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# 肠道菌群在代谢、免疫疾病中作用的研究进展

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## 摘　要

**肠道菌群除了参与机体的消化和营养物质吸收外，还在代谢、免疫调节等过程中发挥重要生理功能。在多种相关疾病患者体内，肠道菌群组成和含量发生显著改变。肠道菌群可以影响宿主的代谢过程，并参与包括肥胖症、二型糖尿病在内的多种代谢疾病。肠道菌群可以通过其代谢产物影响宿主的免疫反应和炎症反应，并参与炎症性肠炎和系统性红斑狼疮等病的发病过程。粪菌移植为多种代谢、免疫疾病提供新的治疗方案，多项粪菌移植的临床试验显示出良好治疗效果，但尚存在争议，需要进一步验证和完善。**

## 关键词

**肠道菌群，代谢疾病，免疫疾病**

# Research Progress of Gut Microbiota's Function in Metabolic and Immunological Diseases

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## Abstract

**Besides functions in digestion and nutrient absorption, microbiota also plays an important role in metabolism and immunological regulation. In many related diseases, there is significant alteration**

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**of microbiota in patients compared to healthy controls. Microbiota can affect host metabolism, taking part in pathogenesis of many metabolic diseases including obesity and Type II diabetes. Microbiota can exert immunity and inflammation regulation functions through their metabolites, and participate in pathogenesis of inflammatory bowel disease and systemic lupus erythematosus. Research on Gut-Brain-Axis has discovered microbiota's function in brain development and cognitive behaviors. Psychobiotics has shown positive effects on mental health. Fecal microbiota transplantation has provided new treatment schemes for many metabolic, immunological and neurological disorders. Many clinical trials of fecal microbiota transplantation have shown promising results for disease management, but are still under debate and need more rigorous testing.**

## Keywords

**Gut Microbiota, Metabolic Diseases, Immunological Diseases**



## 1. 引言

人体中存在的基因超过 99%来自于微生物[1]，而人体中微生物细胞的数量也远远超过机体细胞数[2]。人类肠道菌群中除了数量最多也是被研究最多的细菌外，还包括酵母、单细胞真核生物、寄生虫、病毒等[3]。人在降生时通过母亲的产道就获得了来自母体的菌群。在生命的早期，肠道菌群的构成可以被多种因素影响，比如是否早产、生产的方式(顺产或剖腹产)、喂养方式(母乳或奶粉喂养)、抗生素的使用等[4]。而随着年龄的增长，肠道菌群主要由饮食影响[5] [6]。人类肠道菌群主要由拟杆菌、变形杆菌、厚壁菌门、放线菌、广古菌门构成[7] [8]。

近年来的研究表明，肠道菌群除了参与宿主营养物质消化和吸收外，还具有调控宿主代谢活动、免疫调节、影响神经系统发育等多种生理功能。而肠道菌群失调会造成多种相关疾病。目前的相关研究多为观察性病例对照研究，越来越多的研究开始关注肠道菌群参与疾病发生的相关机制，以及如何通过改变肠道菌群改善疾病的临床症状。本综述总结了代谢、免疫、神经和心理疾病患者肠道菌群的变化情况，肠道菌群参与疾病发生的相关机制研究，以及修饰肠道菌群的相关治疗方法的最新研究进展。此外，还讨论了肠道菌群与疾病发生研究目前尚存在的问题和未来的研究方向。

## 2. 肠道菌群与代谢疾病的关系

### 2.1. 肠道菌群在宿主代谢中的生理功能

肠道菌群组成可以影响宿主对于食物选择的偏好[9]。缺乏必需氨基酸饲料喂养的果蝇会对于氨基酸含量丰富的食物有选择偏好，然而如果果蝇肠道中同时存在发霉醋杆菌(*Acetobacter pomorum*)和乳酸杆菌，这种偏好则会消失。

肠道菌群可以影响内分泌调节。肠道菌群可以通过一些肠道内的多肽影响宿主的进食行为。胃饥饿素在大鼠饥饿感和食欲产生过程中有重要作用[10] [11]，肠道激素类胰高血糖素多肽 1 (Glucagon-like peptide 1, GLP-1) [12]和多肽 YY (Peptide YY, PYY) [13]与人类宿主饱腹感和满足感以及停止进食的选择相关。对小鼠和人类的多项研究显示，肠道菌群产生的短链脂肪酸(SCFA)的增加可以刺激肠道内分泌细

胞产生 GLP-1 [14]和 PYY [15]，并且降低胃饥饿素的分泌[16]。肠道菌群产生的包括丁酸盐和丙酸盐在内的 SCFAs 还可以促进小鼠原代脂肪细胞中瘦素合成[17] [18]。

## 2.2. 代谢疾病中肠道菌群的变化

研究发现，在许多代谢疾病中肠道菌群的种类和数量发生显著变化，如肥胖症、营养不良、二型糖尿病和代谢性肝病等。

### 2.2.1. 肥胖症

虽然导致肥胖症的因素众多，但肠道菌群和肥胖症之间的关联被普遍认同。2006 年，Turnbaugh 等发现将肥胖小鼠的粪菌移植至瘦小鼠肠道内后会引起瘦小鼠的体重增加[19]。一系列流行病学研究显示肥胖症个体和瘦个体之间肠道菌群组成的差别。对同卵双生双胞胎人群的一项研究显示，产生 SCFA 的 *Eubacterium ventriosum* 和肠道罗氏菌(*Roseburia intestinalis*)和肥胖相关[20]，而产丁酸盐的颤螺菌属(*Oscillospira*) [21]和史氏甲烷短杆菌(*Methanobrevibacter smithii*) [22]和瘦型相关(见表 1)。肠道菌群对于宿主代谢的影响可以通过粪菌移植从人类传递到小鼠[23]。肠道菌群可以通过增加宿主能量吸收[24]，提高食欲[25]，提高脂肪储存[26]等方式导致肥胖症的发生。

**Table 1.** Alterations of gut microbiota in metabolic, immunological disorders
**表 1.** 代谢、免疫疾病中肠道菌群的变化情况

| | 疾病名称 | 含量增加的菌群 | 含量降低的菌群 |
|---|---|---|---|
| 代谢疾病 | 肥胖症 | 肠道罗氏菌[20] | 颤螺菌属[21]，史氏甲烷短杆菌，多形拟杆菌[102] |
| | 二型糖尿病 | 普通拟杆菌，普氏菌，梭杆菌属[103] | 嗜黏蛋白艾克曼菌[27] [28] |
| 免疫疾病 | 炎症性肠炎 IBD | 变形菌门，大肠埃希菌，梭杆菌门梭菌属[78] [79] [80] [81] [82] | 拟杆菌属，厚壁菌门，梭菌属，乳杆菌属，双歧杆菌属[104] |
| | 系统性红斑狼疮 | 放线菌门红球菌属，变形菌门克雷伯氏菌属，双歧杆菌[91] | 厚壁菌门，拟杆菌门[91] [92] [93] [94] |

### 2.2.2. 二型糖尿病

在未使用药物治疗的前驱糖尿病患者体内，产丁酸盐的菌种减少，嗜黏蛋白艾克曼菌(*Akkermansia muciniphila*)含量降低，促炎性菌种含量升高[27] [28] (见表 1)。值得指出的是，这些变化并不是二型糖尿病特有的，而是在一些其他伴随炎症反应的慢性非传染性疾病中也存在的。

肠道菌群通过代谢产物影响宿主的胰岛素敏感性。在不健康饮食的条件下，肠道菌群可以提高血浆 BCAA 浓度并造成胰岛素耐受性[29]。变异链球菌(*Streptococcus mutans*)和缓慢爱格士氏菌(*Eggerthella lenta*)产生的咪唑丙酸对胰岛素信号通路有抑制作用[30]。

在以上肥胖症和二型糖尿病肠道菌群的研究中，药物的使用都是一个可能影响肠道菌群构成的因素。例如，降低胆固醇的他汀类药物经常在肥胖症患者中用于防止动脉硬化，它的使用和有益健康的菌群增加相关[31]。二型糖尿病患者经常会使用的降血糖药物二甲双胍不仅对患者肠道菌群组成及含量有影响，还会增强肠道菌群糖异生的功能[32] [33] [34]。

## 2.3. 粪菌移植治疗代谢疾病的进展

### 2.3.1. 粪菌移植 FMT

粪菌移植(Fecal Microbiota Transplantation, FMT)是指将经过筛选的捐献者的粪便标本进行采集、处理

后，经过结肠镜、内窥镜、鼻胃管或灌肠剂等方式植入患者体内的过程，目的是以健康的肠道菌群替换患者肠道内的致病菌群。FMT 在公元 4 世纪中医书籍《肘后备急方》和《本草纲要》中就有服用肠道菌群悬液治疗食物中毒和严重腹泻的记载。美国食品药物管理局在 2013 年通过了使用 FMT 对复发性艰难梭菌(recurrent *Clostridium difficile* infection, rCDI)感染进行治疗。FMT 在临床中治疗 rCDI 相比于使用万古霉素效果更加显著[35]，几项研究中显示 FMT 应用于 rCDI 治愈率在 90%以上[36]。FMT 目前最常用于 rCDI 的治疗[37]。由于肠道菌群在多种疾病中的病理作用，FMT 的其他临床应用可能也正在探索之中，如肥胖症[38]，炎症性肠炎[39]、自身免疫疾病及代谢疾病。然而目前的数据还不足以支持在临床中使用 FMT 治疗以上疾病。

由于医院资源和条件的限制，用于 FMT 的粪菌由粪菌库保存。自从 2012 年世界上首个非营利性粪菌库 OpenBiome 在美国建立起，全世界多个国家都建立了粪菌库。2015 年，中华粪菌库由南京医科大学第二附属医院消化医学中心和第四军医大学西京消化病医院联合发起成立。

FMT 捐献者需要经过严格的筛选[40]。有的粪菌库筛选后合格的捐献者只占到潜在捐献者的 3%。一般情况下，潜在捐献者需要依次经过筛查前问卷调查(筛除身体质量指数不佳、最近使用过抗生素等人群)，临床评估和实验室检测。实验室检测的主要目的是判断捐献者是否具有对粪菌接受者具有潜在威胁的传染性疾病。约一半的潜在捐献者在实验室检测步骤由于粪便标本中含有脆弱双核阿米巴(*Dientamoeba fragilis*)，人芽囊原虫(*Blastocystis hominis*)，艰难梭菌或轮状病毒被筛除[41]。筛选合格的捐献者可以在家或在粪菌库采集样品，捐献者需要在约一个月的时间段内连续取样，在取样开始和取样结束的日期一般都会进行实验室检测以便确保取样时间范围内的样品都是符合安全标准的。

用于一次 FMT 治疗的粪便使用量约为 60 g，新鲜采集的粪便进行研磨后加入生理盐水混匀，随后经过一系列过滤去除未消化的食物残渣和颗粒状物质。经过离心浓缩后，加入甘油后即可冻存于−80℃[42]。不同机构对于患者的不同临床情况会选择不同的移植方式。移植可以通过上消化道(鼻胃管、鼻空肠管等)、下消化道(结肠镜或保留灌肠) [43]或口服胶囊[44]进行。下消化道移植法相比于上消化道移植法一般效果更好[45]。对于结肠发炎的患者采取上消化道方式。通过结肠镜进行的 FMT 可以直接评估炎症轻重和在特定位置植入足量的粪菌[46]。口服胶囊由于其非侵入性的特点比较容易被患者接受，然而价格较高，且胶囊体积较大[47]。

FMT 在临床中的推广存在一些限制和风险。首先，FMT 治疗尚缺乏长期的安全性跟踪研究[48]。在目前现有的短期复查研究中，FMT 效果良好，很少出现不良反应。然而这不能排除 FMT 后长期存在的安全风险。其次，FMT 移植过程中不仅转移了肠道菌群，还包括噬菌体和其他生物活性成分(如胆汁酸)。由于具体的治疗机制以及 FMT 中有效的活性成分还不明确，所以目前生产标准化的 FMT 产品还很困难。提供 FMT 治疗的机构之间对于样品的处理方式也各不相同[49]。最后，FMT 存在传播感染性疾病的风险。即使捐献者需要经过十分严苛的筛选过程，也有可能将具有潜在健康威胁的细菌转移到患者体内。例如在一项研究中，耐药性大肠埃希菌在 FMT 过程中被移植到患者体内[50]。

#### 2.3.2. FMT 用于代谢疾病治疗的研究进展

FMT 是肥胖和代谢综合征的一种新疗法。在几项小规模的临床试验中，低脂个体捐献者的粪便微生物群移植可以使具有代谢综合征的移植接受者有更好的胰岛素敏感性[51] [52]。最新的研究显示，在 24 周内反复进行 FMT 可以有效改善肥胖的二型糖尿病患者肠道菌群，配合生活方式干预可以显著降低血脂[53]。在减重期采样并在复胖过程中实施的自体 FMT(粪菌样品捐献者和接受者是同一个人)在配合饮食调节的情况下，可减缓体重增长[54]。FMT 在一型糖尿病[55]和非酒精性脂肪肝[56]治疗中的应用潜力也正在探索中。

## 3. 肠道菌群与免疫疾病的关系

### 3.1. 肠道菌群在宿主炎症反应和免疫反应中的生理功能

#### 3.1.1. 肠道菌群在宿主免疫反应和炎症反应中的作用

肠道菌群对于维持正常的免疫反应至关重要。研究显示，使用抗生素减少肠道菌群后，小鼠先天免疫和适应性免疫被削弱。肠道巨噬细胞的 I 型干扰素和 II 型干扰素反应受到抑制，限制病毒增殖的能力受损[57]。肠道菌群可以作用于 B 细胞以维持肠道内环境的稳态。在关节炎模型小鼠中，肠道菌群可以促进白介素 1$\beta$ (interleukin-1$\beta$, IL-1$\beta$)和白介素 6 (Interleukin-6, IL-6)的产生，从而促进脾脏和肠系膜淋巴结中的产白介素 10 (interleukin-10, IL-10)的 B 细胞的发育和功能[58]。

不同肠道菌群对于促炎细胞因子产生的影响不同。一些肠道细菌可以促进促炎细胞因子的产生，如嗜黏蛋白艾克曼菌(*Akkermansia muciniphila*)等肠道细菌可以消化肠道表面黏液层中的聚糖，导致肠道表面黏液层厚度降低，肠道屏障受损，形成肠漏症[59]，同时菌群产生的促炎产物增加，导致血液中脂多糖，促炎细胞因子(IL-1$\beta$, IL-6)增加[60]。

另一些肠道细菌则对于促炎细胞因子的产生具有相反的作用，如双歧杆菌可以降低促炎细胞因子的含量。在高脂饲料中添加可以特异性增加双歧杆菌含量的益生元低聚果糖后，小鼠血浆和脂肪组织中的促炎细胞因子量降低，并且对于葡萄糖的耐受性增高[61]。

拟杆菌门是革兰氏阴性菌中最大的门，对人类健康有益。其中拟杆菌属在肠道中最为普遍[62]。脆弱拟杆菌(*Bacteroides fragilis*)可以激活产 IL-10 的 B 细胞，而这些 B 细胞可以抑制 T 细胞介导的炎症反应和结肠炎[63] [64] [65]。脆弱拟杆菌细胞壁的成分多糖 A 可以刺激 B 细胞和 T 细胞合成 IL-10，并且可以防止病毒性脑炎[63]。而经过修饰的不能合成多糖 A 的脆弱拟杆菌失去促进 IL-10 产生的能力，变为促炎性[66]。

#### 3.1.2. 肠道菌群调节宿主免疫反应、炎症反应的机制

肠道菌群可以通过其产生的代谢产物(短链脂肪酸，脂质，维生素等)调节宿主的免疫反应[67] [68]。短链脂肪酸(short chain fatty acid, SCFA)丁酸盐，醋酸盐，丙酸盐等是大肠中膳食纤维发酵的副产品。丁酸盐和丙酸盐可以促进胸腺外调节性 T 细胞的分化[69] [70]。丁酸盐还可以降低脂多糖(Lipopolysaccharide, LPS)诱导的肠道巨噬细胞中促炎性细胞因子(一氧化氮，IL-6)的产生，证明丁酸盐是一种抗炎性代谢产物[71]。肠道菌群将初级胆汁酸转化为次级胆汁酸(脱氧胆酸和石胆酸)。次级胆汁酸可以激活胆汁酸受体并引发抗炎反应，抗炎反应伴随 *Tgfb*，*Il10*，*Foxp3* 等基因表达以及抑制 NF-kB 介导的促炎细胞因子(*Il6*, *Tnfa*, *Il1b* 和 *Ifng*)表达[72] [73]。许多肠道菌群的代谢产物(次级胆汁酸，脂肪酸等)以及次级代谢产物都可以在肠道内调节炎性白细胞和调节性 T 细胞并调控肠道屏障[74]。

### 3.2. 菌群失调在免疫疾病中的病理作用

越来越多的数据证明肠道菌群失调或改变可以造成自身免疫疾病，特定种类的细菌可以促进或降低免疫反应，各种细菌共同作用会造成宿主不同的炎症反应状态。然而肠道菌群直接或间接地作用于免疫系统的具体机制尚不明确。

#### 3.2.1. 炎症性肠炎(Inflammatory Bowel Disease, IBD)

IBD 是由肠道菌群改变、异常免疫反应和肠黏膜屏障受损等因素共同引起的宿主对肠道正常菌群的免疫反应。越来越多的研究显示出 IBD 患者肠道菌群所具有的共同特点[75]。IBD 患者肠道菌群总体丰富性和 $\alpha$ 多样性降低[76]，这与粘膜炎症反应相符[77]。黏附侵袭性细菌如变形菌门的大肠埃希菌和梭杆

菌门的梭菌属在北美、日本和意大利的 IBD 患者肠道中富集[78] [79] [80] [81] [82]。大肠埃希菌的富集还可能促使 IBD 患者肠道中丙型变形菌纲数量的增加[83] (见表 1)。

Th17/Treg 细胞数量稳态的破坏是导致 IBD 的一个重要原因[84]，而肠道菌群可以影响 Th17/Treg 细胞的分化。分节丝状菌(Segmented Filamentous Bacteria)的鞭毛蛋白可以促进 Th17 的分化[85]。肠道菌群的代谢产物 ATP 和 SCFAs 可以分别影响 Th17 细胞和 Treg 细胞的分化[70] [86]。

FMT 治疗 IBD 的有效性和安全性目前仍存在争议。研究显示 FMT 可以在短期内缓解 IBD 的临床症状[87] [88] [89] [90]，且绝大多数患者并没有出现与 FMT 相关的严重不良反应[87]。FMT 对于一些 IBD 患者疗效显著，而对另一些患者没有明显作用，这可能和多种因素相关：患者的基因型、患者肠道菌群的组成、FMT 植入的方式选择、FMT 制备过程和粪菌捐献者个体差别等。FMT 作为临床治疗 IBD 的方法还需要相关研究的理论支撑。

#### 3.2.2. 系统性红斑狼疮

目前肠道菌群在系统性红斑狼疮中作用的相关研究还不多。目前绝大多数数据表明厚壁菌门和拟杆菌门的相对含量在系统性红斑狼疮患者中较健康个体有所降低[91] [92] [93] [94] (见表 1)。

一项针对中国人群的研究表明，系统性红斑狼疮患者相比于健康个体有几个属的肠道菌群增加(如：拟杆菌门的普氏菌属 *Prevotella*，放线菌门的红球菌属 *Rhodococcus* 和变形菌门的克雷伯氏菌属 *Klebsiella*)，以及厚壁菌门的减少(主要由假丁酸弧菌属 *Pseudobutyrivibrio* 以及小类杆菌属 *Dialister* 降低引起) [91]。另一项研究发现系统性红斑狼疮患者肠道菌群与普通人相比有 7 个属的菌群量增加，19 个属菌群量减少，此研究也得出了系统性红斑狼疮患者肠道中厚壁菌门和拟杆菌门相对含量降低的结论[92]。也有一些研究发现一些特定的种属可能在系统性红斑狼疮发病中发挥作用。如厚壁菌门的鹑鸡肠球菌(*Enterococcus gallinarum*)被发现可能具有促进系统性红斑狼疮类疾病发病的作用[95]。

目前关于肠道菌群和 SLE 之间关系的研究多为观察性的病例对照研究，而肠道菌群参与 SLE 致病的机制研究尚十分缺乏。机制类研究将有助于发现新的 SLE 诊断生物标记物，并为通过改变肠道菌群缓解 SLE 症状的临床治疗手段提供更多理论支撑。

由于肠道菌群在 SLE 发病中的作用，研究者们尝试探索使用益生菌缓解 SLE 的症状。动物实验和人类临床试验都显示使用益生菌可以减轻炎症反应和自身免疫反应[96]。在 SLE 动物模型中，双歧杆菌，乳杆菌属，卵瘤胃球菌(*Ruminococcus obeum*)等益生菌有助于调节过度的炎症反应[97]。近期的多项研究显示，在小鼠 SLE 模型中，乳杆菌属可以抑制 IL-6 合成、减少 Th17 细胞数量、提高 Treg 细胞数量并缓解 SLE 相关的症状[98] [99] [100] [101]。

## 4. 研究前景

肠道菌群和代谢、免疫、神经和心理疾病之间的关系主要是相关性，而不具有因果关系。由于导致以上的疾病的因素众多(如遗传、环境、饮食等)，肠道菌群作为病理过程的重要因素越来越受到关注。

对于肠道菌群与代谢疾病和肥胖之间关系的研究，目前多数是建立在啮齿类动物模型基础上的，然而如果想将这些研究成果转化为可以在临床中使用的有效的疗法，还需要在人类中进行的长时间维度的机制类研究。对于特定表型的人群进行宏基因组，宏转录组，蛋白质组学的研究，通过大数据分析可能有助于找到疾病相关的肠道菌群特征[105]。

影响肠道菌群的因素众多，如：地域和人群、饮食结构、环境因素、疾病状况和药物使用情况等。今后研究应当将以上因素也考虑在内，从而使得数据和研究之间有更强的可比性[106] [107] [108]。尤其是在肠道菌群和心理疾病的相关性研究中，需要关注肠道菌群变化的表型是直接由心理疾病中脑活动变

化引起的，还是由于各种心理疾病的表型附加产生的(例如，一些自闭症患者可能会倾向于选择某些食物，而饮食会造成肠道菌群发生变化)。

FMT 成功用于 rCDI 治疗后，将其用于其他肠道菌群相关疾病的治疗是一个研究热点。由于影响 FMT 的因素众多，如：捐献者选择、制备方法、移植方式、患者具体临床情况和肠道菌群构成等，FMT 治疗其他疾病的临床试验结果还具有争议。在 FMT 的实践中，还有一些难点需要解决，比如移植可能引发肠道不适，移植菌群很可能作用短暂等。对于肠道菌群病理作用的相关机制研究将会为 FMT 的临床应用提供更多理论支撑，标准化的 FMT 操作方法也需要建立。

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