·综　　述·　doi:10.3969/j.issn.1671-8348.2019.22.026
网络首发　http://kns.cnki.net/kcms/detail/50.1097.R.20190729.1433.004.html(2019-07-29)

肠道菌群与疾病关系的研究进展

石　冀 综述,高倩萍△审校
(哈尔滨医科大学附属第一医院心内科,哈尔滨 150000)

[摘要] 随着 DNA 测序技术不断更新换代,人们研究肠道菌群的途径越来越方便,关于肠道菌群的研究愈加深入。近十年来,肠道微生物菌群的神秘面纱正被人们逐步揭开。人们体内定植着数以万亿计的肠道菌群,它们既维护着人们机体生理活动的平衡,同时又受到多种因素的影响。当机体内环境改变时,肠道菌群组成及分布将随之改变,反之,因环境等因素改变导致的肠道菌群失调同样能引起机体发生一系列生理病理改变。研究发现肠道菌群可通过影响消化道黏膜屏障功能、产生氧化三甲胺等代谢产物及调节机体免疫功能等机制来影响机体的生理活动,其影响范围可达全身多个系统,包括消化系统、内分泌系统、循环系统等。该文主要阐述肠道菌群与常见疾病之间的相互关系及其影响机体活动的机制。

[关键词] 肠道菌群;克罗恩病;糖尿病;心血管疾病;氧化三甲氨;短链脂肪酸
[中图法分类号] R54　　[文献标识码] A　　[文章编号] 1671-8348(2019)22-3888-04

Research on relation between gastrointestinal flora and disease

SHI Ji, *GAO Qianping*△
(*Department of Cardiology*, *First Affiliated Hospital of Harbin Medical University*, *Harbin*, *Heilongjiang* 150000, *China*)

[**Abstract**] With the upgrading of DNA sequencing technology, the pathway for studying intestinal flora is more and more convenient, and its researches are even deeper and deeper. Over the past decade, the mystery veil of the gut microbial flora is gradually being uncovered. Human beings have trillions of gut flora implanted in our bodies, which not only maintain the balance of the body's physiological activities, but are also affected by a variety of factors. When the internal environment changes in the body, the composition and distribution of gut flora will correspondingly change, and conversely, the gut flora disorders caused by changes in the environmental and other factors can also cause a series of physiological and pathological changes in the body. The studies find that the intestinal flora can affect the physiological activities of the body by affecting the function of digestive tract mucosal barrier, producing metabolites such as trimethylamine N-oxide and regulating the immune function of the body, and their influencing ranges can reach the multiple systems throughout the body, including the digestive system, endocrine system, cardiovascular system and so on. This paper mainly elaborates the relationship between gut flora and diseases and the mechanisms affecting the body activities.

[**Key words**] gut flora; Crohn's disease; diabetes; cardiovascular disease; trimethylamine N-oxide; short chain fatty acids

人体内定植的微生物中尤以肠道菌群最为稳定[1],随着 DNA 测序、代谢组学、蛋白质组学和计算机技术的不断发展,人们对微生物菌群的研究也越来越深入,微生物菌群的神秘面纱渐渐被揭开。肠道菌群多样性变化与肿瘤、消化道疾病、糖尿病及心血管疾病等诸多疾病间存在密切联系。肠道菌群代谢产物氧化三甲胺,被证明可作为独立预测心血管疾病不良预后发生率的新型生物标志物[2]。近年来肠道菌群中还发现一种严格厌氧菌,名叫艾克曼菌[3],它具有改善机体肥胖及糖尿病健康代谢[4]、促进组织重塑和抑制细胞凋亡等作用[5]。更令人振奋的是,它在增加癌症免疫治疗效果上有非常显著的作用[6]。还有报道证明,肠道菌群可以改善绝经期妇女对激素敏感性,降低激素替代治疗导致的高肿瘤患病概率的风

作者简介:石冀(1993－),住院医师,硕士,主要从事心内科工作。　△ 通信作者,E-mail:cindyshyrl@qq.com。

险[7]。本文主要从肠道菌群与疾病的相关性、肠道菌群对于各类疾病的临床治疗意义及肠道菌群影响机体健康状态的相关机制进行阐述。

1 肠道菌群与疾病

肠道菌群的组成与数量虽然会因宿主及环境不同而有所区别，就个体而言，其肠道菌群是有一定微生物弹性的，它可以在一定范围内保持着相对稳定，是人体除染色体外的第二套基因组信息[8]。整体来说，肠道菌群的组成及分布既受到不同疾病及机体外环境的影响，也可以反过来通过调节宿主的免疫系统，直接作用于个体靶器官及组织或通过产生的代谢产物等途径来影响机体的病理生理状态[9-10]。以下将从消化道疾病、糖尿病及心血管疾病方面进行重点阐述。

1.1 消化道疾病 人体的微生物菌群多数定植于肠道，肠道菌群的平衡与失调和消化系统疾病的关系是显而易见的。以克罗恩病为例，通过斑点印迹法与克罗恩病活动期、缓解期及健康患者样品进行特异性探针杂交，比较三者特定的 16s rRNA 在总的 16s rRNA 中的比例，即 rRNA 指数，发现拟杆菌（$P=0.013$）、球形梭菌（$P=0.034$）、肠杆菌（$P=0.0001$）在不同组患者中差异有统计学意义，进一步利用 16s rDNA 的时间温度梯度凝胶电泳（TTGE）对评价优势菌群多样性，对比克罗恩病活动期、缓解期及健康患者的肠道菌群多样性程度。研究发现，克罗恩病患者肠道菌群多样性较高，肠道菌群在克罗恩病中的富集程度明显高于健康人群[11]。另一项对克罗恩病行回肠结肠切除术患者的研究进一步表明，术后病灶复发与硬肠球菌富集有关，而缓解期患者肠梭菌和拟杆菌的比例增加[12]。肠道菌群多样性改变与克罗恩病预后之间密切关系的不仅局限于成年人当中，美国一项多中心前瞻性队列研究发现，瘤胃球菌与儿童克罗恩病发生狭窄并发症有关，韦氏杆菌则与其发生穿透并发症有关[13]。可见肠道菌群的研究在克罗恩病的预防、治疗及预后方面有着重要意义。除此之外，肠道菌群与肝硬化[14]、溃疡性结肠炎[15]等消化道疾病之间也存在着相关性。

1.2 糖尿病 粗纤维饮食可促进肠道菌群改善 2 型糖尿病[16]。这一目的的实现主要是通过肠道普雷沃菌促进肝糖原储存，从而改善糖代谢[17]。江美玲等[18]通过实时荧光定量 PCR 方法对 2 型糖尿病患者与健康志愿者的粪便 16s rRNA 进行检测分析，发现二者总细菌量相似，但糖尿病组柔嫩梭菌、双歧杆菌、肠球菌数量显著高于对照组（$P<0.05$），拟杆菌数量显著低于对照组（$P=0.007$），进一步研究各细菌菌属与空腹血糖水平的相关性发现，拟杆菌属/球形梭菌占总细菌比例（$r=-0.202$，$P=0.033$），拟杆菌属数量（$r=-0.246$，$P=0.009$）与空腹血糖呈负相关，肠球菌属数量（$r=0.221$，$P=0.019$）、肠球菌属占总细菌比例（$r=0.213$，$P=0.013$）与空腹血糖间呈正相关。提示肠道菌群在糖尿病患者的病理生理中存在一定的作用，不过鉴于空腹血糖只反映出短暂时期的血糖状态，各菌属与糖尿病患者长期血糖水平的相关性还有待研究。有人以糖尿病血液透析患者作为研究对象，在原有治疗方案基础上补充益生菌 12 周，发现补充益生菌对于血糖稳态参数、局部炎症和氧化应激生物标志物均可产生有益影响[19]。在糖尿病患者中（$n=23$），接受二甲双胍治疗的患者比未接受二甲双胍治疗的患者肠道杆菌数量更高（12 周 $P=0.038$，28 周 $P=0.001$）[20]。提示二甲双胍可通过影响肠道微生物，从而发挥抗 2 型糖尿病的作用[19]。

1.3 心血管疾病 肠道菌群与心血管疾病间的关系早在二十世纪九十年代就已经被人们所发现，是近十年时间内众多研究者青睐的研究方向之一。关于肠道菌群与心血管疾病的报道层出不穷。王玲等[21]通过实时荧光定量 PCR 法发现冠心病患者肠道菌群失衡，其中大肠埃希菌、幽门螺杆菌、链球菌均明显增加，而双歧杆菌、乳杆菌明显减少。肠道菌群代谢产物氧化三甲氨（TMAO）与心脏左室舒张功能障碍指标及左房容积指数之间存在正相关关系，并且 TMAO 对心衰患者 5 年内发生不良临床事件（死亡/移植）风险具有预测价值[22]。高血压方面，SANTISTEBAN 等[23]通过对自发性高血压大鼠的研究，认为肠道菌群可通过交感神经-肠道轴促进肠道病理变化、菌群失调及肠道炎症的发生，从而在高血压中发挥着重要作用。YU 等[24]还发现了肠道菌群及其代谢产物与房颤之间的关系，他认为 TMAO 可能通过激活 p65 核因子 κB（NF-κB）信号通路，增加自主神经活性，使正常犬心房电生理的不稳定性增加，加重房颤模型的急性电重构。

2 肠道菌群影响机体病理变化的机制

2.1 免疫调节 微生物菌群对机体先天性免疫和适应性免疫均产生影响[9]。例如：梭菌属介导短链脂肪酸（SCFAs）的产生，有助于调节性 T 细胞扩增、免疫抑制和整体肠内稳态的维持。多形拟杆菌诱导转录低氧诱导因子（HIF-1α），从而激活抗微生物肽-37（LL-37），反过来可抑制白色念珠菌定植。多种微生物均可通过激活肠上皮细胞中的核苷酸结合寡聚化

结构域样受体蛋白 6(NLRP6)炎性体,并导致上皮 IL-18 和下游抗微生物肽(AMP)的产生,从而抑制肠道炎症等[25]。THAISS 等[26]对肠道菌群与先天免疫系统之间的相互作用作了详细的阐述,他认为肠道菌群导致疾病的发生原因如下:(1)肠道菌群代谢产物可能刺激形成慢性免疫反应,导致非溶解性炎症的发生;(2)菌群失调后将不能诱导先天免疫系统成熟过程中的免疫耐受,导致机体以后自身免疫性疾病的加重;(3)肠道菌群通过控制组织特异性免疫影响机体病理生理改变。适应性免疫包括 T 细胞参与的细胞免疫和 B 细胞参与的体液免疫,HONDA 等[27]认为肠道菌群可影响机体适应性免疫,并受到黏膜 IgA、Th17 细胞及调节性 T 细胞(Treg)的调控。

2.2 代谢产物 肠道菌群代谢产物氧化三甲胺、短链脂肪酸等可通过影响肠道屏障功能、自主神经活性、慢性炎性反应、葡萄糖代谢及脂质代谢等来影响机体功能[28]。

2.2.1 TMAO TMAO 的产生主要依赖肠道菌群特有的 TMAO 裂解酶对含有胆碱或三甲胺结构食物的分解[29]。需注意的是,这只在杂食主义者中成立,而对长期(>1 年)素食主义者和素食者中,补充红肉营养素 L-肉碱后体内几乎没有 TMAO 形成,这可能与慢性口服 L-肉碱中间代谢产物 γ-丁基甜菜碱(γBB)有关[30],提示肠道菌群的调节是一个慢性过程。TMAO 可促进动脉粥样硬化[31]、增强血小板反应性和血栓形成的发展[32]、导致肾功能和纤维化的损害[33]及不良心室重塑和心力衰竭[34]。TMAO 可用于预测心血管事件发生概率,高水平的 TMAO 浓度被认为与主要心脏不良事件的风险独立相关[2]且成比例关系:TMAO 每增加 10 μmol/L,就会导致全因死亡风险增加 7.6%[35]。

2.2.2 SCFAs SCFAs 来源于纤维膳食,是结肠黏膜细胞的主要能量来源,维持肠道黏膜屏障稳定[36]。通过 G 蛋白耦联受体(GPR43),可促进肠道 IgA 反应,维持肠道免疫稳态[37]。还通过影响 DNA 甲基化调控表观遗传来纠正肥胖患者脂联素和抵抗素的异常表达,从而影响脂代谢过程[38]。

2.3 其他 肠道微生物群还具有防止有害病原体的过度生长、通过胆汁酸代谢吸收脂肪及合成多种维生素等作用[22]。

3 总结及展望

肠道菌群是一个庞大而又神秘的领域,它维持机体基本生命活动的机制是复杂的,还需要更多且更深入的研究,这些可为临床治疗手段提供方向,例如肠道菌群移植、补充益生菌及使用抗生素及改变膳食结构等。不过有人认为菌群移植可减低病毒的微生物丰度,但其对疾病缓解的意义似乎并不明显[39]。关于肠道菌群移植的治疗效果还有待更多的临床证据支持。肠道菌群受饮食、环境、机体健康状态等多方面因素影响,随着 DNA 测序技术的不断成熟、肠道宏基因组计划的实施及代谢组学的不断发展,基因水平的研究为进一步发现肠道菌群是如何影响人体的提供了新的参考。未来的研究方向或许应该是常见药物是通过何种机制改变人体肠道菌群的构成和分布及其存在的潜在药物靶点。

参考文献

[1] DING T, SCHLOSS P D. Dynamics and associations of microbial community types across the human body[J]. Nature, 2014, 509(7500): 357-360.

[2] LI X S, OBEID S, KLINGENBERG R, et al. Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors[J]. Eur Heart J, 2017, 38(11): 814-824.

[3] DERRIEN M, VAUGHAN E E, PLUGGE C M. Akkermansia muciniphila gen nov, sp nov, a human intestinal mucin-degrading bacterium[J]. Int J Syst and Evol microbiol, 2004, 54(5): 1469-1476.

[4] DAO M C, EVERARD A, ARON-WISNEWSKY J, et al. Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology[J]. Gut, 2016, 65(3): 426-436.

[5] CHEVALIER C, OZREN S, DIDIER J, et al. Gut microbiota orchestrates energy homeostasis during cold[J]. Cell, 2015, 163(6): 1360-1374.

[6] ROUTY B, LE CHATELIER E, DEROSA L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors[J]. Science, 2018, 359(6371): 91-97.

[7] MNT L, THYBO C B, LYKKEBOE S, et al. Combined bioavailable isoflavones and probiotics improve bone status and estrogen metabolism in postmenopausal osteopenic women: a randomized controlled trial[J]. Am J Clin Nutr, 2017, 106(3): 909-920.

[8] SOMMER F, ANDERSON J M, BHARTI R, et al. The resilience of the intestinal microbiota influences health and disease[J]. Nat Rev Microbiol, 2017, 15(10): 630-638.

[9] BLANDER J M, LONGMAN R S, ILIEV I D, et al. Reg-

ulation of inflammation by microbiota interactions with the host[J]. Nat Immunol,2017,18(8):851-860.

[10] SCHIATTARELLA G G,SANNINO A,TOSCANO E,et al. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker:a systematic review and dose-response meta-analysis[J]. Eur heart J,2017,38(39):2948-2956.

[11] SEKSIK P,RIGOTTIER-GOIS L,GRAMET G,et al. Alterations of the dominant faecal bacterial groups in patients with Crohn′s disease of the colon[J]. Gut,2003,52(2):237-242.

[12] MONDOT S,LEPAGE P,SEKSIK P,et al. Structural robustness of the gut mucosal microbiota is associated with Crohn′s disease remission after surgery[J]. Gut,2016,65(6):954-962.

[13] KUGATHASAN S,DENSON L A,WALTERS T D,et al. Prediction of complicated disease course for children newly diagnosed with Crohn′s disease:a multicentre inception cohort study[J]. Am J Clin Nutr,2017,389(10080):1710-1718.

[14] BAJAJ J S,LIU E J,KHERADMAN R,et al. Fungal dysbiosis in cirrhosis[J]. Gut,2018,67(6):1146-1154.

[15] JAMES S L,CHRISTOPHERSEN C T,BIRD A R,et al. Abnormal fibre usage in UC in remission[J]. Gut,2015,64(4):562-570.

[16] ZHAO L,ZHANG F,DING X,et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes[J]. Science,2018,359(6380):1151-1156.

[17] KOVATCHEVA-DATCHARY P,NILSSON A,AKRAMI R,et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of prevotella[J]. Cell Metab,2015,22(6):971-982.

[18] 江美玲,许岸高. 2 型糖尿病患者肠道菌群特征分析[J]. 广东医学,2013,34(13):2006-2010.

[19] WU H,ESTEVE E,TREMAROLI V,et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes,contributing to the therapeutic effects of the drug[J]. Nat Med,2017,23(7):850-858.

[20] HUANG F,NILHOLM C,ROTH B,et al. Anthropometric and metabolic improvements in human type 2 diabetes after introduction of an Okinawan-based Nordic diet are not associated with changes in microbial diversity or SCFA concentrations[J]. Int J Food Sci Nutr,2017,69(6):729-740.

[21] 王玲,李群. 冠心病患者肠道菌群分布及其与尿酸代谢的关系分析[J]. 现代消化及介入诊疗,2012,17(6):327-330.

[22] TANG W H,WANG Z,SHRESTHA,et al. Intestinal microbiota-dependent phosphatidylcholine metabolites,diastolic dysfunction,and adverse clinical outcomes in chronic systolic heart failure[J]. J Card Fail,2015,21(2):91-96.

[23] SANTISTEBAN M M,QI Y,ZUBCEVIC J,et al. Hypertension-linked pathophysiological alterations in the gut[J]. Circ Res,2017,120(2):312-327.

[24] YU L,MENG G,HUANG B,et al. A potential relationship between gut microbes and atrial fibrillation:Trimethylamine N-oxide,a gut microbe-derived metabolite,facilitates the progression of atrial fibrillation[J]. Int J Cardiol,2018,255(1):92-98.

[25] THONGPRAYOON C,KAEWPUT W,HATCH S T,et al. Effects of probiotics on inflammation and uremic toxins among patients on dialysis:a systematic review and meta-analysis[J]. Digest Dis Sci,2018,64(2):469-479.

[26] THAISS C A,ZMORA N,LEVY M,et al. The microbiome and innate immunity[J]. Nature,2016,535(7610):65-74.

[27] HONDA K,LITTMAN D R. The microbiota in adaptive immune homeostasis and disease[J]. Nature,2016,535(7610):75-84.

[28] TANG W H,KITAI T. Gut microbiota in cardiovascular health and disease[J]. Circ Res,2017,120(7):1183-1196.

[29] CHO C E,TAESUWAN S,MALYSHEYA O V,et al. Trimethylamine-N-oxide (TMAO) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition:A randomized controlled trial[J]. Mol Nutr Food Res,2017,61(1):324-336.

[30] KOETH R A,LAM-GALVEZ B R,KIRSOP J,et al. L-Carnitine in omnivorous diets induces an atherogenic gut microbial pathway in humans[J]. J Clin Invest,2019,129(1):373-387.

[31] KOETH R A,WANG Z,LEVISON B S,et al. Intestinal microbiota metabolism of L-carnitine,a nutrient in red meat,promotes atherosclerosis[J]. Nat Med,2013,19(5):576-585.

[32] ZHU W,GREGORY J C,ORG E,et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk[J]. Cell,2016,165(1):111-124.

[33] TANG W H,WANG Z,KENNEDY D J,et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease[J]. Circ Res,2015,116(3):448-455.

[34] ORGAN C L,OTSUKA H,BHUSHAN S,et al. Choline diet and its gut microbe-derived metabolite,trimethylamine N-oxide,exacerbate pressure overload-induced heart failure[J]. Circ Heart Fail,2016,9(1):e002314. (下转第 3896 页)

neutrophil migration in vitro and in vivo[J]. J Immunol, 2017,198(3):1023-1033.

[12] SHIMIZU I,YOSHIDA Y,MORIYA J,et al. Semaphorin3E-Induced inflammation contributes to insulin resistance in dietary obesity[J]. Cell Metab,2013,18(4):491-504.

[13] NAKAYAMA H,HUANG L,KELLY R P,et al. Infantile hemangioma-derived stem cells and endothelial cells are inhibited by class 3 semaphorins[J]. Biochem Biophys Res Commun,2015,464(1):126-132.

[14] WU J,XIAO Y W,XIA C,et al. Identification of biomarkers for predicting lymph node metastasis of stomach cancer using clinical DNA methylation data[J]. Dis Markers,2017(2017):5745724.

[15] XUE D,KAUFMAN G N,DEMBELE M,et al. Semaphorin 4C protects against allergic inflammation:requirement of regulatory CD138$^+$ plasma cells[J]. J Immunol, 2017,198(1):71-81.

[16] WEI J C,YANG J,LIU D,et al. Tumor-associated lymphatic endothelial cells promote lymphatic metastasis by highly expressing and secreting SEMA4C[J]. Clin Cancer Res,2017,23(1):214-224.

[17] 叶双梅,韩敏,阚淳一,等. 信号素分子 4C 在食管癌、胃癌和直肠癌中的表达及其意义[J]. 中华医学杂志,2012,92(28):1954-1958.

[18] JIANG X,BJORKSTROM N K,MELUM E. Intact CD100-CD72 interaction necessary for TCR-Induced T cell proliferation[J]. Front Immunol,2017,8:765.

[19] KE Y,DANG E,SHEN S,et al. Semaphorin4D drives CD8$^+$ T-Cell lesional trafficking in oral lichen planus via CXCL9/CXCL10 upregulations in oral keratinocytes[J]. J Invest Dermatol,2017,137(11):2396-2406.

[20] ZHANG C,XIAO C Y,DANG E L,et al. CD100-Plexin-B2 promotes the inflammation in psoriasis by activating NF-κB and the inflammasome in keratinocytes[J]. J Invest Dermatol,2018,138(2):375-383.

[21] TAKEGAHARA N,KUMANOGOH A,KIKUTANI H. Semaphorins:a new class of immunoregulatory molecules[J]. Philos Trans the R Soc Lond B Biol Sci,2005, 360(1461):1673-1680.

[22] WONG A W,BRICKEY W J,TAXMAN D J,et al. CIITA-regulated plexin-A1 affects T-cell-dendritic cell interactions[J]. Nat Immunol,2003,4(9):891-898.

[23] JONGBLOETS B C,RAMAKERS G M,PASTERKAMP R J. Semaphorin7a and its receptors:pleiotropic regulators of immune cell function,bone homeostasis,and neural development[J]. Semin Cell Dev Biol,2013,24(3): 129-138.

[24] GARCIA-AREAS R,LIBREROS S,IRAGAVARAPU-CHARYULU V. Semaphorin7a:branching beyond axonal guidance and into immunity[J]. Immunol Res, 2013,57(1/3):81-85.

[25] GARCIA-AREAS R,LIBREROS S,SIMOES M,et al. Suppression of tumor-derived Semaphorin 7A and genetic ablation of host-derived Semaphorin 7A impairs tumor progression in a murine model of advanced breast carcinoma[J]. Int J Oncol,2017,51(5):1395-1404.

(收稿日期:2019-03-12 修回日期:2019-06-04)

(上接第 3891 页)

[35] SCHIATTARELLA G G,SANNINO A,TOSCANO E,et al. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker:a systematic review and dose-response meta-analysis[J]. Eur heart J, 2017,38(39):2948-2956.

[36] CANFORA E E,BEEK C M,HERMES G D A,et al. Supplementation of diet with galacto-oligosaccharides increases bifidobacteria,but not insulin sensitivity,in obese prediabetic individuals[J]. Gastroenterol,2017,153(1): 87-97.

[37] WU W,SUN M,CHEN F,et al. Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43[J]. Mucosal Immunol,2017,10(4):946-956.

[38] LU Y,FAN C,LIANG A,et al. Effects of SCFA on the DNA methylation pattern of adiponectin and resistin in high-fat-diet-induced obese male mice[J]. Brit J Nutr, 2018,120(4):385-392.

[39] ZUO T,WONG S H,LAM K,et al. Bacteriophage transfer during faecal microbiota transplantation in infection is associated with treatment outcome[J]. Gut,2018,67(4): 634-643.

(收稿日期:2019-03-14 修回日期:2019-07-02)