膳食、肠道微生物与人体健康

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摘要：膳食与宿主的代谢、免疫系统密切相关。大量报道表明膳食显著影响肠道菌群的组成和功能，进一步影响宿主生理。基于肠道菌群膳食干预的健康调控策略已成为研究热点。本文作者综述了近年来国内外高水平团队的相关研究成果，介绍了膳食模式、膳食成分、功能膳食补充剂对肠道微生物及人体健康研究的相互关系，为相关膳食干预策略的开发提供一些借鉴和参考。

关键词：肠道微生物；膳食模式；膳食成分；功能膳食补充剂；人体健康
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Diet, Gut Microbiota and Human Health

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Abstract： Diet is strongly associated with host metabolism and immune system. A number of studies have indicated that diets significantly affect the structure and function of gut microbiota, which further influence the physiological status of the host. Dietary strategies for the modulation of gut microbiota have become an area of ongoing research. This review concludes recent studies on the impacts of dietary patterns, dietary components and functional dietary supplements on gut microbiota and host health, aiming to facilitate the development of dietary strategies for gut microbiota modulation.

Keywords: gut microbiota, dietary pattern, dietary components, functional dietary supplements, human health

膳食与人体健康密切相关，《Lancet》、《JAMA》、《The New England Journal of Medicine》等杂志的报道均证明饮食状况与人群的死亡率及寿命相关[1-3]。近年来的研究也证明膳食是影响肠道菌群的重要因素，其影响程度甚至强于遗传因素[4-5]。大量报道表明不同膳食模式、特定膳食成分以及功能性膳食因子均可显著影响肠道菌群的结构、组成和功能，进而影响人体健康。基于此，作者拟从以上角度对“膳食-肠道菌群-人体健康”的关联作用进行综述。

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1 不当膳食模式诱导的肠道菌群紊乱及负面健康影响

1.1 西方饮食

以红肉、加工食品、高精制糖和低膳食纤维为特征的西方饮食可导致宿主肠道微生态失衡,菌群的多样性下降,肠屏障通透性受损,进一步破坏肠道 TH17/Treg 平衡,引发促炎反应,从而增加炎症性肠病的风险[6]。西方饮食可诱导促炎微生物如某些 *Escherichia coli* 的过度生长,导致短链脂肪酸(SCFAs)浓度显著降低,肠腔内胆盐组成改变,最终导致小鼠肠道屏障功能损伤[7-8]。这些对肠道菌群和肠道通透性的影响还会进一步加剧产内毒素的革兰氏阴性菌向血液中转移,引发系统性炎症,降低脑部胰岛素敏感性和增加神经炎症,最终对记忆功能产生负面影响[9]。Bruce-Keller 等人将饲喂西方饮食小鼠的粪菌移植到抗生素处理过的小鼠后,也引起了受体小鼠的焦虑行为以及情境认知记忆削弱[10]。一项关于西方饮食与心脏功能障碍的研究表明,长期摄入西方高糖和饱和脂肪的饮食通过增加循环系统中氧化三甲胺(TMAO)的水平,引发小鼠心脏功能障碍;TMAO 是一种肠道菌群依赖性代谢产物,已被认为心血管疾病发病的关键因素之一。而将 3,3-二甲基-1-丁醇(三甲胺形成的抑制剂)补充给饲喂西式饮食的小鼠后,显著降低了血浆 TMAO 水平并预防心脏功能的损伤[11]。此外,多项研究表明,西方饮食导致肠道菌群失调和有害代谢产物增加,触发宿主先天免疫激活,从而引发脂肪炎症[12]、动脉粥样硬化[13-14]、非酒精性脂肪肝[15]等疾病。

1.2 高脂饮食

2019 年《Gut》杂志上一篇报道研究了等热量但不同脂质含量的 3 种饮食(20%、30%、40%)对成年人(n = 217,为期 6 个月)肠道菌群和粪便代谢物的影响,发现低脂饮食显著增加菌群 α 多样性以及 *Blautia* 和粪便杆菌属的丰度,同时血液中代谢疾病相关代谢产物(对甲酚和吲哚)也随着减少;而高脂饮食导致肠道中 *Alistipes* 和拟杆菌属显著增加、粪便杆菌属显著减少、总 SCFAs 水平减少,并伴随着血液中促炎因子增加[16],对代谢系统带来隐患。2017 年发表于《Microbiome》上的一项研究利用对高脂饮食敏感性不同的 BL6 小鼠与 Sv129 小鼠验证肥胖小鼠肠道菌群的改变与高脂饮食和肥胖本身之间的关系,发现高脂饮食,而非肥胖,导致了肠道菌群的改变[17],结果提示与遗传背景相比,饮食可能更容易扰动肠道菌群。一项针对母亲孕期饮食类型与婴儿肠道菌群变化的研究(n = 163)发现母亲在孕期饮食不同,胎粪菌群组成不同;母亲在孕期摄入高脂饮食,导致婴儿胎粪中拟杆菌缺失,孩子出生 6 周后该菌依然缺失[18]。动物实验表明,母鼠怀孕期间暴露高脂饮食导致子鼠厚壁菌门增多,引起产 IL-17 的 3 型天然淋巴细胞(ILC3)扩增,增加对肠道炎症的易感性,通过阻断 IL-17 可逆转子代肠道炎症[19]。此外,近年来多项研究表明,高脂饮食导致的肠道菌群失调还可进一步导致精子质量降低[20],食物过敏[21],骨骼损害[22],食管癌变等[23]。

1.3 高盐饮食

2017 年发表于《Nature》的研究发现,高盐饮食通过诱导 TH17 细胞而扰动自身免疫并引发高血压,同时破坏了小鼠的肠道微生物组,尤其是显著减少鼠乳杆菌。有趣的是,对高盐饮食小鼠回补鼠乳杆菌可通过抑制 TH17 细胞异常增高而防止盐诱导的实验性自身免疫性脑脊髓炎和高血压恶化。这样的结果也在临床试验中得到验证[24]。最近《Circulation Research》上发表的一项研究发现,移植健康大鼠的粪菌可显著降低高盐饮食大鼠的血压,而移植高血压大鼠的粪菌可显著升高健康大鼠的血压。高盐饮食显著改变了大鼠的肠道菌群组成,减少脆弱拟杆菌,从而增加血清及肠道中的皮质酮水平以促进血压的提升,而脆弱拟杆菌可通过其代谢产物花生四烯酸抑制皮质酮的产生[25]。也有报道表明高盐饮食通过改变小鼠肠道菌群的组成和功能,显著降低乳酸菌属相对丰度和丁酸产量,加剧促炎基因的表达,使 DSS 和 DNBS 诱导的结肠炎更加严重[26]。此外,孕妇高盐饮食会引起肠道微生物紊乱及免疫系统失调,尤其是刺激 TH17 细胞功能异常,从而增加后代自闭症风险[27]。

2 有益膳食模式对肠道菌群的调节及健康改善作用

2.1 地中海饮食

与高脂高糖为特征的西方饮食模式相比,以植物性食物(即蔬果,豆类,谷类食品)为主,食用橄榄油、每日适量奶酪、酸奶,每周适量鱼、禽、蛋鱼类的地中海饮食被认为是更为健康的膳食模式。2016 年

发表在《Gut》上的一篇研究评估了 153 个意大利人的肠道菌群、肠道代谢组与饮食类型的关系，发现地中海饮食能显著增加普氏菌属和某些降解纤维的厚壁菌；对地中海饮食依从性越高的人，其粪便中 SCFAs 越高，尿液中 TMAO 水平越低[28]。相似地，最近在《Gut》发表的一项研究（n=612，为期 1 年）发现地中海饮食可增加菌群的多样性和短链/支链脂肪酸的产生，减少次级胆汁酸、对甲酚、乙醇的产生，同时地中海饮食富集出的特定细菌类群（*Faecalibacterium prausnitzii*，*Bacteroides thetaiotaomicron*，*Prevotella copri* 等）与老年人的健康指标及认知能力改善正相关，并与炎症标志物呈负相关[29]。类似研究结果也被发表在其它营养学杂志中，证明地中海饮食对菌群的调节可有效降低代谢综合征、心血管疾病的发病风险[30-31]。

2.2 禁食

2017 年《Cell Metabolism》上的一篇研究发现 15 个周期的隔日进食选择性刺激了小鼠体内白色脂肪向米色脂肪的生成，并显著改善了肥胖，胰岛素抵抗和肝脂肪变性；同时，肠道菌群组成发生变化，伴随着菌群发酵产物乙酸盐和乳酸盐升高，并选择性上调米色细胞中单羧酸盐转运蛋白 1 的表达。无菌小鼠并未出现类似情况，但接受隔日进食小鼠的菌群后脂肪棕色化被激活，代谢稳态被改善[32]。2018 年《Cell Metabolism》上的另一项研究证明隔日禁食增加多发性硬化小鼠肠道菌群多样性，使乳杆菌科、拟杆菌科和普雷沃氏菌科富集，并有效调节调节肠道内 TH17/ Treg 细胞比例失衡，从而缓解多发性硬化。这些结果也得到了通过粪菌移植和临床试验的验证[33]。最近一项研究利用多组学技术探究了隔日禁食缓解Ⅱ型糖尿病引起认知障碍的机制，发现隔日禁食选择性富集出以乳杆菌属为主的微生物群落，增加 3-吲哚丙酸、5-羟色胺、SCFAs 和牛磺熊去氧胆酸等菌群代谢产物，从而增强大脑海马的线粒体生成和能量代谢以及神经突触结构，并减轻小鼠的认知记忆障碍；补充上述菌群代谢产物给经抗生素处理过的小鼠后出现类似效果，说明隔日禁食可通过“肠道菌群-代谢物-脑”轴发挥神经保护作用[34]。

另外，近两年《Cell Report》、《Microbiome》上的 2 篇报道探究了其他不同形式的禁食方式对肠道菌群组成和机体健康的影响，如周期性禁食（第 1 天摄入日常卡路里的 50%，第 2~4 天摄入 10%）可刺激乳杆菌属及双歧杆菌科增殖、增加肠道肝细胞数量、缓解肠道炎症、缓解 IBD 病理表征[35]。对小鼠进行短期限制卡路里摄入可导致炎症标记物水平降低，并富集出以乳酸菌占绝对优势的细菌群落；将分离出的一株乳杆菌 CR147 定植于老年小鼠体内可改善肠屏障功能破坏和系统性炎症[36]。

此外，其他有益膳食模式包括生酮饮食、低麸质饮食、素食和日本饮食也被证明可通过调节肠道菌群的组成和功能，进而预防及改善人体多种疾病（表 1）。

表 1　其他有益膳食模式对肠道菌群和宿主健康的影响

Table 1　Effects of other beneficial dietary patterns on gut microbiota and host health

膳食模式	对菌群的影响	对宿主健康的影响	参考文献
生酮饮食	增加 Akk 菌、粪副拟杆菌、乳酸菌属和双歧杆菌属；降低变形菌门	降低菌群的 γ-谷氨酰转肽酶活性，提高海马内 GABA/谷氨酸比值，减少癫痫发生；增强神经血管功能，降低 AD 风险；缓解自闭症	[37-40]
素食饮食	菌群多样性和丰富度更高，增加拟杆菌属、双歧杆菌属、普氏菌属和 *Clostridium* spp	提升氧化平衡、脂肪型态及糖稳态，降低 TMAO 水平心血管疾病等疾病风险	[41-45]
低麸质饮食	降低 *Dorea*，*Blautia*，霍氏杆菌	抑制炎症小体反应激活，缓解肠道炎症，降低体重	[46]
日本饮食	增加毛螺菌科，乳酸杆菌、双歧杆菌和萨特氏菌属数量，减少副拟杆菌科	有利于血脂代谢、肝功能、非特异性免疫抑制可预防肥胖、心血管疾病等代谢类疾病	[47-50]

3 膳食成分对肠道菌群及宿主健康的影响

3.1 膳食脂肪

2018 年《Microbiome》杂志关注了不同来源的脂肪对健康的影响，发现与喂食棕榈油相比，猪油饮食增加了小鼠的脂肪量，伴随糖耐量受损、空腹胰岛素水平降低、肝甘油三酯、胆甾醇酯和单不饱和脂肪酸增加等现象；同时猪油饮食减少了毛螺菌科

丰度、增加了脱硫弧菌科及特定菌种的丰度,菌群的脂质和氨基酸代谢功能也发生变化;而将猪油和棕榈油喂食给无菌小鼠并未发生上述结果[51]。另一项研究证明猪油可显著增加小鼠中拟杆菌、嗜胆菌等的丰度,而鱼油可显著增加放线菌、乳杆菌等的丰度。此外,喂食猪油可激活 Toll 样受体(TLR),降低胰岛素敏感性,诱导小鼠白色脂肪组织发生炎症反应。具体作用机制为菌群与饱和脂肪酸互相互作用,激活趋化因子 CCL2,导致炎症,并通过 TLR 信号传导进一步加剧炎症[52]。

3.2 膳食碳水化合物

2019 年《Microbiome》的一项研究证明喂养高果糖可改变小鼠的肠道菌群, 减少 SCFAs 的产生,导致肠道屏障损伤、结肠 NLRP6 炎性体功能障碍,同时诱导小鼠海马神经炎症反应和神经元丢失[53]。2020 年发表于《Gastroenterology》的研究发现可发酵低聚糖,二糖,单糖和多元醇(FODMAPs)饮食中的乳糖和低聚果糖可通过上调结肠近端上皮细胞中晚期糖基化终末产物受体(AGER)的表达,增加肠粘膜上肥大细胞的数量, 增强小鼠腹部敏感性,进而诱导肠易激综合征症状[54]。另一方面,膳食纤维被证明可以富集利用碳水化合物的菌群,促进 SCFAs(如乙酸、丙酸和丁酸)的产生,从而抑制艰难梭菌感染[55]。发表于《Science》的随机临床研究表明,富含膳食纤维的食物可以改善肠道菌群、促进 SCFAs 的产生,同时抑制对代谢有害的化合物(如吲哚和硫化氢) 的产生, 并通过促进 GLP-1 和 PYY 的分泌。这些作用可以最终改善血糖,降低宿主罹患糖尿病的风险[56]。值得注意的是近期一项研究发现,在肠道菌群失调的小鼠中, 长期吃大量可溶性纤维,可诱导小鼠发生胆汁淤积、肝脏炎症和肝癌,这种作用一定程度上由 SCFAs 介导[57]。

3.3 膳食蛋白质

高动物蛋白质饮食恶化了 DSS 诱导的小鼠结肠炎,相关作用依赖于肠道菌群;而富含植物蛋白质的饮食并未加剧结肠炎[58]。另有研究发现喂食鸡蛋白质可以显著增加成年大鼠肠道中乳杆菌的丰度,同时增加有机酸(包括乳酸)的含量;而喂食大豆蛋白质的大鼠肠道中瘤胃球菌的相对丰度最高,而乳杆菌的相对丰度最低,同时上调大鼠肝脏中转录因子 CD14 受体、脂多糖结合蛋白(LBP)及谷胱甘肽 S-转移酶的水平,可能导致肝功能失调[59]。

4 功能膳食补充剂对肠道菌群及宿主健康的影响

据美国食品药品监督管理局 (FDA)2019 年的数据统计,在过去 10 年中,世界范围内膳食补充剂的使用急剧增长,其中亚太地区增长最快,欧洲和北美也大幅增长,并且至少四分之三的美国人有定期服用膳食补充剂(如多种维生素)的习惯[60]。目前,肠道菌群已成为阐释益生菌、益生元、植物提取物、微量元素等功能膳食补充剂影响宿主健康作用的新着眼点。

4.1 益生菌

已有大量研究证实了益生菌可通过调节肠道菌群改善宿主健康。2018 年《Immunity》杂志的一项研究发现鼠李糖乳杆菌 LGG 在小鼠肠道定殖后可通过调控肠道菌群, 促进丁酸的产生, 进而驱动 Treg 细胞介导的 $CD8^+$细胞中 NFAT1-SMAD3 转录复合体的装配并上调 Wnt10b 的表达, 从而促进小鼠骨骼生成[61]。喂食小鼠清酒乳杆菌 WIKIM30 可调节 Th2 细胞免疫应答,增强 Treg 的分化从而治疗皮炎[62]。Stephanie 等发现多发性硬化(MS)患者口服益生菌组合(包含乳杆菌属、双歧杆菌属、链球菌属)2 个月后,可以增加乳杆菌和双歧杆菌属的丰度并恢复 Akk 菌及 Blautia 等微生物的丰度诱导机体产生抗炎症外周免疫反应[63]。2019 年《Nature Medicine》杂志的一项研究发现特定乳杆菌(鼠乳杆菌和约氏乳杆菌)以及大肠杆菌 Nissle 1917 可通过抑制肠道中病原体的增殖,预防新生小鼠肠道菌群失调导致的迟发性败血症[64]。作者研究团队也证明益生菌可通过调节肠道菌群而影响 FXR-FGF15 信号通路,进而调节胆汁酸代谢并缓解重金属暴露诱导的机体损伤[65]。益生菌可以通过多种作用机制调控宿主健康(表 2)。

4.2 益生元

2017 年《Gut》杂志关注了菊粉对轻度便秘健康成年人大便频率的影响,发现菊粉可以影响整体微生物群的组成,主要表现为增加双歧杆菌和厌氧菌的丰度,同时降低嗜盐菌的丰度,从而缓解便秘[75]。2019 年一项随机交叉试验表明饮食中添加菊粉或菊粉丙酸酯可改善超重和肥胖成年人的胰岛素敏感性,显著影响肠道菌群、血浆代谢物和全身炎症反应[76]。动物模型表明,菊粉通过调节肠道菌群以

表 2　益生菌的作用机制

Table 2　Mechanisms for the functions of probiotics

作用机制	作用方式	参考文献
与肠道微生物的互作	主要通过竞争营养、拮抗、交叉喂养和维持菌群稳定性等途径	[66]
功能性代谢产物	SCFAs、胆汁酸、分泌蛋白、色氨酸、吲哚、细菌素、铁色素、共轭亚油酸、β-半乳糖苷酶等	[67-72]
菌体表面微生物模式分子	脂磷壁酸、肽聚糖、胞外多糖、脂多糖、粘蛋白结合蛋白、表面层蛋白、鞭毛、菌毛等大分子	[73-74]

恢复 IL-22 介导的肠上皮细胞功能,进一步预防代谢综合征[77]。补充抗性玉米淀粉可以缓解 OSA 诱发的大鼠高血压,其具体机制为肠道菌群代谢玉米淀粉产生的短链脂肪酸可以保护肠道屏障,从而缓解高血压[78]。有研究发现食用冬虫夏草菌丝提取物-大分子多糖可改善肠道菌群和肠道完整性,减少代谢内毒素、炎症、胰岛素抵抗和血脂异常,并选择性促进古氏副拟杆菌的生长,从而预防高脂饮食诱发的肥胖和Ⅱ型糖尿病[79]。2020 年一项发表于《Circulation》的最新研究发现缺乏益生元纤维的饮食可通过影响肠道菌群,进而诱发高血压;而 SCFAs 可通过 SCFAs 受体,特别是 GPR43 和 GPR109A 的介导防止高血压、心肌肥大和纤维化的发展[80]。

4.3　植物提取物

白藜芦醇被报道可促进肠道中乳杆菌和双歧杆菌的增殖,抑制普雷沃菌的增殖,降低 TMAO 水平,调节 FXR-FGF15,增加胆汁盐水解酶的活性和肝脏胆汁酸合成,从而缓解三甲胺-N-氧化物(TMAO)诱导的小鼠动脉粥样硬化[81]。从柑橘皮中纯化的富含多甲氧基黄酮的提取物(PMFE)可减轻肠道菌群失调,富集肠道菌群中的卵形拟杆菌,进而改善代谢综合征(MetS)相关的支链氨基酸(BCAA)代谢异常[82]。卡姆果植物提取物可通过增加 AKK 和拟杆菌的丰度,调节胆汁酸代谢,促进棕色脂肪活化并增加能量消耗而缓解小鼠肥胖[83]。人参提取物可改变肥胖小鼠肠道菌群的组成,诱导肠道内的粪肠球菌通过酰基辅酶 A 硫酯酶介导产生肉豆蔻油酸,进而调节能量代谢[84]。

4.4　微量营养素

作者所在团队通过无菌小鼠粪菌移植等试验证明不同形态和剂量的硒摄入可显著影响宿主肠道屏障和肠道免疫状态,且相关作用依赖于肠道菌群[85-86]。2018 年《Gut》杂志的一项研究通过宏基因组学分析发现摄入含铁量高的奶粉可以降低婴儿肠道中双歧杆菌和拟杆菌的丰度,进而降低婴儿对艰难梭菌和金黄色葡萄球菌感染的抵抗力[87]。维生素 D 缺乏导致小鼠肠道菌群多样性降低,厚壁菌门增多,疣微菌门和拟杆菌门减少,脊髓、十二指肠及结肠中的内源性大麻素的水平显著降低,最终导致小鼠的慢性疼痛[88]。Matthew 等研究发现,急性维生素 A 的缺乏显著影响肠道微生物的群落组成和宏转录组水平,尤其诱导了普通拟杆菌的增殖,并通过 AcrR 转录因子来调节普通拟杆菌的转录机制,从而对维生素 A 缺乏的环境作出适应性应答[89]。

5　结　语

膳食与肠道菌群、人体健康间存在着复杂的互作网络,随着组学技术、免疫学研究手段的不断进步,未来研究将会进一步揭示膳食在这其中的关键作用。另一方面,随着大数据的不断积累和挖掘,不同人群的生理、饮食、菌群情况可被更好的关联和解析,针对肠道菌群干预的个性化膳食调节策略将成为热点。

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