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·综 述·

空间环境下肠道菌群失调的研究进展

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摘 要：空间环境中的特殊因素会导致航天员肠道菌群及其代谢产物的失调，对机体会产生系统性的生理影响。本文综述了近年来太空飞行/模拟空间环境对肠道菌群及其代谢产物影响的研究进展。太空飞行/模拟空间环境(space flight/simulated space environment, SF/SPE)可导致侵袭性致病菌的增多及有益菌的减少，肠道炎症加剧与通透性增加，也会引起菌群的有益代谢物减少或有害代谢物增加，进而导致机体内代谢的紊乱，或可诱发其他系统的损伤，从而不利于航天员的健康与工作效率。总结太空飞行/模拟空间环境对肠道菌群产生的影响，可为该领域的后续研究与航天员的在轨健康防护提供科学依据。

关键词：太空飞行；模拟空间环境；肠道菌群；代谢产物

Gut microbial dysbiosis under space environment: a review

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Abstract: Unique factors in the space environment can cause dysbiosis of astronauts' gut microbiota and its metabolites, which may exert systematic physiological effects on human body. Recent progress regarding the effect of space flight/simulated space environment (SF/SPE) on the composition of gut microbiota and its metabolites was reviewed in this paper. SF/SPE may cause the increase of invasive pathogenic bacteria and the decrease of beneficial

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bacteria, aggravating intestinal inflammation and increasing intestinal permeability. SF/SPE may also cause the decrease of beneficial metabolites or the increase of harmful metabolites of gut microbiota, leading to metabolism disorder *in vivo*, or inducing damage of other systems, thus not beneficial to the health and working efficiency of astronauts. Summarizing the effects of SF/SPE on gut microbiota may provide scientific basis for further researches in this field and the on-orbit health protection of astronauts.

Keywords: space flight; simulated space environment; gut microbiota; microbial metabolites

人类的肠道菌群组成复杂，成人肠道内约有3×10^{14}个微生物，目前已发现了 4 000 余种细菌，被称作人体的另一个器官[1-2]。肠道菌群参与人体的营养吸收、代谢和免疫等生理活动，与宿主、环境形成一个相互影响、相互依存的系统。但菌群平衡受多种因素影响(如应激、年龄、饮食结构和地域等)，其动态平衡一旦被打破，微生物及其代谢产物(如肠毒素、短链脂肪酸、氨基酸等)的失调会直接影响机体胃肠道健康[3]，还可导致由菌群代谢物介导的其他系统的功能失调，如免疫系统[4]、神经系统[5-6]和肌骨系统[7-8]等。因此，肠道菌群及其代谢产物对人体具有系统性的生理作用，对机体的健康状态以及工作状态至关重要。

空间环境中具有微重力、辐射、封闭空间和噪声等特殊环境因素，会导致航天员肠道菌群及其代谢产物的失调，从而破坏多种系统的生理平衡状态。空间环境可导致有益菌的减少与侵袭性致病菌的增多，菌群失调会引起肠道通透性增加、诱发细菌移位，加剧肠道炎症反应[9]，而短链脂肪酸、胆汁酸、吲哚衍生物和多胺等菌群代谢物的减少不利于肠屏障的修复[10-11]。空间环境会诱导航天员的肠道菌群发生显著变化，也会产生肠道炎症[12-13]。近几年，航天员的肠道菌群失调以及菌群代谢物介导的生理功能紊乱已引起学者的重视，本文将从肠道菌群组成、菌群代谢产物和菌群的基因表达 3 个角度，综述空间环境对肠道菌群产生的影响，从而为该领域后续的深入研究及航天员的在轨健康防护提供信息与借鉴。

1 太空飞行/模拟空间环境中肠道菌群组成的变化

厚壁菌门(Firmicutes)与拟杆菌门(Bacteroidetes)是人类肠道菌群最主要的构成部分，其比值(Firmicutes-to-Bacteroidetes, F/B)的变化可表征肠道菌群是否失调。有研究者[14-16]发现 F/B 在炎性肠病患者中降低，而在肥胖者中升高，最终引起机体的代谢紊乱。在美国国家航空航天局(National Aeronautics and Space Administration, NASA)的同卵双胞胎实验中[17]，通过采集两名受试者的粪便拭子进行菌群测序发现，与地面受试者相比，太空受试者经过 340 d 的太空飞行，其肠道菌群在门水平上 Firmicutes 增加，而 Bacteroidetes 丰度降低，F/B 在飞行中显著增加(飞行中比飞行前：3.21 vs. 1.45)，但飞行后第 50 天左右可恢复到飞行前水平。Voorhies 等[18]研究了太空飞行 6–12 个月的航天员肠道菌群的变化，发现了 17 个菌属的丰度发生改变。其中 13 个菌属丰度上升，如 Firmicutes 包括瘤胃梭菌(*Clostridium*)、粪杆菌(*Faecalibacterium*)和毛螺菌(*Lachnospira*)等。而瘤胃球菌(*Ruminococcus*)、粪球菌(*Coprococcus*)、真杆菌(*Eubacterium*)和假丁酸弧菌(*Pseudobutyrivibrio*)等丰度下降，其中 *Ruminococcus* 丰度下降至约 20%，*Pseudobutyrivibrio* 丰度降低至约 33%。另外，Bacteroidetes 中的普雷沃菌属(*Prevotella*)、

疣微菌门(Verrucomicrobia)的阿克曼氏菌(*Akkermansia*)、变形菌门(Proteobacteria)的副萨特氏菌(*Parasutterella*)等丰度也明显下降。雷浪伟等[19]分别采用男性人体头低位卧床 60 d 模型模拟太空飞行,发现卧床 1 周时受试者的双歧杆菌属(*Bifidobacterium*)、乳杆菌属(*Lactobacillus*)丰度显著下降。Shama 等[20]采用尾吊小鼠建立模拟失重模型,发现尾吊 21 d 后小鼠的肠道微生物群落 α 多样性指数与 β 指数均减小,说明模拟微重力效应导致菌群群落内多样性降低,且各样本间菌群群落组成的差异减小。同时模拟失重下小鼠的菌群组成发生紊乱,在门的水平上 Bacteroidetes、Firmicutes、放线菌门(Actinomycetes)、蓝藻门(Cyanophyta)、Proteobacteria、脱硫菌门(Desulfobacterota)和 Verrucomicrobia 等丰度发生改变,其中 Firmicutes 的丰度从 27%升至 48%,而 Bacteroidetes 由 65%降至 55%左右。在属水平上,发现 *Akkermansia*、*Lactobacillus* 等 4 个菌属丰度降低、*Lachnospira*、短小杆菌(*Cutibacterium*)、肠杆菌(*Enterorhabdus*)等 6 个菌属丰度增加。Siddiqui 等[21]利用尾吊 20 d 小鼠的大肠与小肠组织进行菌群测序得出与上述相似的结论。模拟微重力效应导致在所有门中厚壁菌门的丰度变为最高(42.7%),超越了拟杆菌门。同时在属水平上,*Akkermansia* 等丰度显著下降、*Lachnospira*、*Enterorhabdus* 等菌属的丰度增加。*Ruminococcus*、*Coprococcus*、*Eubacterium* 和 *Pseudobutyrivibrio* 等为常见的短链脂肪酸(如丁酸等)产生菌,而 *Lactobacillus*、*Bifidobacterium* 等可产乳酸,产丁酸菌与产乳酸菌对肠道的保护具有协同作用[22],其丰度的共同降低不利于维持肠屏障功能。同时 *Lachnospira* 的增加会抑制 *Bifidobacterium*、*Coprococcus* 等益生菌发挥肠道保护作用。*Akkermansia* 是一种新型益生菌,可通过修复肠道黏液、降低脂多糖水平等保护肠道健康[23-24]。本课题组利用大鼠尾吊模型,21 d 后对大鼠粪便进行测序,发现模拟微重力可导致大鼠肠道菌群中 F/B 增加,同时也发现 *Ruminococcus*、*Bifidobacterium*、*Lactobacillus* 等有益菌属丰度下降。综上所述,模拟微重力效应会引起肠道菌群的组成紊乱,导致肠道中有益共生菌的水平显著降低,不利于有益菌与有害菌的肠道定殖竞争,进而打破菌群的平衡状态,这或将进一步导致肠道通透性的增加。

Yang 等[25]利用 21 d 尾吊大鼠模型发现,模拟微重力效应可导致肠道微生物多样性降低。在种水平上,模拟微重力效应导致大鼠脆弱拟杆菌(*Bacteroides fragilis*)与具核状梭杆菌(*Fusobacterium nucleatum*)增加,而长双歧杆菌(*Bifidobacterium longum*)明显减少。*B. fragilis* 具有促炎作用,产生的脆弱杆菌毒素可引起肠上皮细胞的 DNA 损伤、裂解肠上皮细胞的 E-钙黏蛋白、驱动促致癌的多步炎症级联反应而损害肠屏障[26-27]。*F. nucleatum* 也是一种致病菌,可通过分泌囊泡起促炎作用,同时会破坏肠道的黏液保护层[28]。*B. longum* 是一种常见益生菌,可产共轭亚油酸等从而保护肠屏障、改善结肠炎症[29]。Shi 等[30]采用 28 d 尾吊小鼠模型发现,模拟微重力效应使小鼠粪便中的分节丝状菌(segmented filamentous bacteria, SFB)、幽门螺杆菌(*Helicobacter pylori*)、产气荚膜梭菌(*Clostridium perfringens*)丰度升高,其中 SFB 是肠上皮细胞的共生菌,具有免疫调节功能,可诱导肠道黏膜固有层中辅助性 T 细胞 17 的分化及其相关细胞因子的分泌而激活肠道免疫,其丰度的紊乱或可导致肠道免疫功能的失调[31-32]。*H. pylori* 与 *C. perfringens* 均为常见的致病菌,二者可以通过对肠上皮细胞的黏附以及产生代谢毒素(如空泡毒素、黏液酶、α 毒素等),破坏肠上皮细胞

的膜结构、诱导细胞骨架重排、破坏肠黏膜等，进而引起肠道损伤[33-34]。因此，模拟微重力效应会导致有害菌的丰度升高，从而增加了有害菌对肠上皮细胞的黏附及其毒力因子的细胞毒性，会诱导机体肠道内炎性水平的升高、肠上皮细胞间黏附连接的破坏等，进而增加肠通透性。文献表明，太空飞行/模拟空间环境(space flight/simulated space environment, SF/SPE)能够显著影响肠道菌群的组成，会对肠上皮细胞造成一定的生理损伤，总结详见图 1[17-21]。

2 太空飞行/模拟空间环境中肠道菌群代谢产物的变化

肠道菌群参与营养物质的代谢、转化等，并产生一系列代谢产物，常见的包括短链脂肪酸、次级胆汁酸、脂类、吲哚衍生物和酚类等[35-36]，菌群代谢物作为底物或信号分子，能够局部地、系统地发挥调控作用，影响能量的产生、转化及

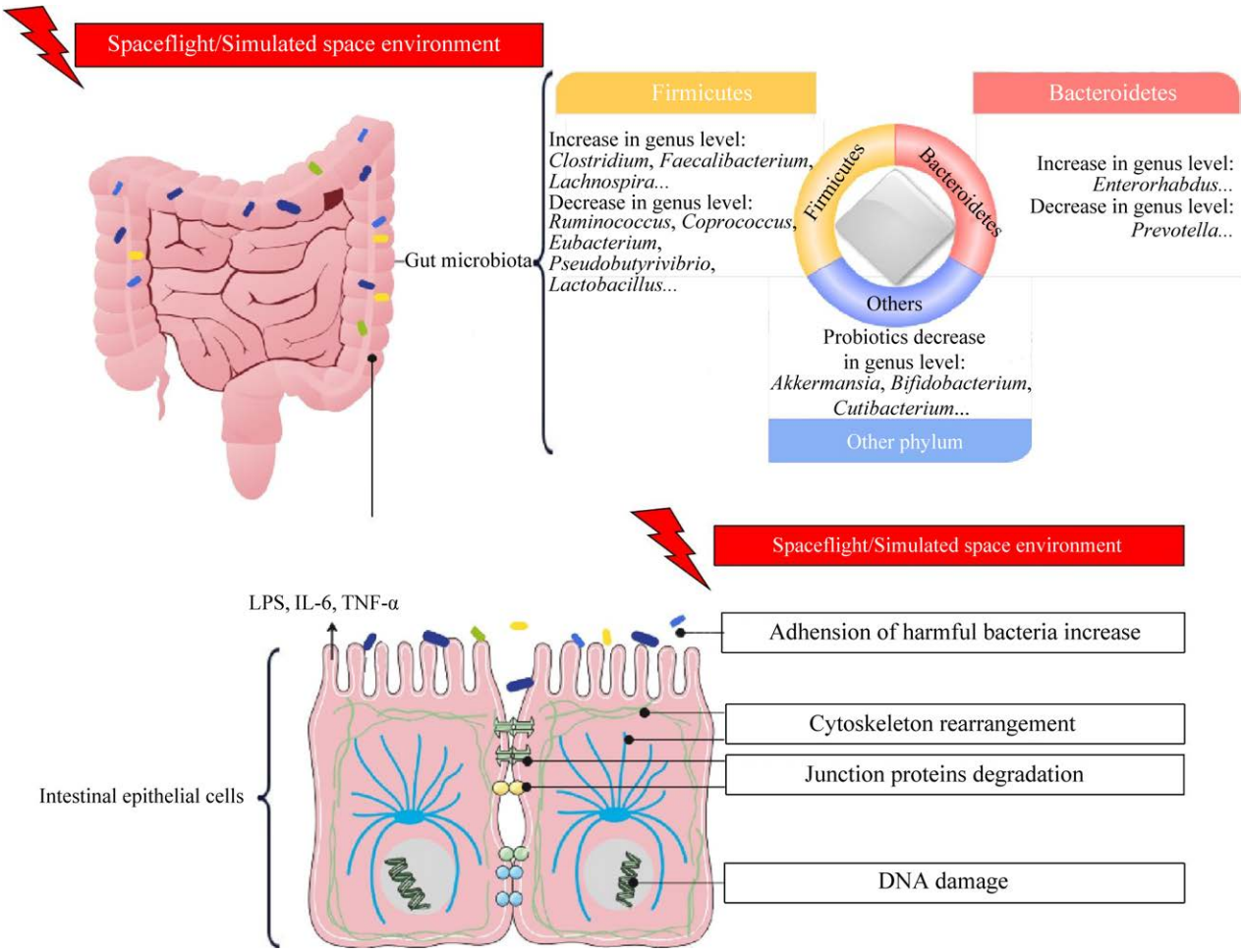

图 1 太空飞行/模拟空间环境中肠道菌群的变化与生理影响[17-21] LPS：脂多糖；IL-6：白介素 6；TNF-α：肿瘤坏死因子 α

Figure 1 Changes and physiological effects of gut microbiota in space flight/simulated space environment[17-21]. LPS: Lipopolysaccharides; IL-6: Interleukin-6; TNF-A: Tumor necrosis factor-A.

储存，调控病原菌在肠道内的定殖，还可调控机体氧化应激水平等[37-38]。有研究发现，菌群代谢物的紊乱可作为代谢疾病早期诊断及预后的潜在生物标志物[39]。NASA 的双胞胎实验[17]对两名受试者的粪便进行非靶向代谢组学分析，发现太空受试者的吲哚衍生物、苯基类衍生物、次级胆汁酸等几类菌群代谢物均发生显著变化。其中，吲哚-3-丙酸、吲哚乳酸等吲哚衍生物的水平降低。吲哚-3-丙酸由生孢梭菌(*Clostridium sporogenes*)等调控产生，可促进黏蛋白表达而增强肠道黏液层功能、降低肠道通透性、抑制内毒素透过肠屏障进入血液循环等[40]，吲哚-3-丙酸还是一种有效的神经保护活性物质，可促进神经再生和修复。吲哚乳酸是 *Bifidobacterium* 等将色氨酸降解为吲哚丙酸的一种中间代谢体，具有抗氧化活性，并且对促进肠上皮细胞紧密连接表达具有重要作用[41]。吲哚-3-丙酸与吲哚乳酸水平的紊乱不利于肠屏障的保护，并且可导致肠神经系统的紊乱而影响肠屏障功能，或可直接或间接作用于大脑而导致神经退行性疾病的发生[42]。硫代石胆酰甘氨酸属于次级胆汁酸，可由 *Eubacterium*、*Clostridium* 等菌属产生，在飞行中硫代石胆酰甘氨酸水平下降说明太空飞行导致菌群紊乱进而影响胆汁酸代谢，亦或可通过肠肝循环进而影响肝脏的生理功能，但目前无相关文献提示硫代石胆酰甘氨酸对肠道及其他系统的调控作用。NASA 的双胞胎实验[17]还发现，在飞行中 3-硫酸吲哚酚、硫酸苯酯、硫酸对甲酚和对甲酚葡糖苷酸等水平显著上升，其中，3-硫酸吲哚酚属于吲哚衍生物，可抑制肠上皮细胞紧密连接相关基因的表达，并通过引发线粒体自噬而损伤肠上皮细胞进而损伤肠屏障[43]，还可对心血管系统产生促氧化作用而导致动脉粥状硬化[44]，作为一种尿毒症毒素会诱导肾小管细胞的内质网压力等而损伤肾脏。苯基硫酸盐、硫酸对甲酚、葡糖苷酸对甲酚等苯基类衍生物在太空飞行中含量显著升高，三者也属于肠源性尿毒症毒素，可由 *Enterorhabdus*、*Faecalibacterium* 等调控产生。苯基硫酸盐对肾脏足细胞具有线粒体毒性而诱导蛋白尿的产生[45]，对甲酚葡糖苷酸与肾脏病患者的炎症标志物呈正相关[46]，其水平的升高或可表征肾脏的毒性损伤。Jollet 等[47]采用人体干浸 21 d 模拟微重力，收集粪便样本测定短链脂肪酸含量，发现模拟微重力效应导致丙酸的浓度显著降低。丙酸可由 *Bacteroidales*、*Eubacterium* 等调控产生，能够为肠上皮细胞提供能量，并对肠道、血管、骨骼肌等具有系统性的抗炎活性，入血后可通过改善血管钙化而保护心血管系统、促进成骨细胞分化而维持骨稳态、促进骨骼肌葡萄糖摄取并缓解胰岛素抵抗引起的慢性炎症等[48-50]。本课题组利用气相色谱法检测了尾吊 21 d 大鼠粪便中短链脂肪酸的含量，发现模拟微重力导致异丁酸与丁酸的含量均显著下降。丁酸可由 *Ruminococcus*、*Bifidobacterium* 等菌属产生，其水平的下降或可导致肠道的运动减弱，以及抗氧化与抗炎能力降低等，不利于维持肠上皮屏障的完整性。

Jin 等[51]采用大鼠尾吊 21 d 模型通过检测盲肠内容物发现，模拟微重力效应显著提高了肠道菌群相关代谢产物，如木糖、异亮氨酸、α-生育酚等，显著降低了环己烯四醇 β 环氧化物、4-羟基吡啶、5′-单磷酸胞苷、芥子酸、吲哚乙酸和半乳糖醛酸等代谢物水平。木糖的增多或可提示糖代谢的改变，主要参与多糖降解的为 *Bacteroidetes* 菌属，其水平降低可能为改变糖代谢的原因之一，环己烯四醇 β 环氧化物是一种葡萄糖苷酶(催化葡萄糖的生成)的抑制剂，其水平的降低也会导致机体内糖代谢的紊乱。异亮氨酸作为一种支链氨基酸，其生物合成由 *Prevotella*、*Bacteroides* 等共同参与，可通过激活腺苷酸活化

蛋白激酶[adenosine 5′-monophosphate (AMP)-activated protein kinase, AMPK]信号通路、调节ATP 敏感性钾离子通道等调控胰岛 B 细胞生长与胰岛素分泌,有研究表明低水平的异亮氨酸可通过上调糖代谢调控因子 Fgf 21 表达而改善糖代谢[52]，而高水平异亮氨酸会诱导心血管代谢性疾病。因此模拟微重力效应导致异亮氨酸的增多或可导致机体内胰岛素水平紊乱,Hughson 等[53]就曾报道过在国际空间站生活 6 个月的航天员产生胰岛素抵抗的情况。Wang 等[54]利用尾吊小鼠 4 周模型发现模拟微重力效应会导致小鼠产生葡萄糖耐受不良、胰岛素抵抗的现象，并且导致肝脏中的糖异生作用增强。芥子酸属于酚类物质，其水平的降低与 *Bifidobacterium*、*Lactobacillus* 等的丰度下降相关，芥子酸可以增强肠道抗氧化水平、降低促炎因子水平、增强肠上皮细胞的紧密连接表达等维持肠道屏障。吲哚乙酸是一种吲哚衍生物，主要由 *Lactobacillus* 等产生，具有抗炎、抗氧化活性，可促进肠道紧密连接的表达。半乳糖醛酸可由 *Bacteroides* 代谢产生，可作为碳源帮助致病菌在肠道定殖，当半乳糖醛酸的水平进一步降低后可诱导肠道炎性水平的升高[55]。综上所述，肠道菌群参与机体中糖代谢、氨基酸代谢、胆汁酸生物合成、色氨酸代谢和多酚代谢等多种过程,太空飞行或模拟微重力效应会导致多种菌群代谢产物的水平变化，一方面，一些活性代谢物与有害代谢物对肠屏障具有直接的调控作用,有益物的减少及有害代谢物的增加可能导致肠屏障功能的受损,肠上皮通透性的增加可进一步使肠源性毒素进入血液循环，进一步引起肝脏、血管、肾脏等其他器官造成损伤。同时，一些活性代谢物具有系统性的生理活性,随血液循环到达全身各系统后对血管、骨、肌肉等具有调控作用，其水平的紊乱或不利于心血管、骨骼肌、中枢神经系统等的健康。另一方面，菌群代谢物水平的改变或可提示机体内胆汁酸代谢、糖代谢等代谢过程的紊乱，机体甚至会出现葡萄糖耐受不良、胰岛素抵抗等生理问题。

3 太空飞行/模拟空间环境中肠道菌群基因的变化

目前，已知的人类肠道微生物具有 20 万个非冗余基因组，这些基因组共编码了 1.7 亿个蛋白质序列[1]，有文献表明，通过分析肠道菌群基因的变化可以揭示太空飞行/空间环境对航天员肠道微生物的耐药性和致病性的影响。Liu 等[56]分析了经历 35 d 太空飞行的航天员肠道菌群中的抗性基因，与飞行前 1 周相比，飞行后 1 d 的耐药基因总数增加。因微生物具有转移抗性基因的能力,作者进一步分析了肠道菌群的移动遗传元件，结果发现太空飞行导致菌群的质粒、整合子、转座子增加，或可促进菌群间抗生素抗性基因的转移，从而增强了细菌抗生素耐药，但其具体机制未阐明。Liu 等[56]还发现太空飞行会导致肠道菌群的毒力基因增加,或可提示了肠道菌群的侵袭力与其毒素产生能力增强,损害肠屏障的保护功能，进一步导致毒素泄漏损害其他器官。Sun 等[57]利用尾吊 45 d 的小鼠粪便，对菌群的抗生素耐药基因进行差异分析以预测耐药抗生素,发现模拟微重力效应可导致肠道菌群中对杆菌肽与万古霉素的耐药能力增加,而菌群对头孢菌素、卡苏加霉素的耐药性显著降低。由此可见，太空飞行模拟微重力效应会影响肠道菌群的耐药能力与致病能力,这可能造成航天员用药的效果与安全性未知,极大地增加了航天员的患病与治疗风险,因此菌群的抗生素耐药性对航天员健康具有重要意义，亟待进行深入研究。此外，相关文献有助于探究细菌的进化与促进抗菌药物的研发，但目前相关的研究文献很少，在未来需

要进一步地探究与讨论。

4 总结与展望

太空飞行/模拟微重力效应会导致肠道菌群的组成发生紊乱，肠道致病菌(如 *B. fragilis*、*F. nucleatum* 和 *C. perfringens* 等)丰度的上调会竞争肠道的黏附位点，进而通过损伤肠上皮细胞结构、诱导促炎因子等破坏肠屏障，有益菌(如 *Ruminococcus*、*Bifidobacterium* 和 *Akkermansia* 等)丰度的下降会降低其在肠道内定殖的竞争力，导致其难以发挥其活性作用，进而导致肠通透性增加。肠道菌群参与机体的多种代谢过程，次级胆汁酸类、糖类、氨基酸类等菌群代谢物可提示机体内代谢水平的紊乱，或可成为航天生理损伤的潜在生物标志物。同时，有益代谢物(如丙酸、芥子酸、吲哚乳酸等)水平的降低会减弱肠道的防御能力，进入血液循环后脑、骨骼、肌肉等其他系统的生理活性也会降低。肠源性有害代谢物(如 3-硫酸吲哚酚、苯基硫酸盐、葡糖苷酸对甲酚等)的增多可直接对肠上皮细胞产生毒性作用而破坏肠上皮屏障，或可透过肠屏障进入血液循环，进而导致血管、肝脏、肾脏等其他器官的生理损伤。

太空飞行/模拟微重力效应会导致机体肠道菌群的组成发生紊乱，菌群组成对肠道健康具有重要意义。但鉴于相关研究条件与研究方法的局限性，目前尚无文献揭示太空飞行/模拟微重力效应导致肠道菌群组成失调的潜在机制，以及太空飞行/模拟微重力效应如何通过肠道菌群导致肠屏障损伤的具体机制。同时，太空飞行/模拟微重力效应可使肠道菌群的代谢产物的水平紊乱，现有文献显示，短链脂肪酸、吲哚类衍生物等多类菌群代谢物对机体健康具有系统性的调控作用，在太空飞行/模拟微重力效应均发生变化。但目前相关研究有限，在未来应深入探究与阐明菌群代谢物如何影响肠屏障功能，及代谢物进入血液循环后如何通过肠-脑轴、肠-肝轴、肠-肌轴等调控其他器官的生理功能，从而为航天员的健康提供科学的理论保障。

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