠中 Th17 细胞的极化,过多的 IL-17A 产生会导致中性粒细胞的募集[48],引起肠道免疫损伤、腹泻等胃肠道症状。

3.5. SARS-CoV-2 与肠道微生物

人类微生物群由每个人携带的 10~100 万亿个共生微生物细胞组成,主要是细菌[49] [50]。肠道包含

大约 10^{14} 常驻细菌, 统称为肠道微生物群。肠道菌群具有多种影响宿主新陈代谢的生化 and 生理功能[51], 而且肠道微生物群组成及其产物对免疫系统和炎症过程有积极影响。肠道菌群不仅能够诱导抗炎反应, 而且还能维持促炎和抗炎反应之间的平衡, 以调节对病原体的免疫反应。因此, 免疫系统和肠道微生物群之间存在协同作用, 有助于预防和充分管理可能影响宿主健康的不同感染。同样, 肠道微生物群衍生的代谢物也能够通过抑制病毒复制和通过增加上皮耐力和调节性 T 细胞产生来改善免疫反应, 从而与肠道微生物群的免疫调节和抗病毒作用协同作用[52] [53]。COVID-19 有可能改变患者肠道微生物群的组成, 其特征是具有益生菌作用的细菌丰度降低。有趣的是, 这些细菌的某些菌株产生的代谢物可以靶向其他冠状病毒的 S 蛋白, 从而防止其传播和有害影响。同时, 肠道菌群失调的存在会加剧炎症和氧化应激, 造成恶性循环, 使疾病永久化。病毒分子释放的干扰素可消耗专性厌氧菌双歧杆菌、乳酸杆菌和真杆菌, 并促进致病菌棒状杆菌和钉杆菌[54] [55]。一项对 15 名患者粪便样本进行测序的初步研究表明, COVID-19 感染显著改变了粪便微生物组, 其特征是有益共生体减少和机会性病原体富集[56], SARS-CoV-2 与肠道中 ACE2 受体的结合减少了可用游离受体的数量并破坏了色氨酸的吸收, 导致肠道微生物群吸收不良和生态失调。在 SARS-CoV-2 感染患者中, 瘤胃球菌与炎症标志物呈最高的正相关, 其次是与 COVID-19 严重程度相关的 *Clostridium hathewayi*、*Clostridium ramosum* 和 *Coprobacillus* sp. 的丰度; 此外, 观察到与抗炎细菌 *Faecalibacterium prausnitzii* 的丰度呈负相关[57], 肠道中含有能够发酵氨基酸的细菌, 包括精氨酸[58], 肠道微生物群组成的这些改变可导致 L-精氨酸发酵细菌的丰度增加, 从而导致游离 L-精氨酸水平进一步降低。通过增加髓源性抑制细胞数量、阻碍局部 T 细胞功能和增加 ROS 生成, 肠道中的 L-精氨酸耗竭可放大肠道炎症[59], 肠道菌群的改变可以促进 SARS-CoV-2 的生长并触发炎症细胞因子的产生, 从而引起“细胞因子风暴”, 从而损害组织, 引发感染性休克, 并导致多器官衰竭[60]。

4. 益生菌的辅助治疗作用

COVID-19 感染可以导致肠道微生物群改变, 相关研究表明益生菌在减少胃肠道症状的持续时间和严重程度方面显示出功效, 同时可以显著加速病毒灭亡和症状缓解。

双歧杆菌是革兰氏阳性厌氧菌的一个属, 常见于人类肠道微生物组中。这些细菌以其免疫调节特性而闻名, 并已被证明对人类健康有益[61]。双歧杆菌可刺激免疫系统, 其给药已被证明可促进促炎细胞因子的产生, 例如干扰素- γ (IFN- γ)、肿瘤坏死因子- α (TNF- α)、白细胞介素-2 (IL-2)、白细胞介素-12 (IL-12) 和白细胞介素-18 (IL-18), 在小鼠模型中病毒感染之前, 表明对病毒感染具有保护作用。这可能是避免 SARS-CoV-2 感染后宿主反应失衡以控制病毒的原因。此外, 脾脏和肺部自然杀伤细胞(natural killer cell, NK)活性的增加与小鼠模型中病毒复制的减少有关[62] [63]。炎症是 COVID-19 的标志, 过度炎症会对肺部和其他器官造成重大损害。双歧杆菌已被证明可以通过调节促炎细胞因子的产生和降低 IL-6 和 TNF- α 水平来减少炎症[62]-[64]。双歧杆菌通过分泌抗菌物质或竞争肠道中常见的粘附位点, 与大肠杆菌和鼠伤寒沙门氏菌等致病菌竞争[65]。通过这种方式, 双歧杆菌表现出的竞争能力可以避免其他病原体的安装, 并可能有助于预防与 COVID-19 严重程度相关的肠道菌群失调。双歧杆菌已被证明可以降低肠道通透性[66], 并促进肠道细胞中粘蛋白的产生和紧密连接蛋白的表达, 这对维持肠道屏障至关重要。

乳酸杆菌可产生多种代谢物, 如短链脂肪酸, 这些代谢物可以调节免疫反应并促进抗炎作用[67]。这些短链脂肪酸可以影响免疫细胞功能、细胞因子的产生和呼吸道屏障的完整性。此外, 某些乳酸杆菌菌株已显示出产生抗病毒化合物的能力, 如细菌素和胞外多糖[68]。乳酸杆菌还可以产生抗菌肽和抑制病毒进入和复制的物质; 与致病病毒竞争结合位点, 限制病毒的附着和进入, 一些菌株还可产生细菌素和胞外多糖, 抑制病毒复制; 某些乳酸杆菌菌株与肠细胞受体结合, 刺激 MUC-2 和 MUC-3 的上调, 抑制细菌易位和病原体粘附; 乳酸杆菌释放抑制 ACE 的肽, 可能阻止病毒进入; 刺激自然杀伤(NK)细胞; 与

Toll 样受体 4 (TLR4)结合, 影响免疫反应; 各种乳酸杆菌菌株可增强抗病毒细胞因子(IL-12、IFN- γ), 同时减少炎症因子 IL-4、IL-6、TNF- α ; 乳酸杆菌可减轻 TNF- α 诱导的 IL-8 的产生[69]。

5. 结论与展望

SARS-CoV-2 可以通过多种机制引起肠道菌群失调, 进而导致胃肠道症状。这些机制包括通过肠肺轴传播、与 ACE2 受体结合对肠道造成直接损害, 以及引发细胞因子风暴。众所周知, 老年患者或患有糖尿病、高血压、哮喘和癌症的人群, 其肠道微生物群多样性通常较低, 这使得他们在感染 COVID-19 时发病率和死亡率较健康人群更高。因此, 对于这些具有基础疾病的人来说, 早期及时采取干预措施显得尤为重要。老年人和慢性病患者可能会从改善肠道微生物群中显著受益。肠道微生物群可以通过摄入益生菌、益生元和合生元等措施来优化。通过这些方法改善肠道微生物群的组成, 不仅能够预防严重 COVID-19 病情, 还可能为治疗策略提供新的方向。在高风险和重症患者, 以及一线卫生工作者中补充益生菌, 可能有助于限制 COVID-19 的感染。尽管如此, 目前尚无随机对照试验提供确凿的证据来支持这一做法。然而, 间接证据确实支持了补充益生菌可以降低 COVID-19 病情严重程度(包括死亡率)的假设。全球范围内, 许多临床试验正在进行中, 旨在描述益生菌在预防和治疗 COVID-19 方面的潜在作用。

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