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# “肠道菌群－肠－肝轴”在非酒精性脂肪肝病中的作用研究进展

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## 摘　要

**非酒精性脂肪性肝病(NAFLD)是指在无异常酒精摄入的情况下，以肝细胞脂质蓄积为主要病理改变并伴有慢性炎症反应的代谢性疾病，被认为是代谢综合征的主要肝脏表现。研究发现，在肠道和肝脏之间的存在着物质和信号的双向通信，具有功能上的协同性，而在NAFLD的发生发展过程中，肠道菌群及其代谢物也发生不同程度的改变并通过肠－肝轴影响着NAFLD的疾病进程。因此，本文将主要从肠道菌群－肠－肝轴的结构组成和肠道菌群－肠－肝轴在NAFLD发病中的机制进行综述，为NAFLD的预防和治疗提供新的见解。**

## 关键词

**非酒精性脂肪肝病，肠道菌群－肠－肝轴，肠道屏障，肠道菌群**

# Progress on the Role of “Gutbacteria-Gut-Liver Axis” in Non-Alcoholic Fatty Liver Disease

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## Abstract

**Non-alcoholic fatty liver disease (NAFLD) is a metabolic disease characterized by lipid accumulation in liver cells and chronic inflammatory response in the absence of abnormal alcohol intake. It**

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**is considered to be the main liver manifestation of metabolic syndrome. Studies have found that there is two-way communication of substances and signals between the gut and the liver, which is functionally synergistic. While gut microbiota and its metabolites are also changed in different degrees and affect the disease course of NAFLD through the gut-liver axis during the occurrence and development of NAFLD. Therefore, this paper will mainly review the structure and composition of intestinal microbiota-enteric-liver axis and the mechanism of gut microbiota-gut-liver axis in the pathogenesis of NAFLD.**

## Keywords

**Nonalcoholic Fatty Liver, Gut Bacteria-Gut-Liver Axis, Intestinal Barrier, Gut Bacteria**



## 1. 引言

非酒精性脂肪肝病(Non-Alcoholic Fatty Liver Disease, NAFLD)是世界上最常见的肝脏疾病之一，指在没有异常酒精摄入或某些遗传条件下，以肝细胞脂肪变性超过5%为主要病理特征的一种代谢性疾病[1]。随着脂质蓄积和炎症的加重，NAFLD会发展为非酒精性脂肪性肝炎(Non-Alcoholic Steatohepatitis, NASH)，而NASH则可能导致肝纤维化[2]、肝硬化甚至肝癌[3]，并增加心血管风险[4]。根据卡尔加里大学卡明医学院的Abdel-Aziz Shaheen教授对NAFLD发病情况进行的Meta分析，2022年的NAFLD全球发病率为32.4%，并且这一比例还在持续增加中[5]。

NAFLD最早由Fleming等人于1981年提出[6]，关于其机制的研究至今已40余年。以往“二次打击学说”令人广为信服，该学说认为，持续的糖脂代谢失衡及伴随的胰岛素抵抗，导致甘油三酯在肝脏大量蓄积是“首次打击”；随后在肝细胞脂质蓄积的基础上，造成线粒体功能障碍，进而诱发氧化应激和内质网应激，并激活肝内免疫细胞释放炎症因子等从而导致NAFLD则是“二次打击”[7]。然而，随着研究的深入，这一学说已不足以阐述临床问题，研究证明胰岛素抵抗[8] [9]、脂质代谢紊乱[10] [11]、内毒素血症[12] [13]、肝脏炎症[14] [15] [16]和肠道屏障破坏[17]及基因易感性等多种因素共同参与NAFLD的发生与发展，故而在此基础上有专家提出了“多重平行打击学说”[18]。2020年2月，国际脂肪肝命名小组提议将非酒精性脂肪肝病更名为代谢相关脂肪性肝病(Metabolic Associated Fatty Liver Disease, MAFLD)，对理解NAFLD的发病机制迈出了重大一步[19]。作为机体最主要的吸收器官同时也是重要的代谢器官，肠道的微环境紊乱会对机体代谢水平产生重要影响，因此在多种致病因素中，对于肠道和肝脏联系的研究尤其引人注目。

肝脏和肠道起源于同一胚层，有着很多解剖和功能上的联系[20]。肝脏是人体最大的器官，其中75%的供血来自门静脉系统，而门静脉则主要汇聚了胃、胰腺和肠道等代谢相关器官的静脉血入肝脏，另一方面，肝脏代谢产生的物质可以经过胆管进入肠道，影响肠道的功能，因此肝脏与肠道之间存在密切的联系，形成“肠－肝轴”(Gut-Liver Axis)，肠－肝轴中的各种细胞、炎症因子、代谢产物之间相互作用，相互影响，形成了一个复杂的网络[21] [22]。肠道微生物及其代谢产物在机体的代谢和免疫反应等正常生理过程中发挥着重要的调节作用，并因此被看作是一种虚拟的内分泌器官[23] [24]，例如肠道菌群可以代谢产生如丁酸和丙酸等短链脂肪酸(Short-Chain Fatty Acids, SCFAs)，SCFAs为肠上皮提供营养和能量来

源，也影响脂肪生成和糖异生[25]，SCFAs 还可以激活 g 蛋白偶联受体(GPCRs)中的 GPR43 和 GPR41，从而激活抗炎信号级联反应[25] [26]；肠道菌群可调节色氨酸的血浆浓度进而影响 5-羟色胺的外周生成[27]，5-羟色胺是神经系统中的关键神经递质，可通过多种途径影响机体代谢和机体免疫[28]；肠道菌群也会调节胆汁酸代谢，从而在维持葡萄糖、胆固醇和甘油三酯的稳态上发挥作用[29] [30] [31]，然而，在 NAFLD 的相关领域中，对“肠－肝轴”的研究多集中于肠道微生物及其代谢产物，忽略了肠道作为器官所发挥的作用，与其说是“肠－肝轴”不如说是“肠道菌群－肝轴”。本文将从“肠道菌群－肠－肝轴”的角度对其在 NAFLD 发生发展中的已知作用机制做一综述，旨在为“肠道菌群－肠－肝轴”与 NAFLD 的研究提供参考。

## 2. “肠道菌群－肠－肝轴”的 s 生理构成

“肠道菌群－肠－肝轴”指微生物、肠道和肝脏的相互作用，其中发挥主要媒介作用的就是肠道粘膜。肠道粘膜是生物在进化的过程中形成的一个复杂有机系统，既用来负责营养物质的吸收，同时又负责免疫感知，限制潜在有害抗原和微生物，其复杂的功能调节是通过肠道黏膜结构成分和分子间的相互作用来实现的，它们以一种动态的方式运行，以维持肠道完整性和免疫稳态[32] [33]。肠道黏膜屏障通过把肠道微生物群和宿主隔离开从而在“肠道菌群－肠－肝轴”的稳态中发挥重要作用，同时也是肠道信号与肝脏信号交互的重要基础，肠道屏障的功能可能会因黏膜结构的严重损伤或屏障调节成分的细微变化而受到损害。如图 1 所示，根据现代医学研究，肠道粘膜屏障按其功能可以分为微生物屏障、黏液屏障、机械屏障和免疫屏障[34] [35]，其中肠道菌群不止构成了微生物屏障，还通过其他途径影响其他屏障的功能，故本节对黏液屏障、机械屏障和免疫屏障进行综述，微生物屏障将在后文详述。

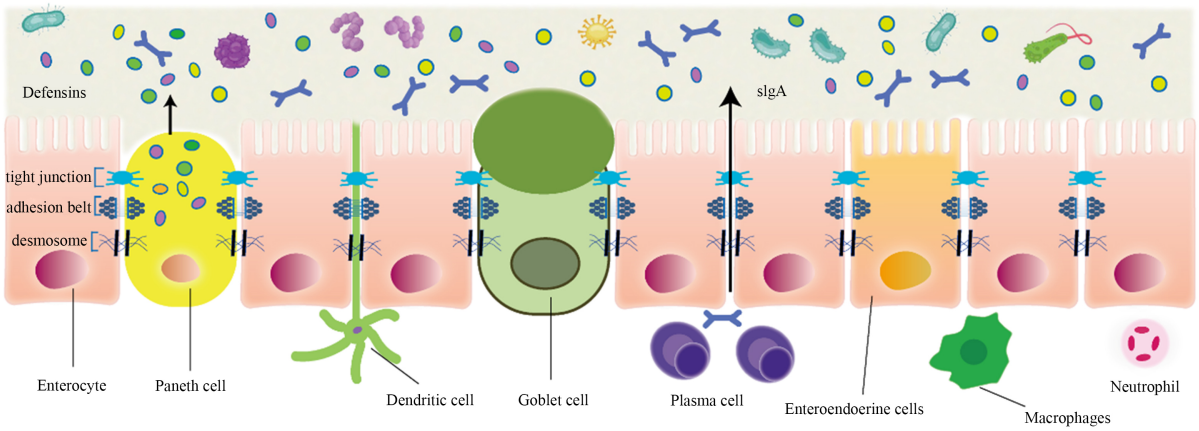


**Figure 1.** Intestinal mucosa barrier
**图 1.** 肠黏膜屏障

### 2.1. 黏液屏障

黏液屏障是外部分子进入肠腔时所遇到的第一道防御，从物理性质上看是一层黏液层，该黏液层将细菌与肠腔隔开，阻止细菌直接接触肠道上皮细胞[36]。肠道黏液主要由杯状细胞分泌的黏液蛋白 2 (Mucin-2, MUC2)组成，另外还有胃液、胆汁、消化酶、抗菌肽、脂质、细胞碎片和其他胃肠道分泌物[37]。高度糖基化的黏液蛋白，在肠道上皮上吸收水分子从而形成黏稠的凝胶型网状结构。不同肠段黏液层厚度不一，从十二指肠到大肠，黏液层逐渐增厚，小肠的主要功能是营养物质的吸收，厚厚的黏液层不利于营养物质的摄取，所以小肠的黏液层较薄。而结肠和大肠较厚，可大体分为内、外两层。靠近肠腔一

侧的外层是共生菌定居的部位，称为疏松黏液层；内层是紧密附着黏液层，以“过滤器”的形式阻碍微生物向肠上皮细胞的渗入。2 层黏液有相似的组成成分，但内层黏液更为稠密；通过蛋白水解作用，内层黏蛋白网状结构变得稀释移行为外层疏松黏液层[36] [38]。研究显示：大鼠结肠末端的黏液层每 1~2 个小时更新一次，随着黏液持续分泌，内黏液层向外黏液层移动，形成板层状结构。大鼠结肠末端内黏液层厚约 50 μm，人类的约厚 200 μm [39]。

### 2.2. 机械屏障

位于黏液层之下的，即是机械屏障，也是影响肠道粘膜的选择透过性的最重要因素[40] [41]。机械屏障指的是由两个相邻的肠道上皮细胞及其之间的细胞连接所形成的极性结构，其细胞组成包括吸收性肠细胞、杯状细胞、肠内分泌细胞、潘氏细胞和微折叠细胞[42] [43]，各种上皮细胞则通过由紧密连接和粘附连接组成的顶端连接复合体以及桥粒连接在一起[44] [45]。紧密连接是相邻的肠道上皮细胞之间最顶端的细胞间粘连[46]，紧密连接是肠道机械屏障发挥作用的主要决定因素，在调节肠道通透性以及离子和小分子在上皮表面的扩散中起着关键作用[47]。紧密连接的功能与其结构密不可分，紧密连接作为一种复合型蛋白结合体，由多种跨膜蛋白和细胞骨架连接蛋白构成，其中跨膜蛋白包括 claudin 家族、occludin 家族和和连接粘附分子 JAM，细胞骨架连接蛋白则主要为 zonula 闭锁蛋白家族(ZO-1，ZO-2 和 ZO-3) [46] [48] [49]。各种整合蛋白、跨膜蛋白从细胞内延伸到细胞间隙并彼此连接，zonula 闭锁蛋白则将各连接蛋白锚定在细胞上，从而形成紧密连接[50]。粘附连接是由钙粘蛋白连接到肌动蛋白的细胞骨架形成的细胞间连接，桥粒位于各连接复合体的最下方，是由桥粒芯胶蛋白、桥粒芯糖蛋白、桥粒斑蛋白和角蛋白丝相互作用形成的，粘附连接和桥粒一起封闭了紧密连接空余的细胞旁空间，使得相邻的肠道上皮细胞之间更加贴合，同时也是细胞间通信的场所[33] [44] [51]。

### 2.3. 免疫屏障

肠道黏膜免疫屏障主要由各类免疫细胞(如中性粒细胞、单核/巨噬细胞、树突状细胞、肥大细胞、先天淋巴样细胞、B 细胞、T 细胞等)、免疫相关蛋白(sIgA、IgE、IgG、抗菌肽等)和部分炎症细胞因子(如 IL-1、IL-18、IL-1$\beta$ 等)发挥作用[52] [53] [54]。肠道黏膜免疫屏障一般被分为三个层次，第一层主要是上皮细胞分泌的抗菌肽和潘氏细胞分泌的防御素；第二层主要由浆细胞分泌的免疫球蛋白 A (Immunoglobulin A, IgA)组成，可防止细菌易位；第三层才是相关的各类免疫细胞[55]。根据不同细胞的分布位置，这些免疫细胞可分为上皮内细胞和固有层细胞。上皮内细胞主要分布着 $\alpha/\beta$ T 细胞、$\gamma/\delta$T cells 和单核/巨噬细胞，这些上皮内淋巴细胞都表达 I 型细胞因子，可以被肠道上皮细胞释放的细胞因子激活并释放抗菌肽进入肠腔[54]。上皮内单核吞噬细胞延伸出突起，可以透过一些间隙直接接触肠腔，并将抗原肽传递给固有层树突状细胞[56] [57]。在固有层中，除淋巴细胞外，主要是 $CD4^+$T 细胞，NKT 细胞和粘膜相关固有 T 细胞，这些细胞在它们识别的微生物抗原或代谢物类型上高度特化[58]。

## 3. 肠道菌群与肠道屏障的相互作用

人体肠道中有大约 $10^{14}$ 个微生物，包含 9 个主要的菌门和约 500 种以上的微生物[59]，其基因组序列相当于人体的 150~200 倍[60]。肠道菌群并非单独存在于肠道中，肠道菌群与肠道屏障协调合作，才能维持肠道的稳态，从而发挥维持机体健康的重要作用。

### 3.1. 肠道菌群与肠道黏液屏障的相互作用

肠道菌群依附于肠道屏障而存在，正常的肠道菌群定植于肠道的黏液层中，黏液层中的分布不匀的各种消化液、抗菌肽、防御素等物质，促使菌群在各部分肠道中分布和存在方式各不相同，即占据了不

同的生态位，并形成菌膜占位性保护，正常菌群通过营养竞争和分泌抑菌素抵抗外来致病菌的生长，构成了经典的微生物屏障[61]。黏液层除了为肠道菌群提供定值的场所，还可以为肠道菌群提供营养，研究证明多形拟杆菌(Bacteroides thetaiotaomicron)、嗜粘单胞菌(A. muciniphila)、taotaomicron 拟杆菌(Bacteroides thetaotaomicron)、双歧杆菌(Bifidobacterium bifidum)、脆弱拟杆菌(Bacteroides fragilis)、耐腐瘤胃球菌(Ruminococcus gnavus)和扭力瘤胃球菌(Ruminococcus torques)等可以在能量不足的情况下降解黏液并作为能量来源[62] [63] [64]。肠道菌群对黏液屏障的形成也起着重要的作用。首先，肠道菌群是形成适当黏液层的基础，研究证明在无菌小鼠(GF 小鼠)肠道中，被黏液填充满的杯状细胞数量占全部杯状细胞的比例明显低于正常小鼠[65]，而给予无菌小鼠脂多糖(LPS)和肽聚糖刺激后，GF 小鼠的杯状细胞分泌黏液功能有所恢复[66] [67]。进一步研究发现，细菌的 LPS、鞭毛蛋白、脂磷酸(LPA)等物质会激活核因子(NF-κb)，而 NF-κb 则结合在 MUC2 的启动子上的相应结合位点，促进 MUC2 表达[68]。此外，肠道中存在一种名为阿克曼黏细菌(Akkermansia muciniphila)的菌属，该菌属是一种黏蛋白降解细菌，会分解消耗肠道的黏蛋白，当其与杯状细胞再生黏蛋白达成动态平衡时维持黏液层稳定。阿克曼黏细菌异常增殖可能导致黏液层被分解过多，从而导致肠道屏障损伤，诱发肠道炎症[69]。肠道菌群也通过产生代谢物来影响肠道黏液屏障。短链脂肪酸是肠道菌群代谢的主要产物，研究表明，厚壁菌属的成员如 Roseburia，Faecalibacterium prausnitzii，直肠真杆菌等产生的丁酸盐可以激活 M2/WNT/ERK 信号通路，提高杯状细胞 Muc2 蛋白的表达从而维持肠道黏液屏障的正常更新代谢[70]；硫酸盐还原菌属(Sulfate-Reducing Bacteria)代谢所产生的硫化物则会溶解聚合的黏液层，使黏液层变薄[71]；脆弱类杆菌产生的 BFT 毒素也可降解黏液蛋白，破坏黏液层结构[72]。

### 3.2. 肠道菌群与肠道机械屏障的相互作用

肠道机械屏障的完整性是通过肠上皮细胞和细胞间连接复合物保障的，其主要功能是限制肠腔内的致病菌毒素和抗原的渗透，当上皮细胞损伤时，机械屏障通透性大大增加，肠腔内如大分子蛋白质、致病菌可通过破损的机械屏障进入固有层，诱导肠道炎症的发生[73]。肠道菌群与肠机械屏障之间的关系十分密切，肠道菌群可直接或间接影响肠上皮细胞的发育和能量代谢。肠道菌群会影响肠隐窝干细胞向肠上皮细胞的分化，正常情况下，生理性肠上皮细胞脱落以 4~7 天为一周期[74]，在肠上皮细胞受到细菌及 LPS 侵袭损伤时，隐窝干细胞的 Wnt/β-catenin 信号通路激活，增强向肠上皮细胞的分化，使损伤的肠上皮细胞得到补充[75]。肠道菌群也通过影响细胞间链接的形成来影响肠道屏障功能。阿克曼黏细菌还会产生一种细胞外囊泡(AmEV)，可以增加闭合蛋白 ZO-1 的表达，调节肠道屏障的完整性[76]；而一些致病菌如柠檬酸杆菌可以促进机体表达 IL-22 以上调上皮紧密连接蛋白 Claudin-2 引起肠道屏障的破坏[77]。产丁酸菌代谢产生丁酸盐还可以调控与肠上皮细胞肌动蛋白相结合的突触足蛋白(Actin-Associated Protein Synaptopodin, SYNPO)表达，对维持肠道机械屏障的完整性和细胞运动至关重要[78]。

### 3.3. 肠道菌群与肠道免疫屏障的相互作用

免疫系统对肠道菌群的作用体现在免疫系统影响肠道菌群的分布，不同部分肠道内抗菌物质的不同、免疫细胞种类和数目不同，导致了抗微生物入侵的屏障的分布差异，从而影响了肠道菌群在肠内的占位[61]。尽管目前尚不清楚肠道菌群的组成如何影响肠道免疫，但已有研究表明肠道免疫系统的功能会受到某些特定菌株的影响[79]。肠道菌群会对固有免疫系统产生影响，作为联合固有免疫和特异性免疫的枢纽，树突状细胞(Dendritic Cells, DC)会受到 Prevoltella. copri 菌株的影响，Prevoltella. copri 菌产生的琥珀酸会通过 DC 细胞表面琥珀酸受体 GPR91 增强其诱导 T 细胞产生免疫应答的能力[80]；给予无菌小鼠脆弱拟杆菌会抑制自然杀伤细胞(NKT 细胞)向结肠固有层中的分布[81]；固有免疫样(Innate-Like) T 细胞亚群的

增殖也会受到多形拟杆菌(B. thetaiotaomicron)、干酪乳杆菌(Lactobacillus casei)以及阴沟杆菌(Enterobacter cloacae)的影响[82]。肠道内的菌群还会影响特异性免疫。分段丝状菌(Segmented Filamentous Bacteria, SFB)能够通过增加血清淀粉样蛋白 A (serum amyloid protein A, SAA)的表达促进 Th17 的分化和促进 IL-22 分泌来维持肠道免疫[83]，同时 SFB 还会诱导 RORγt* T 细胞在肠系膜淋巴结中的分化及其在胃肠道的不同节段的分布[84]；脆弱类杆菌的菌体成分荚膜会诱导调节性 T 细胞(regulatory T cells, Treg)细胞产生 IL-10 [85] [86]，梭菌属也被证明可促进 Treg 的增殖[87]，从而增强肠道屏障，另外有研究显示肠道菌群的代谢产生的次级胆汁酸可通过调节促进外周调节性 T 细胞(Peripheral Regulatory T Cells, pTreg)调节宿主免疫反应[88]。

## 4. 肠道菌群与肠道屏障互作对 NAFLD 的影响

### 4.1. 肠道菌群失调在 NAFLD 发展中的作用

肠道内的各种菌群在正常情况下以一定比例共存，维持着肠道微生态稳态，参与机体代谢和免疫等生理过程。临床研究证明，与健康者相比，NAFLD 患者中存在肠道菌群组分和种属的失调，提示肠道菌群紊乱可能参与 NAFLD 的发病过程[89]。研究显示，将脂肪肝病人的肠道菌群移植给正常无菌小鼠后可引发脂肪肝而将饮食减肥后肥胖儿童的肠道菌群移植给正常无菌小鼠后则无明显变化[90] [91]，为肠道菌群引发脂肪肝的因果性和潜在机制提供了有力证据。但是，关于 NAFLD 患者肠道菌群的具体丰度和组成的研究结果却不尽相同，目前所能确认的最一致的变化就是在 NAFLD 患者中变形菌门(Proteobacteria)、肠杆菌科(Enterobacteriaceae)、埃氏菌(Escherichia)和多氏菌(doreia)的相对丰度增加，而瘤胃球菌科(ruminococcaceae)、普拉梭菌(Faecalibacterium Prausnitzii)、粪球菌属(Coprococcus)、优杆菌属(Eubacterium)、普雷沃氏菌属(Prevotella)和 Anaerospacter 的相对丰度减少[92] [93] [94] [95]。在动物试验中，比较统一的是 NAFLD 小鼠中厚壁菌门的丰度显著增加，同时拟杆菌门减少，厚壁菌门/拟杆菌门比例升高[96]。革兰氏阴性菌的比例增加也是 NAFLD 小鼠的典型肠道菌群特征，当革兰氏阴性菌死亡时会释放大量内毒素(LPS)，LPS 与内毒素结合蛋白(Endotoxin Binding Protein, LBS)结合后，通过 Toll 样受体 4 (TLR4)转导，激活免疫答应，释放 IL-1，IL-6，TNF-$\alpha$ 等促炎症因子，导致慢性低度炎症和肥胖[97]。

### 4.2. 肠道菌群代谢产物失调在 NAFLD 中发挥的作用

肠道菌群的代谢产物如短链脂肪酸(Short-Chain Fatty Acid, SCFAs)、三甲胺氧化物(Trimethylamine N-Oxide, TMAO)、胆酸(Cholic Acids, BAs)等可以直接或间接地影响肠道屏障功能和营养吸收，并与肠道免疫系统相互作用[98]。微生物代谢产物被吸收到血管中后通过门静脉进入肝脏，并与相关受体结合，引发毒性、炎症和基因表达反应的复杂相互作用，最终调控 NAFLD 的进展。

SCFA 是肠道菌群最丰富的代谢产物，主要包括乙酸酯、丙酸酯和丁酸酯，研究证明，与非肥胖健康个体相比，非肥胖 NAFLD 患者的粪便中 SCFAs 明显减少。SCFAs 对 NAFLD 的缓解作用在人类研究和动物研究中都得到了很好的证实。在人类研究中，结肠靶向补充丙酸酯显著降低超重成人肝细胞内脂质含量；在小鼠模型中，丁酸钠可以抑制西方饮食诱导的肝脏脂肪变性和炎症[99]；醋酸钠对尼古丁诱导的过量肝脏脂肪变性也有着良好保护作用[100]。SCFAs 通过多种方式对 NAFLD 产生调节作用：乙酸盐经门静脉进入肝脏，抑制过氧化物酶体增殖物激活受体 $\alpha$ (PPAR $\alpha$)、和 ERK1/2 信号通路来促进脂肪分解、脂肪酸氧化并抑制脂肪酸合成从而抑制肝脏脂质积累[101]；丙酸盐和丁酸盐诱导激活 amp 激活蛋白激酶(AMPK)活化，降低固醇调节元件结合转录因子 1c (SREBP-1c)的活性来抑制脂肪生成基因的表达[102]，进而通过影响糖和脂代谢来调节能量稳态，还抑制肝脏巨噬细胞的激活，从而缓解肝脏炎症症状[103]；此外，SCFAs 还在表观遗传水平上通过修饰 DNA 甲基化来影响脂联素和抵抗素的转录表达来抑

制 NAFLD 的发展[104]。尽管很多研究证明 SCFAs 对 NAFLD 有良好的作用，但 SCFAs 的其他作用可能会促进 NAFLD 发展。研究发现，高脂饮食的小鼠体内的乙酸盐比正常小鼠要高很多，且这表明能量获取的增加导致脂肪的形成[105]。乙酸进入血液后随血液循环进入肝脏，为周围组织提供能量，并被肝脏用作产生新脂质的底物，产生甘油三酯，造成肝脏脂质蓄积[106]。此外，SCFAs 中的乙酸盐被肠道吸收入血后也随着血流进入大脑，激活副交感神经系统，副交感神经进一步激活胃的内分泌细胞，使饥饿激素(ghrelin)释放增加，饥饿激素大量产生引起机体产生空腹感进而促进饮食[107]。

TMAO 主要来源于肠道，肠道菌群将膳食营养物质如胆碱、甜菜碱和左旋肉碱等等转化为 TMA，TMA 通过肠黏膜被吸收到血液中并汇入肝脏，在肝黄素单加氧酶(FMOs)的作用下转化为 TMAO [108]。多项研究表明 TMAO 水平与肥胖、动脉粥样硬化和 NAFLD 等代谢相关疾病的发展密切相关。在一项以医院为基础的病例对照研究中，Barrea 等人对 330 名受试者进行临床研究，发现高循环 TMAO 水平与肥胖和 MAFLD 的严重程度有关[109]；一项荟萃分析显示，血液循环中的氧化三甲胺水平与患者肥胖程度呈明显依赖关系[110]；在动物实验中，研究表明 TMAO 增加肝脏甘油三酯积累，损害肝功能[111]。然而，TMAO 与 NAFLD 发生和发展之间关系的确切机制尚不清楚，目前认为 TMAO 会增加胰岛素抵抗，诱发糖代谢紊乱，加重脂肪组织的炎症[112]。脂肪组织分泌多种促炎分子导致巨噬细胞活化，然后诱导肝脏产生 c 反应蛋白(CRP)并启动促炎信号通路，脂肪组织来源的巨噬细胞被认为是 NASH 发展的关键参与者[113]。此外，氧化三甲胺通过肝法内甾体 X 受体(FXR)信号通路介导 BAs 合成并改变肝脏 BAs 组成，MAO 通过阻断胆汁酸激活的法脂类 X 受体(FXR)信号通路而加剧肝脂肪变性[114]。

次级胆汁酸同样是肠道菌群代谢的特殊产物，多项研究证明胆汁酸的改变会影响 NAFLD 的发展。次级胆汁酸可以激活肠道胆汁酸受体，诱导成纤维细胞因子 FGF15/19 增加，进而抑制 CYP7A1 的活性，从而调节胆固醇代谢，减少肝脏脂质积累[115]；次级胆汁酸还是胆汁酸受体 TGR5 的强效激动剂，胆汁酸受体 TGR5 被激活后通过促进 GLP-1 的分泌来改善调节血糖，改善胰岛素敏感性[116]。目前胆汁酸和胆汁酸受体调节药物被视为治疗 NAFLD 的有效靶点之一。

## 5. 展望

“肠道菌群－肠－肝轴”的改变与 NAFLD 的发生发展密切相关。肠道菌群影响宿主的代谢、能量吸收及肠道内分泌等功能，从而肝脏的胆汁合成、脂肪代谢和能量利用。肠黏膜屏障的异常能够引起肠道通透性升高，致使肠腔内的病原微生物及其代谢产物易位，通过血液进入门静脉系统，释放出大量炎症因子，进一步加重肠黏膜屏障的损伤，更易导致肠道细菌移位及内毒素的吸收，种种原因形成恶性循环，加重肝脏炎症，故基于“肝病肠治”的方式治疗 NAFLD 方法成为可能。通过调节肠道菌群种类和丰度、改善肠道粘膜屏障功能和调节肠道菌群代谢产物信号等，有望成为治疗 NAFLD 的新靶点和新途径。

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## 参考文献

[1] Chalasani, N., Younossi, Z., Lavine, J.E., *et al.* (2018) The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology*, **1**, 328-357. https://doi.org/10.1002/hep.29367

[2] Powell, E.E., Wong, V.W. and Rinella, M. (2021) Non-Alcoholic Fatty Liver Disease. *The Lancet*, **397**, 2212-2224. https://doi.org/10.1016/S0140-6736(20)32511-3

[3] Zhou, F., Zhou, J., Wang, W., *et al*. (2019) Unexpected Rapid Increase in the Burden of NAFLD in China from 2008 to 2018: A Systematic Review and Meta-Analysis. *Hepatology*, **70**, 1119-1133. https://doi.org/10.1002/hep.30702

[4] Lindenmeyer, C.C. and McCullough, A.J. (2018) The Natural History of Nonalcoholic Fatty Liver Disease—An Evolving View. *Clinics in Liver Disease*, **22**, 11-21. https://doi.org/10.1016/j.cld.2017.08.003

[5] Riazi, K., Azhari, H., Charette, J.H., *et al*. (2022) The Prevalence and Incidence of NAFLD Worldwide: A Systematic Review and Meta-Analysis. *The Lancet Gastroenterology & Hepatology*, **7**, 851-861. https://doi.org/10.1016/S2468-1253(22)00165-0

[6] Fleming, K.A., Morton, J.A., Barbatis, C., *et al*. (1981) Mallory Bodies in Alcoholic and Non-Alcoholic Liver Disease Contain a Commonantigenic Determinant. *Gut*, **22**, 341-344. https://doi.org/10.1136/gut.22.5.341

[7] Day, C.P. and James, O.F.W. (1998) Steatohepatitis: A Tale of Two "Hits"? *Gastroenterology*, **114**, 842-845. https://doi.org/10.1016/S0016-5085(98)70599-2

[8] Enooku, K., Kondo, M., Fujiwara, N., *et al*. (2018) Hepatic IRS1 and ß-Catenin Expression Is Associated with Histological Progressionand Overt Diabetes Emergence in NAFLD Patients. *Journal of Gastroenterology*, **53**, 1261-1275. https://doi.org/10.1007/s00535-018-1472-0

[9] Softic, S., Boucher, J., Solheim, M.H., *et al*. (2016) Lipodystrophy Due to Adipose Tissue-Specific Insulin Receptor Knockout Results in Progressive NAFLD. *Diabetes*, **65**, 2187-2200. https://doi.org/10.2337/db16-0213

[10] Neuschwander-Tetri, B.A. (2010) Hepatic Lipotoxicity and the Pathogenesis of Nonalcoholic Steatohepatitis: The Central Role of Nontriglyceride Fatty Acid Metabolites. *Hepatology*, **52**, 774-788. https://doi.org/10.1002/hep.23719

[11] Lambert, J.E., Ramos Roman, M.A., Browning, J.D. and Parks, E.J. (2014) Increased De Novo Lipogenesis Is a Distinct Characteristic of Individuals with Nonalcoholic Fatty Liver Disease. *Gastroenterology*, **146**, 726-735. https://doi.org/10.1053/j.gastro.2013.11.049

[12] Jin, C.J., Engstler, A.J., Ziegenhardt, D., *et al*. (2017) Loss of Lipopolysaccharide-Binding Protein Attenuates the Development of Diet-Induced Non-Alcoholic Fatty Liver Disease in Mice. *Journal of Gastroenterology and Hepatology*, **32**, 708-715. https://doi.org/10.1111/jgh.13488

[13] Carpino, G., Del, B.M., Pastori, D., *et al*. (2020) Increased Liver Localization of Lipopolysaccharides in Human and Experimental NAFLD. *Hepatology*, **72**, 470-485. https://doi.org/10.1002/hep.31056

[14] Schuster, S., Cabrera, D., Arrese, M., *et al*. (2018) Triggering and Resolution of Inflammation in NASH. *Nature Reviews Gastroenterology & Hepatology*, **15**, 349-364. https://doi.org/10.1038/s41575-018-0009-6

[15] Davis, R.P., Surewaard, B.G.J., Turk, M., *et al*. (2019) Optimization of *in vivo* Imaging Provides a First Look at Mouse Model of Non-Alcoholic Fatty Liver Disease (NAFLD) Using Intravital Microscopy. *Frontiers in Immunology*, **10**, Article 2988. https://doi.org/10.3389/fimmu.2019.02988

[16] Saviano, A., Henderson, N.C. and Baumert, T.F. (2020) Single-Cell Genomics and Spatial Transcriptomics: Discovery of Novel Cell States and Cellular Interactions in Liver Physiology and Disease Biology. *Journal of Hepatology*, **73**, 1219-1230. https://doi.org/10.1016/j.jhep.2020.06.004

[17] Wang, W., Zhao, J., Gui, W., *et al*. (2018) Tauroursodeoxycholic Acid Inhibits Intestinal Inflammation and Barrier Disruption in Mice with Non-Alcoholic Fatty Liver Disease. *British Journal of Pharmacology*, **175**, 469-484. https://doi.org/10.1111/bph.14095

[18] Buzzetti, E., Pinzani, M. and Tsochatzis, E.A. (2016) The Multiple-Hit Pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD). *Metabolism*, **65**, 1038-1048. https://doi.org/10.1016/j.metabol.2015.12.012

[19] Eslam, M., Sanyal, A.J., George, J., *et al*. (2020) MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology*, **158**, 1999-2014. https://doi.org/10.1053/j.gastro.2019.11.312

[20] Seo, Y.S. and Shah, V.H. (2012) The Role of Gut-Liver Axis in the Pathogenesis of Liver Cirrhosis and Portal Hypertension. *Clinical and Molecular Hepatology*, **18**, 337-346. https://doi.org/10.3350/cmh.2012.18.4.337

[21] Kouichi, M. and Hirohide, O. (2014) Role of Gut Microbiota and Toll-Like Receptors in Nonalcoholic Fatty Liver Disease. *World Journal of Gastroenterology*, **20**, 7381-7391. https://doi.org/10.3748/wjg.v20.i23.7381

[22] 蒋贤哲, 张博彦, 罗海玲, 等. 肠肝轴在动物营养代谢和免疫中的作用[J]. 生物技术通报, 2022, 38(7): 128-135.

[23] Fujisaka, S., Watanabe, Y. and Tobe, K. (2022) The Gut Microbiome: A Core Regulator of Metabolism. *Journal of Endocrinology*, **256**, e220111. https://doi.org/10.1530/JOE-22-0111

[24] Donaldson, G.P., Ladinsky, M.S., Yu, K.B., *et al*. (2018) Gut Microbiota Utilize Immunoglobulin A for Mucosal Colonization. *Science*, **360**, 795-800. https://doi.org/10.1126/science.aaq0926

[25] Yajima, M., Karaki, S.I., Tsuruta, T., *et al*. (2016) Diversity of the Intestinal Microbiota Differently Affects Non-Neuronal and Atropine-Sensitive Ileal Contractile Responses to Short-Chain Fatty Acids Inmice. *Biomedical Research*, **37**, 319-328. https://doi.org/10.2220/biomedres.37.319

[26] Parada, V.D., De la Fuente, M.K., Landskron, G., *et al*. (2019) Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Frontiers in Immunology*, **10**, Article No. 277. https://doi.org/10.3389/fimmu.2019.01486

[27] Agus, A., Planchais, J. and Sokol, H. (2018) Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. *Cell Host Microbe*, **23**, 716-724. https://doi.org/10.1016/j.chom.2018.05.003

[28] De Vadder, F., Grasset, E., Manneras, H.L., *et al*. (2018) Gut Microbiota Regulates Maturation of the Adult Enteric Nervous System via Enteric Serotonin Networks. *Proceedings of the National Academy of Sciences of the United States of America*, **115**, 6458-6463. https://doi.org/10.1073/pnas.1720017115

[29] Fuchs, C., Claudel, T. and Trauner, M. (2013) Bile Acid-Mediated Control of Liver Triglycerides. *Seminars in Liver Disease*, **33**, 330-342. https://doi.org/10.1055/s-0033-1358520

[30] De Fabiani, E., Mitro, N., Gilardi, F., *et al*. (2003) Coordinated Control of Cholesterol Catabolism to Bile Acids and of Gluconeogenesis via a Novel Mechanism of Transcription Regulation Linked to the Fasted-to-Fed Cycle. *Journal of Biological Chemistry*, **278**, 39124-39132. https://doi.org/10.1074/jbc.M305079200

[31] Jiao, N., Baker, S.S., Chapa-Rodriguez, A., *et al*. (2018) Suppressed Hepatic Bile Acid Signalling Despite Elevated Production of Primaryand Secondary Bile Acids in NAFLD. *Gut*, **67**, 1881-1891. https://doi.org/10.1136/gutjnl-2017-314307

[32] Plaza-Díaz, J., Solís-Urra, P., Rodríguez-Rodríguez, F., *et al*. (2020) The Gut Barrier, Intestinal Microbiota, and Liver Disease: Molecular Mechanisms and Strategies to Manage. *International Journal of Molecular Sciences*, **21**, Article 8351. https://doi.org/10.3390/ijms21218351

[33] Camilleri, M., Madsen, K., Spiller, R., Van Meerveld, B.G. and Vern, G.N. (2012) Intestinal Barrier Function in Health and Gastrointestinal Disease. *Neurogastroenterology & Motility*, **24**, 503-512. https://doi.org/10.1111/j.1365-2982.2012.01921.x

[34] Vancamelbeke, M. and Vermeire, S. (2017) The Intestinal Barrier: A Fundamental Role in Health and Disease. *Expert Review of Gastroenterology & Hepatology*, **11**, 821-834. https://doi.org/10.1080/17474124.2017.1343143

[35] Nalle, S.C. and Turner, J.R. (2015) Intestinal Barrier Loss as a Critical Pathogenic Link between Inflammatory Bowel Disease and Graft-versus-Host Disease. *Mucosal Immunology*, **8**, 720-730. https://doi.org/10.1038/mi.2015.40

[36] Pelaseyed, T., Bergström, J.H., Gustafsson, J.K., *et al*. (2014) The Mucus and Mucins of the Goblet Cells and Enterocytes Provide the First Defense Line of the Gastrointestinal Tract and Interact with the Immune System. *Immunological Reviews*, **260**, 8-20. https://doi.org/10.1111/imr.12182

[37] Lievin-Le, M.V. and Servin, A.L. (2006) The Front Line of Enteric Host Defense against Unwelcome Intrusion of Harmful Microorganisms: Mucins, Antimicrobial Peptides, and Microbiota. *Clinical Microbiology Reviews*, **19**, 315-337. https://doi.org/10.1128/CMR.19.2.315-337.2006

[38] Ermund, A., Schütte, A., Johansson, M.E.V., Gustafsson, J.K. and Hansson, G.C. (2013) Studies of Mucus in Mouse Stomach, Small Intestine, and Colon. I. Gastrointestinal Mucus Layers Have Different Properties Depending on Location as well as over the Peyer's Patches. *American Journal of Physiology*: *Gastrointestinal and Liver Physiology*, **305**, G341-G347. https://doi.org/10.1152/ajpgi.00046.2013

[39] Gunnar, C. and Hansson, M.E.J. (2010) The Inner of the Two Muc2 Mucin-Dependent Mucus Layers in Colon Is Devoid of Bacteria. *Gut Microbes*, **1**, 51-54. https://doi.org/10.4161/gmic.1.1.10470

[40] Salim, S.Y. and Soderholm, J.D. (2011) Importance of Disrupted Intestinal Barrier in Inflammatory Bowel Diseases. *Inflammatory Bowel Diseases*, **17**, 362-381. https://doi.org/10.1002/ibd.21403

[41] Turner, J.R. (2009) Intestinal Mucosal Barrier Function in Health and Disease. *Nature Reviews Immunology*, **9**, 799-809. https://doi.org/10.1038/nri2653

[42] Kurashima, Y. and Kiyono, H. (2017) Mucosal Ecological Network of Epithelium and Immune Cells for Gut Homeostasis and Tissue Healing. *Annual Review of Immunology*, **35**, 119-147. https://doi.org/10.1146/annurev-immunol-051116-052424

[43] Suzuki, T. (2013) Regulation of Intestinal Epithelial Permeability by Tight Junctions. *Cellular and Molecular Life Sciences*, **70**, 631-659. https://doi.org/10.1007/s00018-012-1070-x

[44] Nekrasova, O. and Green, K.J. (2013) Desmosome Assembly and Dynamics. *Trends in Cell Biology*, **23**, 537-546. https://doi.org/10.1016/j.tcb.2013.06.004

[45] Groschwitz, K.R. and Hogan, S.P. (2009) Intestinal Barrier Function: Molecular Regulation and Disease Pathogenesis. *Journal of Allergy and Clinical Immunology*, **124**, 3-20. https://doi.org/10.1016/j.jaci.2009.05.038

[46] Furuse, M., Fujita, K., Hiiragi, T., Fujimoto, K. and Tsukita, S. (1998) Claudin-1 and -2: Novel Integral Membrane Proteins Localizing at Tight Junctions with No Sequence Similarity to Occludin. *Journal of Cell Biology*, **141**, 1539-1550. https://doi.org/10.1083/jcb.141.7.1539

[47] Berkes, J., Viswanathan, V.K., Savkovic, S.D. and Hecht, G. (2003) Intestinal Epithelial Responses to Enteric Pathogens: Effects on the Tight Junction Barrier, Ion Transport, and Inflammation. *Gut*, **52**, 439-451. https://doi.org/10.1136/gut.52.3.439

[48] Furuse, M., Hirase, T., Itoh, M., *et al*. (1993) Occludin: A Novel Integral Membrane Protein Localizing at Tight Junctions. *The Journal of Cell Biology*, **123**, 1777-1788. https://doi.org/10.1083/jcb.123.6.1777

[49] Cereijido, M., Contreras, R.G., Flores-Benítez, D., *et al*. (2007) New Diseases Derived or Associated with the Tight Junction. *Archives of Medical Research*, **38**, 465-478. https://doi.org/10.1016/j.arcmed.2007.02.003

[50] Lynn, K.S., Peterson, R.J. and Koval, M. (2020) Ruffles and Spikes: Control of Tight Junction Morphology and Permeability by Claudins. *Biochimica et Biophysica Acta* (*BBA*)—*Biomembranes*, **1862**, Article ID: 183339. https://doi.org/10.1016/j.bbamem.2020.183339

[51] Hermiston, M.L. and Gordon, J.I. (1995) *In vivo* Analysis of Cadherin Function in the Mouse Intestinal Epithelium: Essential Roles in Adhesion, Maintenance of Differentiation, and Regulation of Programmed Cell Death. *The Journal of Cell Biology*, **129**, 489-506. https://doi.org/10.1083/jcb.129.2.489

[52] Chieppa, M., Rescigno, M., Huang. A.Y. and Germain, R.N. (2006) Dynamic Imaging of Dendritic Cell Extension into the Small Bowel Lumen Inresponse to Epithelial Cell TLR Engagement. *Journal of Experimental Medicine*, **203**, 2841-2852. https://doi.org/10.1084/jem.20061884

[53] Rescigno, M., Urbano, M., Valzasina, B., *et al*. (2001) Dendritic Cells Express Tight Junction Proteins and Penetrate Gut Epithelial Monolayers to Sample Bacteria. *Nature Immunology*, **2**, 361-367. https://doi.org/10.1038/86373

[54] McDonald, B.D., Jabri, B. and Bendelac, A. (2018) Diverse Developmental Pathways of Intestinal Intraepithelial Lymphocytes. *Nature Reviews Immunology*, **18**, 514-525. https://doi.org/10.1038/s41577-018-0013-7

[55] Burcelin, R. (2016) Gut Microbiota and Immune Crosstalk in Metabolic Disease. *Molecular Metabolism*, **5**, 771-781. https://doi.org/10.1016/j.molmet.2016.05.016

[56] Mazzini, E., Massimiliano, L., Penna, G. and Rescigno, M. (2014) Oral Tolerance Can Be Established via Gap Junction Transfer of Fed Antigens from $CX3CR1^+$ Macrophages to $CD103^+$ Dendritic Cells. *Immunity*, **40**, 248-261. https://doi.org/10.1016/j.immuni.2013.12.012

[57] Niess, J.H., Brand, S., Gu, X., *et al*. (2005) $CX_3CR1$-Mediated Dendritic Cell Access to the Intestinal Lumen and Bacterial Clearance. *Science*, **307**, 254-258. https://doi.org/10.1126/science.1102901

[58] Corbett, A.J., Eckle, S.B., Birkinshaw, R.W., *et al*. (2014) T-Cell Activation by Transitory Neo-Antigens Derived from Distinct Microbial Pathways. *Nature*, **509**, 361-365. https://doi.org/10.1038/nature13160

[59] Gomes, A.C., Hoffmann, C. and Mota, J.F. (2018) The Human Gut Microbiota: Metabolism and Perspective in Obesity. *Gut Microbes*, **9**, 308-325. https://doi.org/10.1080/19490976.2018.1465157

[60] Qin, J., Li, R., Raes, J., *et al*. (2010) A Human Gut Microbial Gene Catalogue Established by Metagenomic Sequencing. *Nature*, **464**, 59-65. https://doi.org/10.1038/nature08821

[61] Lee, M. and Chang, E.B. (2021) Inflammatory Bowel Diseases (IBD) and the Microbiome-Searching the Crime Scenefor Clues. *Gastroenterology*, **160**, 524-537. https://doi.org/10.1053/j.gastro.2020.09.056

[62] Luis, A.S., Jin, C., Pereira, G.V., *et al*. (2021) A Single Sulfatase Is Required to Access Colonic Mucin by a Gut Bacterium. *Nature*, **598**, 332-337. https://doi.org/10.1038/s41586-021-03967-5

[63] Ouwerkerk, J.P., de Vos, W.M. and Belzer, C. (2013) Glycobiome: Bacteria and Mucus at the Epithelial Interface. *Best Practice & Research Clinical Gastroenterology*, **27**, 25-38. https://doi.org/10.1016/j.bpg.2013.03.001

[64] Birchenough, G., Schroeder, B.O., Backhed, F. and Hansson, G.C. (2019) Dietary Destabilisation of the Balance between the Microbiota and the Colonicmucus Barrier. *Gut Microbes*, **10**, 246-250. https://doi.org/10.1080/19490976.2018.1513765

[65] Schütte, A., Ermund, A., Becker-Pauly, C., *et al*. (2014) Microbial-Induced meprin $\beta$ Cleavage in MUC2 Mucin and a Functional CFTR Channel Are Required to Release Anchored Small Intestinal Mucus. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, 12396-12401. https://doi.org/10.1073/pnas.1407597111

[66] Rodriguez-Pineiro, A.M. and Johansson, M.E. (2015) The Colonic Mucus Protection Depends on the Microbiota. *Gut Microbes*, **6**, 326-330. https://doi.org/10.1080/19490976.2015.1086057

[67] Jakobsson, H.E., Rodriguez-Pineiro, A.M., Schutte, A., *et al*. (2015) The Composition of the Gut Microbiota Shapes the Colon Mucus Barrier. *EMBO Reports*, **16**, 164-177. https://doi.org/10.15252/embr.201439263

[68] Tashiro, M., Iwata, A., Yamauchi, M., *et al*. (2017) The N-Terminal Region of Serum Amyloid A3 Protein Activates NF-$\kappa$B and up-Regulates MUC2 Mucin mRNA Expression in Mouse Colonic Epithelial Cells. *PLOS ONE*, **12**, e181796. https://doi.org/10.1371/journal.pone.0181796

[69] Cheng, D. and Xie, M.Z. (2021) A Review of a Potential and Promising Probiotic Candidate—Akkermansia mucini-

phila. *Journal of Applied Microbiology*, **130**, 1813-1822. https://doi.org/10.1111/jam.14911

[70] Liang, L., Liu, L., Zhou, W., *et al*. (2022) Gut Microbiota-Derived Butyrate Regulates Gut Mucus Barrier Repair by Activating the Macrophage/WNT/ERK Signaling Pathway. *Clinical Science*, **136**, 291-307. https://doi.org/10.1042/CS20210778

[71] Ijssennagger, N., Belzer, C., Hooiveld, G.J., *et al*. (2015) Gut Microbiota Facilitates Dietary Heme-Induced Epithelial Hyperproliferation by Opening the Mucus Barrier in Colon. *Proceedings of the National Academy of Sciences of the United States of America*, **112**, 10038-10043. https://doi.org/10.1073/pnas.1507645112

[72] Rhee, K.J., Wu, S., Wu, X., *et al*. (2009) Induction of Persistent Colitis by a Human Commensal, Enterotoxigenic Bacteroides Fragilis, in Wild-Type C57BL/6 Mice. *Infection and Immunity*, **77**, 1708-1718. https://doi.org/10.1128/IAI.00814-08

[73] Odenwald, M.A. and Turner, J.R. (2017) The Intestinal Epithelial Barrier: A Therapeutic Target? *Nature Reviews Gastroenterology & Hepatology*, **14**, 9-21. https://doi.org/10.1038/nrgastro.2016.169

[74] Martinez-Sanchez, L., Ngo, P.A., Pradhan, R., *et al*. (2023) Epithelial RAC1-Dependent Cytoskeleton Dynamics Controls Cell Mechanics, Cell Shedding and Barrier Integrity in Intestinal Inflammation. *Gut*, **72**, 275-294. https://doi.org/10.1136/gutjnl-2021-325520

[75] Zhou, J., Lin, H., Wang, Z., *et al*. (2020) Zinc L-Aspartate Enhances Intestinal Stem Cell Activity to Protect the Integrity of the Intestinal Mucosa against Deoxynivalenol through Activation of the Wnt/*β*-Catenin Signaling Pathway. *Environmental Pollution*, **262**, Article ID: 114290. https://doi.org/10.1016/j.envpol.2020.114290

[76] Hagi, T. and Belzer, C. (2021) The Interaction of *Akkermansia muciniphila* with Host-Derived Substances, Bacteria and Diets. *Applied Microbiology and Biotechnology*, **105**, 4833-4841. https://doi.org/10.1007/s00253-021-11362-3

[77] Tsai, P., Zhang, B., He, W., *et al*. (2017) IL-22 Upregulates Epithelial Claudin-2 to Drive Diarrhea and Enteric Pathogen Clearance. *Cell Host & Microbe*, **21**, 671-681.E4. https://doi.org/10.1016/j.chom.2017.05.009

[78] Wang, R.X., Lee, J.S., Campbell, E.L. and Colgan, S.P. (2020) Microbiota-Derived Butyrate Dynamically Regulates Intestinal Homeostasis through Regulation of Actin-Associated Protein Synaptopodin. *Proceedings of the National Academy of Sciences of the United States of America*, **117**, 11648-11657. https://doi.org/10.1073/pnas.1917597117

[79] D'Alessandro, G., Antonangeli, F., Marrocco, F., *et al*. (2020) Gut Microbiota Alterations Affect Glioma Growth and Innate Immune Cells Involved in Tumor Immunosurveillance in Mice. *European Journal of Immunology*, **50**, 705-711. https://doi.org/10.1002/eji.201948354

[80] Rubic, T., Lametschwandtner, G., Jost, S., *et al*. (2008) Triggering the Succinate Receptor GPR91 on Dendritic Cells Enhances Immunity. *Nature Immunology*, **9**, 1261-1269. https://doi.org/10.1038/ni.1657

[81] Olszak, T., An, D., Zeissig, S., *et al*. (2012) Microbial Exposure during Early Life Has Persistent Effects on Natural Killer T Cell Function. *Science*, **336**, 489-493. https://doi.org/10.1126/science.1219328

[82] Robertson, S.J., Goethel, A., Girardin, S.E. and Philpott, D.J. (2018) Innate Immune Influences on the Gut Microbiome: Lessons from Mouse Models. *Trends in Immunology*, **39**, 992-1004. https://doi.org/10.1016/j.it.2018.10.004

[83] Ivanov, I.I., Atarashi, K., Manel, N., *et al*. (2009) Induction of Intestinal Th17 Cells by Segmented Filamentous Bacteria. *Cell*, **139**, 485-498. https://doi.org/10.1016/j.cell.2009.09.033

[84] Sano, T., Huang, W., Hall, J.A., *et al*. (2015) An IL-23R/IL-22 Circuit Regulates Epithelial Serum Amyloid A to Promote Local Effector Th17 Responses. *Cell*, **163**, 381-393. https://doi.org/10.1016/j.cell.2015.08.061

[85] Levy, M., Kolodziejczyk, A.A., Thaiss, C.A. and Elinav, E. (2017) Dysbiosis and the Immune System. *Nature Reviews Immunology*, **17**, 219-232. https://doi.org/10.1038/nri.2017.7

[86] Pal, S., Saini, A.K., Kaushal, A., *et al*. (2022) The Colloquy between Microbiota and the Immune System in Colon Cancer: Repercussions on the Cancer Therapy. *Current Pharmaceutical Design*, **28**, 3478-3485. https://doi.org/10.2174/1381612829666221122115906

[87] Atarashi, K., Tanoue, T., Shima, T., *et al*. (2011) Induction of Colonic Regulatory T Cells by Indigenous Clostridium Species. *Science*, **331**, 337-341. https://doi.org/10.1126/science.1198469

[88] Campbell, C., McKenney, P.T., Konstantinovsky, D., *et al*. (2020) Bacterial Metabolism of Bile Acids Promotes Generation of Peripheral Regulatory T Cells. *Nature*, **581**, 475-479. https://doi.org/10.1038/s41586-020-2193-0

[89] Safari, Z. and Gérard, P. (2019) The Links between the Gut Microbiome and Non-Alcoholic Fatty Liver Disease (NAFLD). *Cellular and Molecular Life Sciences*, **76**, 1541-1558. https://doi.org/10.1007/s00018-019-03011-w

[90] Hoyles, L., Fernández-Real, J., Federici, M., *et al*. (2018) Molecular Phenomics and Metagenomics of Hepatic Steatosis in Non-Diabetic Obese Women. *Nature Medicine*, **24**, 1070-1080. https://doi.org/10.1038/s41591-018-0061-3

[91] Wang, R., Li, H., Yang, X., *et al*. (2018) Genetically Obese Human Gut Microbiota Induces Liver Steatosis in Germ-Free MiceFed on Normal Diet. *Frontiers in Microbiology*, **9**, Article 1602.

https://doi.org/10.3389/fmicb.2018.01602

[92] Del, C.F., Nobili, V., Vernocchi, P., *et al*. (2017) Gut Microbiota Profiling of Pediatric Nonalcoholic Fatty Liver Disease and Obesepatients Unveiled by an Integrated Meta-Omics-Based Approach. *Hepatology*, **65**, 451-464. https://doi.org/10.1002/hep.28572

[93] Raman, M., Ahmed, I., Gillevet, P.M., *et al*. (2013) Fecal Microbiome and Volatile Organic Compound Metabolome in Obese Humans with Nonalcoholic Fatty Liver Disease. *Clinical Gastroenterology and Hepatology*, **11**, 868-875. https://doi.org/10.1016/j.cgh.2013.02.015

[94] Zhu, L., Baker, S.S., Gill, C., *et al*. (2013) Characterization of Gut Microbiomes in Nonalcoholic Steatohepatitis (NASH) Patients: A Connection between Endogenous Alcohol and NASH. *Hepatology*, **57**, 601-609. https://doi.org/10.1002/hep.26093

[95] Aron-Wisnewsky, J., Vigliotti, C., Witjes, J., *et al*. (2020) Gut Microbiota and Human NAFLD: Disentangling Microbial Signatures from Metabolic Disorders. *Nature Reviews Gastroenterology & Hepatology*, **17**, 279-297. https://doi.org/10.1038/s41575-020-0269-9

[96] Mouzaki, M., Comelli, E.M., Arendt, B.M., *et al*. (2013) Intestinal Microbiota in Patients with Nonalcoholic Fatty Liver Disease. *Hepatology*, **58**, 120-127. https://doi.org/10.1002/hep.26319

[97] Chassaing, B., Ley, R.E. and Gewirtz, A.T. (2014) Intestinal Epithelial Cell Toll-like Receptor 5 Regulates the Intestinal Microbiota to Prevent Low-Grade Inflammation and Metabolic Syndrome in Mice. *Gastroenterology*, **147**, 1363-1377. https://doi.org/10.1053/j.gastro.2014.08.033

[98] Chu, H., Duan, Y., Yang, L. and Schnabl, B. (2019) Small Metabolites, Possible Big Changes: A Microbiota-Centered View of Non-Alcoholic Fatty Liver Disease. *Gut*, **68**, 359-370. https://doi.org/10.1136/gutjnl-2018-316307

[99] Zhao, Z., Wang, Z., Zhou, D., *et al*. (2021) Sodium Butyrate Supplementation Inhibits Hepatic Steatosis by Stimulating Liver Kinase B1 and Insulin-Induced Gene. *Cellular and Molecular Gastroenterology and Hepatology*, **12**, 857-871. https://doi.org/10.1016/j.jcmgh.2021.05.006

[100] Dangana, E.O., Omolekulo, T.E., Areola, E.D., *et al*. (2020) Sodium Acetate Protects against Nicotine-Induced Excess Hepatic Lipid in Male Rats by Suppressing Xanthine Oxidase Activity. *Chemico-Biological Interactions*, **316**, Article ID: 108929. https://doi.org/10.1016/j.cbi.2019.108929

[101] Liu, L., Fu, C. and Li, F. (2019) Acetate Affects the Process of Lipid Metabolism in Rabbit Liver, Skeletal Muscleand Adipose Tissue. *Animals*, **9**, Article 799. https://doi.org/10.3390/ani9100799

[102] Li, Y., Xu, S., Mihaylova, M.M., *et al*. (2011) AMPK Phosphorylates and Inhibits SREBP Activity to Attenuate Hepatic Steatosis and Atherosclerosis in Diet-Induced Insulin-Resistant Mice. *Cell Metabolism*, **13**, 376-388. https://doi.org/10.1016/j.cmet.2011.03.009

[103] Skelly, A.N., Sato, Y., Kearney, S. and Honda, K. (2019) Mining the Microbiota for Microbial and Metabolite-Based Immunotherapies. *Nature Reviews Immunology*, **19**, 305-323. https://doi.org/10.1038/s41577-019-0144-5

[104] Yao, H., Fan, C., Lu, Y., *et al*. (2020) Alteration of Gut Microbiota Affects Expression of Adiponectin and Resistin through Modifying DNA Methylation in High-Fat Diet-Induced Obese Mice. *Genes & Nutrition*, **15**, Article No. 12. https://doi.org/10.1186/s12263-020-00671-3

[105] Ridaura, V.K., Faith, J.J., Rey, F.E., *et al*. (2013) Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice. *Science*, **341**, 1069-1070. https://doi.org/10.1126/science.1241214

[106] Zhao, S., Jang, C., Liu, J., *et al*. (2020) Dietary Fructose Feeds Hepatic Lipogenesis via Microbiota-Derived Acetate. *Nature*, **579**, 586-591. https://doi.org/10.1038/s41586-020-2101-7

[107] Perry, R.J., Peng, L., Barry, N.A., *et al*. (2016) Acetate Mediates a Microbiome-Brain-$\beta$-Cell Axis to Promote Metabolic Syndrome. *Nature*, **534**, 213-217. https://doi.org/10.1038/nature18309

[108] Janeiro, M.H., Ramirez, M.J., Milagro, F.I., Martínez, J.A. and Solas, M. (2018) Implication of Trimethylamine N-Oxide (TMAO) in Disease: Potential Biomarker or New Therapeutic Target. *Nutrients*, **10**, Article 1398. https://doi.org/10.3390/nu10101398

[109] Barrea, L., Muscogiuri, G., Annunziata, G., *et al*. (2019) A New Light on Vitamin D in Obesity: A Novel Association with Trimethylamine-N-Oxide (TMAO). *Nutrients*, **11**, Article 1310. https://doi.org/10.3390/nu11061310

[110] Dehghan, P., Farhangi, M.A., Nikniaz, L., Nikniaz, Z. and Asghari-Jafarabadi, M. (2020) Gut Microbiota-Derived Metabolite Trimethylamine N-Oxide (TMAO) Potentially Increases the Risk of Obesity in Adults: An Exploratory Systematic Review and Dose-Response Meta- Analysis. *Obesity Reviews*, **21**, e12993. https://doi.org/10.1111/obr.12993

[111] Schoeler, M. and Caesar, R. (2019) Dietary Lipids, Gut Microbiota and Lipid Metabolism. *Reviews in Endocrine and Metabolic Disorders*, **20**, 461-472. https://doi.org/10.1007/s11154-019-09512-0

[112] Gao, X., Liu, X., Xu, J., *et al*. (2014) Dietary Trimethylamine N-Oxide Exacerbates Impaired Glucose Tolerance in

Mice Fed a High Fat Diet. *Journal of Bioscience and Bioengineering*, **118**, 476-481. https://doi.org/10.1016/j.jbiosc.2014.03.001

[113] Koeth, R.A., Wang, Z., Levison, B.S., *et al*. (2013) Intestinal Microbiota Metabolism of L-Carnitine, a Nutrient in Red Meat, Promotes Atherosclerosis. *Nature Medicine*, **19**, 576-585. https://doi.org/10.1038/nm.3145

[114] Tan, X., Liu, Y., Long, J., *et al*. (2019) Trimethylamine N-Oxide Aggravates Liver Steatosis through Modulation of Bile Acid Metabolism and Inhibition of Farnesoid X Receptor Signaling in Nonalcoholic Fatty Liver Disease. *Molecular Nutrition & Food Research*, **63**, e1900257. https://doi.org/10.1002/mnfr.201900257

[115] Gottlieb, A. and Canbay, A. (2019) Why Bile Acids Are So Important in Non-Alcoholic Fatty Liver Disease (NAFLD) Progression. *Cells*, **8**, Article No. 1358. https://doi.org/10.3390/cells8111358

[116] Trabelsi, M.S., Daoudi, M., Prawitt, J., *et al*. (2015) Farnesoid X Receptor Inhibits Glucagon-Like Peptide-1 Production by Enteroendocrine L Cells. *Nature Communications*, **6**, Article No. 7629. https://doi.org/10.1038/ncomms8629