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病理状态下肠道微生态的调节

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摘要

人类微生态是寄居在人体中的微生物聚集体，且主要存在于胃肠道 (GIT) 中。肠道微生态随着人体发育而演化，并在人类健康和疾病中起着重要作用。近年来，由于微生态会影响宿主代谢、生理学和免疫系统发育，而且微生态紊乱可能导致许多疾病，其越来越受到人们的关注。肠道微生态可能与恶性肿瘤有一定联系，如胃癌和结直肠癌；也可能与其他一些疾病有关，如非酒精性脂肪肝 (NAFLD)、被称为工业化世界“生活方式疾病”的肥胖和糖尿病、冠心病以及中枢神经系统紊乱。虽然分子技术革命为我们更准确地研究肠道微生态提供了必要的工具，但是我们需要更精确地阐明其与某些人类疾病病理变化的关系，明确微生态在不同疾病中的作用是新的治疗策略发展的基础。本文概述了肠道微生态对人类健康的重要影响以及调整肠道菌群结构的潜在用途，如菌群移植用于治疗耐药艰难梭菌 (*C. difficile*) 的感染。通过微生态干预调整肠道区域以改善人类健康的概念虽刚刚兴起，但其治疗意义显著。因此，抑制有害菌、促进有益菌可能会保护人类健康，并且这些努力将为探索发展更加合理的治疗方案打下基础。

1. 引言

数以万亿计的微生物定植在人体，且大部分位于胃肠道(GIT)。从小肠近端(10^3 mL^{-1}) 到结肠(10^{11} g^{-1})，肠道细菌的数量就增加了约8个数量级[1]。例如，一位70 kg的成年男性，定植其身上的细菌估计达3.8×10^{13}，相当于0.2 kg[2]。宏基因测序技术能检测出超过1000种肠道细菌，其中主要有四大门：厚壁菌门(Firmicutes)、拟杆菌门(Bacteroidetes)、放线菌门(Actinobacteria)和变形杆菌门(Proteobacteria)。这些细菌基因组包含了300多万个基因，大约是整个人类基因的100多倍[3]。这些肠道细菌早在胎儿发育过程中就已获得，并且越来越多的证据表明胎盘、羊水和胎粪中存在肠道细菌[4–7]。虽然肠道微生态系统发育保守[8]，但是其组成会受到宿主生活过程中个人卫生、饮食、服药和疾病状态的影响[9,10]。这些影响在婴幼儿阶段显得更为重要，这个时期原始菌群开始定植，其稳定性和内稳态通常在2~5岁时建立起来[11]。

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近年来，肠道菌群由于其对人体健康的影响而受到越来越多的关注[12]。肠道菌群的组成和功能几乎在机体的每个生化过程中都发挥着重要作用。我们早已认识到，肠道菌群可以帮助宿主防御病原体，建立健康的肠道结构和免疫系统，并帮助消化难以消化的膳食纤维[13]。最近，肠道菌群与非酒精性脂肪肝(NAFLD)、冠心病、癌症、肥胖和糖尿病等疾病之间的联系也被认可[14]。本文中我们总结和提供了有关肠道菌群对人类健康作用的最新研究结果，以及肠道微生态调节的不足之处和解决办法。

2. 肠道菌群在人体健康中的作用

肠道菌群是健康人体赖以生存的必需品。短链脂肪酸(SCFA)，包括丁酸盐、乙酸盐和丙酸盐，是肠道菌群分解膳食纤维的发酵产物。尽管这些膳食纤维不能被人体吸收，但它们的代谢产物为肠道细胞提供了必需的营养物，并且在维持肠道健康中起重要作用。霍氏真杆菌(*E. hallii*)被认为是一种产短链脂肪酸菌，并且最近的研究表明其能够产生高水平的甘油/二醇脱水酶，这是一种将甘油转化为3-羟基丙醛的关键酶，同时也是参与产生维生素B12的必需酶[15]。5-羟色胺，作为一种在结肠嗜铬细胞中合成的神经递质，可以调节广泛的生理活动，如肠道运动和血小板功能，其水平是通过以梭菌(clostridial species)为主要组成成分的产孢子菌的分解作用来调节的[16]。其他研究也探究了肠道菌群与肠道代谢产物之间的关系。

肠道菌群可代谢含苯环的基酸，如色氨酸。色氨酸代谢产物的水平，如吲哚硫酸盐和吲哚-3-丙酸，与肠道菌群高度相关，吲哚-3-丙酸的产生依赖于产孢梭菌(*Clostridium sporogenes*)的定植[17]。此外，粪肠杆菌(*Faecalibacterium prausnitzii*)菌落的变化与尿液代谢物的多个代谢途径相关[18]。艰难梭菌(*C. difficile*)与粪胆固醇和粪甾醇水平之间的关联已被明确，这表明肠道菌群在脂质代谢中起关键作用[19]。总的来说，这些研究突出说明了肠道菌群在维持人类正常生理活动中的重要作用。正常肠道生态系统的失衡可能与一些疾病相关，如癌症、NAFLD、肥胖和糖尿病、冠心病、肾功能不全和神经退行性疾病(图1)，这些联系将在下面的章节中进行叙述。

2.1. 癌症

幽门螺杆菌(*Helicobacter pylori*)的水平与胃癌[20]

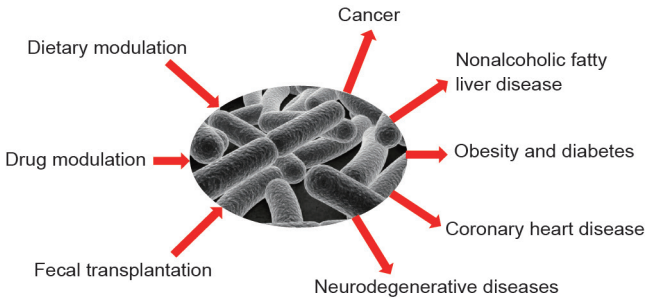

图1. 病理状态下肠道菌群的作用和调节。

和结直肠癌[21]风险的相关性已得到广泛认可。革兰氏阴性菌存在于人体胃中，可引起各种疾病，包括胃炎、消化性溃疡和胃癌[21]。其他肠道常驻细菌也被认为是增加人类结肠癌风险的主要因素，包括牛链球菌(*Streptococcus bovis*)[22,23]、脆弱拟杆菌(*Bacteroides fragilis*)[24]和大肠杆菌(*E. coli*)[25]。这些细菌可引起炎症并可以引发炎症性肠病，进而促使结直肠癌的发生发展。该风险增加的机制被认为与Toll样受体(TLRs)和触发下游信号通路有关，如NF-κB、ERK、JNK和p38，导致生长因子和炎症介质的上调，从而促进肿瘤形成[26]。

2.2. 非酒精性脂肪肝

NAFLD是西方和亚洲国家最常见的慢性肝病[27,28]，被认为是代谢综合征中的肝脏表现。由于其与肥胖密切相关，因此大家广泛认为NAFLD的发病机制有多种，包括与肥胖相关的肠道菌群紊乱的作用[29,30]。

有研究表明，肠道细菌的组成变化与肥胖有关，也与NAFLD的流行和发展密切相关[31–34]。Zhu等[34]的研究表明肠道产生的内源性酒精与酒精性脂肪肝(NASH)之间的联系可能是NAFLD的发病机制。在NAFLD患者中观察到肠道菌群的组成存在着显著变化，如厚壁菌门的某些特定菌种丰度下降[33]。与健康对照组相比，在NASH的肥胖患者中也发现拟杆菌门减少[34]。此外，Wang等[30]研究了非肥胖成年人NAFLD患者的粪便菌群的组成及其变化与肝脏生化变化的相关性。Boursier等[35]的研究表明NAFLD的严重性与肠道菌群的失调和肠道微生态的代谢功能变化相关，拟杆菌属(*Bacteroides*)和瘤胃球菌属(*Ruminococcus*)分别与NASH和纤维化的严重程度独立相关。这些研究表明，肠道微生态组成的改变与NAFLD的发展密切相关。

目前有关肠道菌群组成和NAFLD发病的几个不同机制已经被揭示。首先，肠道菌群具有增加所摄取食物

的能量的潜力[36]，能改变食欲信号[37,38]，并增强参与从头合成脂肪、β-氧化或炎症介导的肝脂肪变性的基因表达[39,40]。其次，肠道菌群和肠源性细菌的易位或其代谢物的易位可能影响肝脏炎症的发展[41,42]。小肠细菌过度生长综合征(SIBOS)在NAFLD患者中非常普遍[43]，这似乎与这些患者的肠壁通透性增加有关[44]。肠壁通透性在NAFLD的发病机制中起重要作用，相应地会导致肝细胞炎症[44,45]和胰岛素抵抗[32,39]。值得注意的是，脂多糖(LPS)受体、CD14和TLR-4的表达水平在并发SIBOS的NASH患者中也更高[46]。这一发现表明SIBOS，尤其是革兰阴性菌群引起的SIBOS，可以通过TLR-4促进NASH的发展。研究表明，在NASH进展过程中，库弗细胞中CD14的上调与LPS介导的重度肝炎应有关[47]。

2.3. 肥胖和糖尿病

大量人体和动物实验研究证据表明，肠道菌群组成的改变与肥胖和2型糖尿病(T2D)相关。如，Bäckhed等[48]的研究显示尽管无菌小鼠多消耗了29%的食物，但是野生型小鼠的体重却比无菌小鼠的体重增加了40%，而重新有菌化的原无菌小鼠的体重增加了57%。这个研究成果使研究者对研究肥胖小鼠肠道微生态组成的兴趣大增。研究表明，与相应的消瘦小鼠相比，肥胖小鼠(ob/ob)肠道菌群中的拟杆菌门的丰度减少了50%[49]，而厚壁菌门的丰度增加。进一步的证据表明，饮食诱导的肥胖可能产生高水平的厚壁菌门，特别是柔膜菌纲(Mollicutes class)。此外，将肥胖小鼠的粪样移植到无菌小鼠会导致无菌小鼠的体重相对于消瘦小鼠粪样移植的无菌小鼠的体重增加[50]。消瘦小鼠的粪样移植对于肥胖小鼠同样有效，并且其肠道菌群含有更高丰度的拟杆菌门[51]。

人群研究也突出显示了肠道菌群组成与肥胖之间的关系。Turnbaugh等[50]研究表明人类肥胖与拟杆菌门和厚壁菌门水平的变化相关。值得注意的是，将肥胖人体的肠道细菌移植到无菌小鼠体内，与接受消瘦相关的细菌定植的无菌小鼠相比，前者体脂明显增加[36]。肥胖或消瘦相关肠道细菌的移植定植效果已被Zhang及其同事的研究所证实[52]。肥胖儿童和(或)肥胖倾向的儿童，如普拉德–威利综合征(Prader-Willi syndrome)儿童，接受富含膳食纤维的饮食可以减少体重[53]。无菌小鼠接受含膳食纤维的饮食干预前的粪样比接受干预后的粪样显示出更多的体脂积累[52]。肠道菌群组成的变化也与T2D相关[54]。在糖尿病患者中呈现厚壁菌门和梭菌纲(class Clostridia)的比例总体减少，蛋白菌的比例增加，这与肥胖患者中肠道菌群变化的研究发现相反[55]。此外，梭菌(*Clostridium* sp.)和乳酸杆菌(*Lactobacillus* sp.)似乎对诱发T2D有很重要的作用[56]。与健康人群相比，糖尿病群体中产短链脂肪酸菌的丰度较低[3]。

肠道菌群组成与肥胖之间的联系被认为是由肠道菌群的代谢功能介导的，也就是说，肠道细菌产生SCFA，而SCFA能够为维持健康和完整的肠道屏障提供必需的营养素和能量。没有这些肠道细菌，可能会因缺乏必要的SCFA而使GIT变得有缺陷。这种有缺陷的肠道结构会抑制营养物向肝脏的转运，导致它们转化为脂肪而沉积。肠道菌群的另一个重要功能是调节脂质吸收，该过程作用的实现，是通过其从胆汁酸中除去甘氨酸和牛磺酸的极性基团，使消化道乳化和吸收的脂肪减少，未结合胆汁酸吸收增加，从而影响胆固醇代谢[57,58]。Kishino等[59]证实了肠道胚芽乳杆菌中多不饱和脂肪酸向饱合脂肪酸代谢的编码基因。

2.4. 冠心病

与肥胖和T2D相关的肠道菌群也可能促进冠心病的发生。此外，在患有动脉粥样硬化的人的粪样和口腔内发现了金丽单胞菌属(*Chryseomonas*)，韦荣球菌属(*Veillonella*)和链球菌属(*Streptococcus*)[60]。这一证据表明，这些肠道菌群的存在与冠心病有直接关联。另一个囊括893名受试人群的研究构建了一个新模型，该模型提示26%的高密度脂蛋白源于肠道微生态，且独立于年龄、性别和宿主遗传学因素[61]。肠道菌群通过胆汁酸调节脂质代谢和胆固醇，这为肠道菌群与冠心病之间的关系提供了一个可能的机制。冠心病与细菌代谢的膳食胆碱和左旋肉碱之间的联系已被证实[62,63]。胆碱和左旋肉碱都可以被肠道菌群代谢生成三甲胺(TMA)，然后在肝脏中进一步代谢为三甲胺-*N*-氧化物(TMAO)。TMAO已被认为是一种促动脉粥样硬化剂[64]。产TMAO的肠道菌群与冠心病之间的关联的潜在机制与TMAO生成酶的作用有关，即黄素单加氧酶-3，其参与干扰胆固醇逆向转运，使人体总胆固醇重新平衡[65,66]。进一步的证据表明，用非致死性细菌抑制剂3,3-二甲基-1-丁醇靶向调节肠道细菌的产物TMA，可以降低TMAO的水平，并预防动脉粥样硬化病变[67]。

2.5. 神经退行性疾病

越来越多的证据表明肠道菌群通过双向的微生态–

肠–脑轴参与调节神经系统疾病[68]。动物实验研究显示，与常规的无特定病原体的小鼠相比，无菌小鼠表现出肌肉活动的增加和焦虑样行为的减少[69]。无菌小鼠也能表达较低水平的海马血清素1A受体和杏仁核*N*-甲基-D-天冬氨酸受体(NMDAR)亚基NR2B的mRNA[70]，以及较高水平的海马齿状回颗粒层中脑源性神经营养因子(BDNF)[70]。其他研究发现，丁酸梭菌(*Clostridium butyricum*)定植可以恢复认知缺陷[71]。使用干酪乳杆菌(*Lactobacillus farciminis*)[72]、罗伊氏乳杆菌(*Lactobacillus reuteri*)[73]、脆弱拟杆菌(*Bacteroides fragilis*)[74]或鼠李糖乳杆菌(*Lactobacillus rhamnosus*)菌株[75,76]，也可以潜在地预防小鼠应激诱导的社交缺陷并降低小鼠应激诱导的血浆皮质酮的水平[76]，这表明肠道微生态可能是神经退行性疾病的潜在治疗靶点，该结果被Möhle等证实[77]。他们使用广谱的抗生素(如氨苄青霉素和万古霉素)治疗神经退行性疾病的成年小鼠，研究得出，抗生素治疗减少了神经元祖细胞来源的海马神经形成和记忆储存，并且认知测试也受到影响。然而，在使用八种益生菌的混合物后，即嗜热链球菌(*Streptococcus thermophilus*)、短双歧杆菌(*Bifidobacterium breve*)、长双歧杆菌(*Bifidobacterium longum*)、婴儿双歧杆菌(*Bifidobacterium infantis*)、嗜酸乳杆菌(*Lactobacillus acidophilus*)、植物乳杆菌(*Lactobacillus plantarum*)、副干酪乳杆菌(*Lactobacillus paracasei*)和德氏乳杆菌(*Lactobacillus delbrueckii*)亚种保加利亚乳杆菌(*Lactobacillus delbrueckii*)，实验小鼠的这些缺陷完全恢复[77]。值得注意的是，所有这些益生菌调节与迷走神经切除的小鼠相似，这表明迷走神经是连接细菌、肠和脑的一条主要的调控信息传导途径[76]。

神经炎症可能与涉及神经退行性疾病的多神经变性途径密切相关[78]。帕金森病患者的粪便菌群组成显示具有“抗炎”作用的产丁酸盐的细菌减少，如*Blautia*菌属、粪球菌属(*Coprococcus*)和罗斯伯里菌属(*Roseburia*)，而肠道粘膜菌群显示粪杆菌属(*Faecalibacterium*)的水平降低[79]。也有报道显示在肌萎缩小鼠模型的粪样中的大肠杆菌(*E.coli*)和产气荚膜梭菌(*Butyrivibrio fibrisolvens*)的丰度降低[80]，这意味着细菌可能在神经退行性疾病的神经炎症中起关键作用。有关肠–脑轴存在的更多证据则来自关于神经递质变化的肠道细菌调节的研究。Barrett等[81]的研究揭示，微需氧性乳酸杆菌属和双歧杆菌属能够使谷氨酸代谢成γ-氨基丁酸(GABA)。此外，据报道蓝细菌(Cyanobacteria)产生神经毒素，如β-*N*-甲基氨基-L-丙氨酸(BMAA)，导致各种神经功能障碍[82]。

3. 肠道菌群调节

3.1. 肠道细菌组成的膳食调节

肠道菌群越来越被认为是一个被遗忘的“器官”，其在疾病发展中发挥着关键作用，但关于如何调控肠道菌群以保持健康这一问题仍然有待解决。目前研究结果显示，饮食干预应该是调节肠道菌群的首选治疗方法。Amato等[83]的研究显示西方饮食可能导致厚壁菌门的水平增加和普雷沃氏菌属(*Prevotella*)的水平减少，且这两者都与肥胖和T2D相关。在动物模型中，厚壁菌门和拟杆菌门的水平与高脂饮食密切相关[84]。连续给予实验小鼠高脂饮食，4周后显示厚壁菌门的丰度增加和软皮菌类(Tenericutes)的丰度降低。在连续给予高脂饮食8周后，拟杆菌门的水平降低[84]。使用素食或益生菌来改善不健康的肠道，也许是因为其产生的代谢物为一些益生菌的营养食物，可促进益生菌的生长[85]。用肉食或素食进行干预实验，4天后实验对象的肠道菌群组成发生了很大的改变，在肉食动物中，与氨基酸发酵有关的细菌丰度增加，如*Alistipes putredinis*、嗜胆菌属(*Bilophila*)和拟杆菌属；而在素食动物中，与碳水化合物发酵有关的细菌丰度下降，如罗斯氏菌属、直肠真杆菌属(*Eubacterium rectale*)、布氏瘤胃球菌属(*Ruminococcus bromii*)和普通猪粪杆菌属(*Faecalibacterium prausnitzii*)[85]。最近对肠道菌群与126种宿主内外源性因素（如疾病状态和饮食因素）之间相关性的研究发现，高碳水化合物饮食与高水平的双歧杆菌呈正相关，但是高碳水化合物饮食与乳杆菌属、链球菌属和罗斯氏菌属的水平呈负相关[86]。此外，红葡萄酒的消费与具有抗炎效果的猪粪杆菌属水平的增加相关[87]。

益生元，如膳食纤维和一些低聚糖，已显示有益于人类健康[88]。食用益生元能够引起肠道菌群的变化已被广泛报道。例如，与安慰剂对照组相比，在接受低聚糖干预的人群中粪便双歧杆菌增加了10倍[89,90]。此外，在婴儿时补充益生菌似乎比在成人时补充更有效[91]，这主要是由于肠道微生态在婴儿时期正处于形成中，因此对婴儿影响更大，这也致使其更容易被调控。因此，在补充了鼠李糖乳杆菌GG(LGG)的儿童中发现了乳杆菌和双歧杆菌的丰度增加[92]。此外，学龄前儿童补充鼠李糖乳杆菌GG可以诱导乳球菌属(*Lactococcus*)和乳杆菌属的水平增加，以及大肠杆菌的水平降低[93]。

3.2. 药物调节肠道细菌组成

抗生素常用来治疗病原体感染，其对肠道微生物具有深远的影响。Zhao等[94]研究报道，用庆大霉素和头孢曲松治疗小鼠，引起*Barnesiella*菌属、普雷沃氏菌属和*Alistipes*菌属的水平降低，却引起拟杆菌属、肠球菌属、*Erysipelotrichaceae incertae sedis*和支原体(*Mycoplasma*)的水平增加。此外，小鼠模型显示这种治疗可以引起一系列代谢产物，如SCFA、氨基酸和一级胆汁酸的减少，低聚糖、胆碱和次级胆汁酸的增加[94]。

对抗生素治疗的反应因人而异。对接受两个疗程环丙沙星治疗的三个个体的10个月期间的肠道细菌的分析表明，肠道微生态相对稳定，并且人与人间肠道微生态的差异显著[95]。此外，抗生素治过程中导致肠道微生态的迅速变化，主要表现为细菌多样性的丧失。尽管在抗生素停药一周后主要菌落的定植水平得到一定程度的恢复，但未达到完全恢复[95]。这个发现揭示肠道微生态环境是抵抗变化的，除非它经历长期的反复干预。许多中草药富含多酚，其必须与肠道细菌相互作用后才具有生物可利用性和生物活性[96]，并且可以调节肠道微生态。此外，中草药常具有温和的抗菌能力[97]，如果长期使用，可能会永久调节肠道微生态。因此，通过中草药调节肠道菌群来管理疾病具有巨大的潜力。

3.3. 粪菌移植调节肠道细菌组成

1958年首次报道了粪菌移植(FMT)在艰难梭菌治疗中的应用[98]。近来，将粪菌移植用于调节肠道微生态和根除艰难梭菌菌落的治疗有所增加。粪菌移植治疗艰难梭菌似乎是有效的：81%的艰难梭菌感染病例在第一次粪菌移植治疗后得以解决[99]。这一结果已在232名感染艰难梭菌的加拿大患者的临床试验中得以验证。研究也表明，粪菌制备方法(新鲜制备与冷冻制备)对改变肠道微生态的效果没有影响[100]，凸显出了冷冻样品制备的优点，即可以在患者治疗之前有时间将安全措施实施到位。供体和各自受体的肠道微生态在移植初期具有相关性高的特点，但会随时间而逐渐产生差异。并且，粪菌移植受者中的拟杆菌门和厚壁菌门的数量增长到与粪菌供体相当的水平，而其中的艰难梭菌的水平可以从4%降低到0.2%[99]。其他细菌的改变也与粪菌移植相关，包括优势菌种从变形杆菌门(Proteobacteria)到厚壁菌门和拟杆菌门的转变[101–103]。考虑到肠道微生态的稳定性[95]，从长远角度来讲，对于感染艰难梭菌的患者，也许需要接受多次粪菌移植，以建立健康的微生物系统。

4. 展望

本文涵盖了一些有关肠道菌群与各种疾病状态之间的关系以及调节肠道菌群组成方法的典型研究。我们不旨在大而全的描述，而是要突出一些出色的、最近发表的研究成果。从这方面来讲，肠道菌群显然对人类健康具有不可忽视的影响。同时，肠道微生态可以通过各种方法来调节，如膳食、药物和粪菌移植。因此，我们有必要去定义健康肠道的微生态组成，并且了解个体特征(如年龄、性别和种族)如何影响肠道微生态的组成。鉴于我们的肠道微生态的内在稳定性，长期介入性随访也显得很有必要。

目前，肠道细菌的致病机制还有待更深入的了解。虽然了解到肠道菌群通常由一些代谢产物(如胆汁酸、SCFA和胆碱)介导发挥功能，但是我们对引起这些变化的特定细菌仍然不清楚。对于这类功能细菌的了解是调节肠道细菌的基础。目前，尽管对一些代谢产物的水平与特异性肠道细菌之间的相关性进行了广泛的研究[18]，但其因果关系仍然未知。因此，研究这些潜在的分子机制仍然是未来研究的重点，需要来自多学科研究学者的共同努力，包括临床医生、微生物学家、分子生物学家和生物化学家。最后，关于肠道细菌在神经变性疾病中作用的创新研究揭示了一个尤未满足的领域，需要特别关注肠道微生物及其代谢产物如何进入大脑并影响人类的各种神经功能。

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Compliance with ethics guidelines

Yulan Wang, Baohong Wang, Junfang Wu, Xiangyang Jiang, Huiru Tang, and Ole H. Nielsen declare that they have no conflict of interest or financial conflicts to disclose.

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