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肠道微生物群在治疗脂肪性肝病方面的进展与挑战

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摘要

代谢功能障碍相关脂肪性肝病（MASLD）拥有惊人的发病率。据估计，全球有高达四分之一的人群受到该疾病的困扰，这也使其成为全世界最常见的肝病。MASLD的特征为肝脏脂肪的过度堆积，通常与肥胖、血脂异常和胰岛素抵抗等合并症相关；然而，该病同样也发病于瘦人群体。因此，开发针对这种复杂疾病的有效疗法至关重要。目前，尚无获得批准的MASLD相关治疗药物，因此研究替代方法迫在眉睫。大量研究表明，MASLD为多面性疾病，通常与饮食习惯导致的代谢紊乱有关。有证据表明，在MASLD从单纯脂肪变性到脂肪性肝炎，甚至肝细胞癌（HCC）的发生和发展过程中，肠道微生物群的变化起着根本性作用。在本文中，我们对基于肠道微生物群治疗MASLD和代谢功能障碍相关脂肪性肝炎（MASH）方面这一新兴领域相关的文献进行了批判性研究，包括粪便微生物群移植（FMT）、益生菌、益生元、短链脂肪酸、抗生素、靶向代谢途径和免疫检查点激酶阻断等干预措施。

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1. 引言

代谢功能障碍相关脂肪性肝病（MASLD）（原称非酒精性脂肪性肝病）的全球发病率高达25% [1]。近期，国际专家一致同意用“MASLD”这一新名词取代原称“非酒精性脂肪性肝病”，从而更准确地描述肝脂肪变性的多方面起源——遗传、代谢和环境[2]。在多个国家中，该疾病与日益增加的肥胖症密切相关。然而，在所有的MASLD病例中，瘦人群体占比多达20%，这表明除了超重，该病还涉及更为复杂的病理生理学问题[3]。预计至2030年，中国MASLD的患病率将上升至29.1%，成为该病高发区域之一。在欧洲，同期MASLD的患病率或可增

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加至14.0%~29.5% [4]。总体而言，MASLD已成为全球性流行病。

该病最初的病理生理学特征为单纯的脂肪变性（脂肪在> 5%的肝细胞中蓄积），随后可发展为代谢功能障碍相关脂肪性肝炎（MASH）和终末期肝病，包括晚期纤维化、肝硬化和肝细胞癌（HCC）[5]。鉴于该疾病发病率较高且仍在不断增加，MASLD相关肝硬化已成为全球肝癌[6–7]和肝移植[8]的主要原因。该病占所有肝细胞癌病例的10%~38%。值得注意的是，有报道称在非肝硬化MASH中，肝细胞癌的发病率也显著增加[9]。

此外，脂肪肝引起的慢性炎症会引起各种并发症，如心血管合并症[10]、代谢综合征[11]、骨质疏松症[12]、糖尿病[13]以及慢性肾脏疾病[14]。

然而，迄今为止尚无任何药物获批用于该病的治疗[15]，因此，促进治疗方法的发展势在必行。越来越多的研究将MASLD定义为一种与营养造成的代谢紊乱相关的多面性疾病[16]。然而，研究反复表明，在MASLD的发病以及从单纯脂肪变性到脂肪性肝炎甚至HCC发展过程中，肠道微生物群和肠-肝轴起到核心作用[17–18]。由于3-（4-羟基苯基）乳酸[19]、乙醛[20]和三甲胺氮氧化物（TMAO）等肠道衍生代谢物可通过库普弗细胞（KCs）M1型极化影响纤维化的发展[21]，并通过对外周免疫细胞的调节对其他肝脏病变的发展产生影响[22]，因此目前临床研究正在努力确定如何利用微生物群对MASLD进行有效的预防和治疗。

1.1. 肝脏疾病中的微生物群

微生物群是指定殖于人体表面的各种不同微生物的总和，包括细菌、古生菌、病毒和真菌。肠道中存在着人体最复杂的微生物群之一，主要由细菌组成，特别是五个主要的细菌门：厚壁菌门、拟杆菌门、变形菌门、放线菌门和疣微菌门，它们在特定的肠道生态位中发挥着不同的功能[23]。除细菌外，肠道微生物群还包括古生菌、真菌、病毒和噬菌体。在胃肠道中发现的微生物中，真菌占比不到1%。然而与细菌相比，真菌的体积和生物量较大，因此其或可对代谢产生更大的影响[24–27]。微生物群内不同微生物之间相互影响，在人体生理学中发挥积极作用。微生物群位于宿主与环境的交界处，既充当代谢较为活跃的器官，又是环境影响宿主生理学的整合点[28]。它可以维持消化、免疫系统驯化和维生素生物合成等多种功能，并能迅速适应不断变化的环境[29]。一般而言，以多样性降低和病原菌扩张为特征的有害微生物群可导致微生物代谢改变、肠屏障功能受损以及微生物来源分子从肠道转移至肝脏。微生物群的高度可塑性及其在MASLD病理生理学中的核心作用使其成为治疗MASH的一个有前景的靶点[30]。

1.2. 肠屏障功能与细菌易位

目前已发现多种细菌参与MASLD疾病的发展，包括脆弱拟杆菌、大肠杆菌以及幽门螺旋杆菌。肠道微生物群组成的变化会损伤肠道屏障，增加微生物相关分子模式（MAMPs）[如脂多糖（LPS）]的转移[31]。几种与MASLD相关的细菌可产生LPS，激活肝细胞上的Toll样受体（TLRs），从而引发炎症[32–33]。另一方面，嗜黏蛋白阿克曼菌（*A. muciniphila*）和双歧杆菌属等有益菌可产生具有抗炎特性的短链脂肪酸（SCFAs），改善肠道屏障功能，防止MASLD的发生[34–36]。

MASLD发展为MASH的特征为肝脏免疫细胞浸润，导致炎症和纤维化。肠道微生物群可产生促炎细胞因子，激活免疫细胞上的Toll样受体，进而影响免疫细胞的活化和浸润并引发炎症[37]。肠道微生物群组成的改变通过影响Toll样受体信号传导和免疫细胞活化，从而导致MASH的发展[37–38]。例如，研究表明血液中LPS水平升高与MASH的严重程度相关[39]。肠道微生物群还会影响肝星状细胞（HSC）的活化，而活化的HSC可导致细胞外基质蛋白的沉积，加速肝纤维化的发展[40–41]。此外，革兰氏阴性菌外膜上的LPS可激活Toll样受体，刺激肿瘤坏死因子-α（TNF-α）、白介素（IL）-1β和IL-6的产生[42]。而肠道微生物群失调会导致厚壁菌门/拟杆菌的比例升高，这也与肝脏中TNF-α和IL-6水平升高相关[43]。

1.3. MASLD中的微生物胆汁酸（BA）代谢

肠道微生物群失调可能会改变胆汁酸的组成，促进次级胆汁酸的产生，如脱氧胆酸（DCA）和石胆酸（LCA），它们对肝细胞具有毒性，可导致肝癌[44]。研究表明，DCA可激活法尼醇X受体（FXR），促进肝癌细胞增殖[45]。此外，LCA可激活孕烷X受体（PXR），诱导肿瘤增殖和转移相关基因的表达[46]。此外，肥胖相关肠道生物群的改变也会导致DCA水平升高。目前已证明DCA可诱导HSC出现衰老相关分泌表型（SASP）。该SASP表型可通过分泌炎症因子和肿瘤促进因子，促进肝细胞癌的发展。重要的是，通过调节微生物群阻断DCA的产生可有效预防肥胖小鼠肝细胞癌的发展，这表明DCA-SASP轴在肥胖相关肝细胞癌中发挥关键作用[17]。

肠道微生物群产生的代谢物在循环代谢物中占据很大比例[47]。菌群失调可导致TMAO（一种胆碱代谢产物）

的产生，而研究已证明TMAO可通过诱导血管生成和炎症，促进肝癌的发展[48]。

1.4. 肠道真菌组和病毒组在MASLD中的新作用

在MASLD患者的肠道中已鉴定出几种真菌，包括白色念珠菌（*C. albicans*）和酿酒酵母（*S. cerevisiae*）。这些真菌会产生有害代谢物，如乙醇和乙醛，这些代谢物会损伤肝细胞并引发炎症[49–50]。研究发现，与健康对照组相比，MASLD患者中肠道共生真菌中白色念珠菌的含量丰富。白色念珠菌可促进肠道炎症，诱导产生促炎细胞因子（如IL-17和IL-22），从而导致肝纤维化和肝细胞癌[51]。此外，曲霉菌（*Aspergillus*）可与肝细胞相互作用，诱发氧化应激和炎症，导致肝损伤[50]。青霉菌（*Penicillium*）可导致肠道菌群紊乱，诱发线粒体功能障碍，导致氧化应激和肝损伤[52]。相比之下，有益真菌[如布拉氏酵母菌（*S. boulardii*）]，可以调节肠道微生物群的组成，减轻肠道炎症，这可能对MASLD的发展有防护作用[53–54]。

最后，我们必须认识到肠道病毒是肠道群体的重要组成部分。它们大多数为噬菌体，这也意味着它们可以对特定细菌群进行特异性感染。在近期的多项研究中均报道了某些噬菌体丰度与多种代谢改变之间的相关性[55–58]。例如，Yang等[57]通过鸟枪法宏基因组测序发现，肥胖者肠道微生物群中拟菌病毒科的大量存在或与肥胖和糖尿病有关。人类腺病毒感染被确定为是MASLD疾病进展的一个重要危险因素，它可通过降低瘦素的表达增加食物摄入量，以及通过激活脂肪生成和促炎途径增加葡萄糖的摄取，从而导致慢性炎症和脂肪代谢的改变[55]。

2. 靶向微生物群治疗脂肪肝

2.1. 粪便微生物群移植

多项研究均报道了粪便微生物群移植（FMT）对代谢综合征患者代谢的改善作用[59–62]。由于代谢综合征与MASLD之间的密切联系已被反复证实[63]，因此，粪便微生物群的改变作为一种潜在的共同病因，正作为MASLD的一种治疗对象被广泛讨论。在自身免疫性疾病、代谢综合征以及MASLD中均可观察到FMT对肠道通透性的改善作用（图1）[64–66]。

然而，FMT对MASLD的临床影响仍有待确定。目前也仅在小型可行性试验中对FMT的疗效进行了探索，以确定其在改变MASLD患者肠道微生物群组成方面的治疗潜力。Vrieze等[59]证明，代谢综合征患者在接受来自瘦型供体的FMT六周后，胰岛素敏感性得到显著改善；此外，他们肠道中罗斯拜瑞氏菌（*Roseburia intestinalis*）的丰度增加到2.5倍，丁酸盐产量也有所增加。作为一种微生物代谢物，丁酸盐会触发肝损伤的关键机制，其水平的降低与预后不良有关[67]。同样，Witjes等[61]证实，来自瘦型和素食捐赠者的同种异体FMT改变了脂肪性肝病患者的肠道微生物群组成，受体的血浆代谢物和MASLD标志物均发生了有益变化。De Groot等[60]研究了FMT对接受或未接受减肥手术（对照组）的代谢综合征供体的影响，结果显示胰岛素敏感性降低、肠道转运时间加快、炎症标志物减少，以及一些肠道微生物群也发生了变化。

然而，其他一些初步试验对微生物群移植改善MASLD这一假设提出质疑。一项随机临床试验对15例MASLD患者进行了同种异体FMT治疗，并与接受自体FMT治疗的患者进行了对比，结果发现6个月后，同种异体FMT治疗未能降低肝脏脂肪含量[62]。同样地，患者的胰岛素抵抗也未能得到改善[62]。该研究表明，同种异体FMT可降低基线时高通透性患者的小肠通透性，增加受体的粪便微生物群多样性，但未观察到任何特定分类群之间的显著差异[62]。总体而言，FMT（或可结合生活方式的改变）最终能否作为MASLD的有效临床疗法仍存在疑问。如果答案为肯定，则还需辅以大量的研究来确定其治疗的持久性[68]。此外，需要更多的研究来更好地定义供体和受体的具体情况，以预测移植群体的移植情况[69]。尽管存在挑战，FMT仍被认为具有巨大的潜力，值得开展进一步的临床研究来评估其在MASLD治疗方面的有效性。然而，这也需要大量的数据支撑，先进的分层或有助于了解这种治疗方法对脂肪肝疾病的多系统影响[70]。

2.2. 不同生物制剂在未来肝病治疗中的应用

目前，肠道菌群失调已被认定为是导致MASLD发病的驱动因素，鉴于益生菌、益生元或合生元对肠道微生物群的调节作用，现已有将口服益生菌、益生元或合生元作为MASLD的治疗手段的建议。在各种随机临床试验和基础研究中，已经证明该疗法可以重建肠道微生物群的生理状态。益生菌的定义为“当服用足够剂量时，可为宿主带来健康益处的活的生物体”，益生菌的服用方式多种多样，如滴剂、粉剂、发酵食品和片剂[70]。益生元被描述为“促进微生物生长和活性的代谢底物”，通常在胃肠道中有益于健康[71]。合生元是益生菌和益生元的协同组合，可以通过同时刺激微生物生长和新陈代谢使宿主受益[72]。

一些研究旨在阐明这三种生物制剂对慢性肝病的影

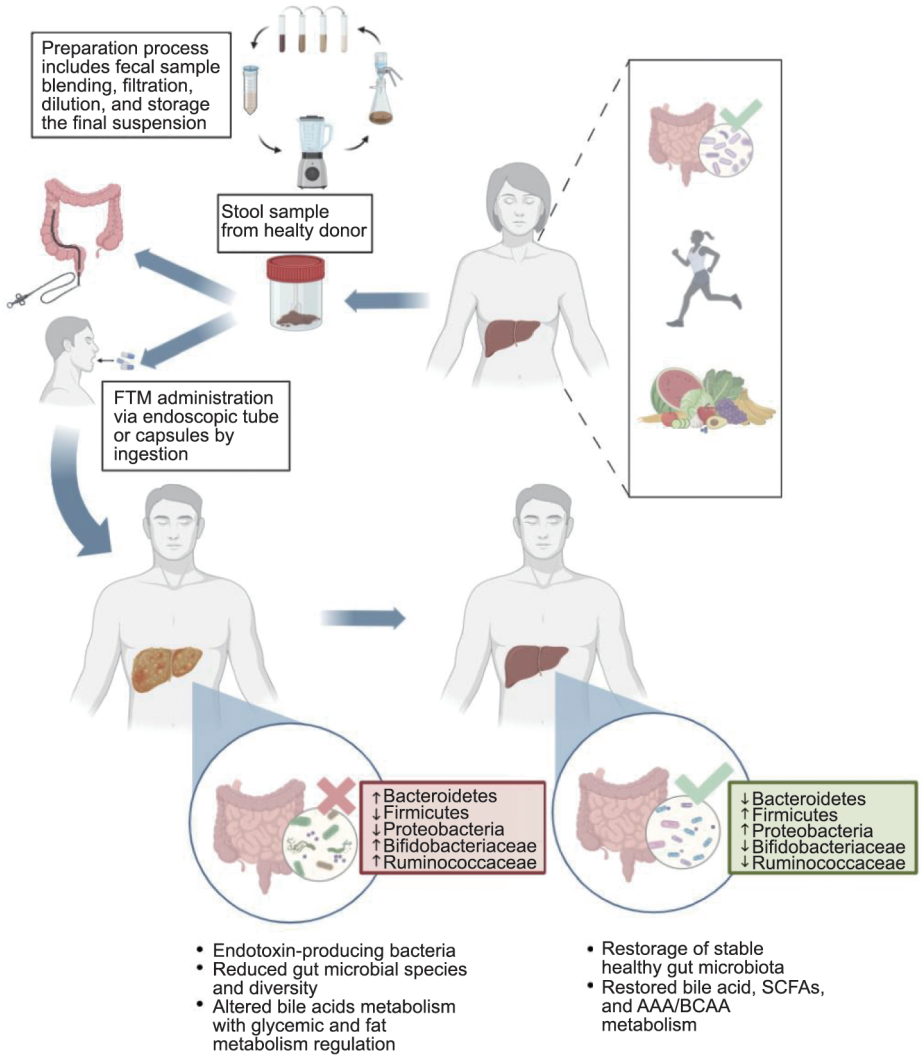

图1. FMT过程示意图。选取健康的捐献者作为粪便移植的供体，捐献者往往具有优势的微生物群和良好的生活习惯。粪便采集后进行预处理，为随后的给药做好准备，给药可通过内窥镜检查或胶囊方式进行。目标人群是确诊患有MASLD并同时伴有菌群失调的患者。预期结果是在受者体内建立更健康的微生物群，同时减缓MASLD的发展。AAA：芳香族氨基酸；BCAA：支链氨基酸。

响。在最近的一项双盲、安慰剂对照试验中，Chong等[73]评价了益生元菊粉联合甲硝唑治疗62例MASLD患者的效果。在经历了4周极低卡路里饮食（600 kcal·d^{-1}）后，服用甲硝唑1周后再服用菊粉11周的患者谷丙转氨酶（ALT）水平相比安慰剂组明显降低。但患者的体重指数（BMI）在治疗期间无显著变化。Aller等[74]的试验报告也得到同样的结论：研究人员每天给30名MASLD患者服用含有5亿保加利亚乳杆菌和嗜热链球菌（*S. thermophilus*）的混合物，结果发现治疗组的谷草转氨酶（AST）和ALT在三个月后有所下降，而BMI没有变化。与其他研究中的健康对照组相比，该治疗还与MASLD患者体内高水平的厚壁菌门/拟杆菌门有关，如罗氏菌属和链球菌属[75–77]。

在第二项双盲随机安慰剂对照研究中，通过48名并发MASLD的2型糖尿病（T2D）患者，评估了联合服用由14种菌株组成的活体多菌株益生菌混合物和omega-3脂肪酸的疗效[78]。该研究证明这种组合具有改善肝脏脂肪沉积、血脂和代谢特征的潜力，同时它还可以改善全身炎症[78]。总的来说，益生菌和益生元对MASLD的有利影响已在一些临床试验中显示出来，但这些结果还需在更大规模的研究中被证实，并且这些有益作用的潜在机制也需要进一步阐明。

尽管市场上大多数益生菌都是细菌，但多数研究均佐证布拉氏酵母菌是一种有效的益生菌，可以调节肠道菌群失调、抑制病原体定殖、调节免疫系统、改善炎症、稳定肠道屏障，从而改善营养物质的吸收[79]。Martins等[79]的一项研究中，使用布拉氏酵母菌作为益生菌治疗伤寒沙门氏菌感染的小鼠，研究发现，益生菌可以抑制炎症反应，减少TNF-α和趋化因子C-X-C基序配体1（CXCL1）等促炎细胞因子的产生。

作为益生菌和益生元的组合，合生元在治疗肝病方面的潜在疗效已多次得到证明。在随机对照临床试验中，Bakhshimoghaddam等[78]研究了含有菊粉和动物双歧杆菌（*B. animalis*）的酸奶与健康生活方式（即饮食和运动）的结合是否会对MASLD的疾病进展产生影响。该项研究对102名伊朗MASLD患者进行观察，发现与对照组相比，治疗组中有85.29%的患者脂肪肝分级得到改善，并且接受治疗的患者还表现出ALT、AST、碱性磷酸酶（ALP）和γ-谷氨酰转肽酶（γ-GT）水平的下降[78]。

同样，Malaguarnera等[80]研究了双歧杆菌与低聚果糖联合应用对MASH的影响及其潜在的疗效。6个月后，患者的转氨酶水平显著降低[80]。同样，Eslamparast等[81]在低聚果糖的基础上，给52名MASLD患者补充了几种乳酸杆菌、链球菌和双歧杆菌的益生菌混合物，同时患者还必须坚持均衡饮食和体育锻炼，28周后，他们观察到合生元疗法显著降低了MASLD患者的肝酶和炎症指标。因此，这两种组分的协同应用具有更好的治疗前景。然而，正如益生菌和益生元一样，更大规模（以及更多的种族多样性）的研究是必要的，以确定这些物质在MASLD和（或）MASH治疗中的潜在常规应用。最后，在高脂肪饮食诱导的肥胖小鼠中发现，从真菌中提取的葡聚糖益生元可以通过调节肠道微生物群，减少胃脂肪沉积、减轻体重、降低肝脏甘油三酯水平[82]。

然而，用这些物质改善肠道菌群失调的概念也受到了一些研究的质疑。最近，在Scorletti等[83]的一项随机试验中，应用低聚果糖联合动物双歧杆菌治疗104名MASLD患者一年后，这些患者的肝脏脂肪沉积或纤维化并没有明显改善。

总的来说，研究已证明益生元、益生菌和合生元可作为辅助性补充剂减少炎症、肝脂肪变性以及改善肝脏硬度。多项荟萃分析表明，使用益生元、益生菌和合生元治疗对肝脏ALT和AST有积极影响[84–90]。Sharpton等[91]对21项随机对照试验进行了荟萃分析，研究了9种益生菌和12种合生元对MASLD患者肠道微生物组的影响，结果表明，益生菌/合生元的使用与炎症、肝脏硬度和脂肪变性的改善有关。此外，Khan等[84]也对包括12项益生菌/合生元疗效的随机对照试验进行了荟萃分析，结果表明，补充益生菌/合生元可降低AST和ALT的水平，显著改善肝纤维化评分，同时还可降低超敏C反应蛋白（hs-CRP）和TNF-α等炎症标志物的水平。在Liu等[85]进行的另一项荟萃分析中，研究人员对15项补充益生菌和合生元的随机对照试验中肝酶和肝硬度的改善情况进行了研究，结果发现患者的脂肪化状况有所改善。

尽管益生菌在调节肠道微生物群和治疗MASLD方面拥有较大潜力，但这一领域的研究仍存在很大程度的异质性，也缺乏大规模、对照良好的临床试验支撑。未来需要进一步的研究，以更全面地了解益生菌在MASLD治疗方面的应用。

2.3. 基于胆汁酸通路的疗法

MASLD患者的肝脏会积聚过多的甘油三酯和胆固醇。胆固醇通过两种主要的生物合成途径代谢为胆汁酸，这两种途径受到反馈机制的密切调节[92]，胆汁酸代谢的病理生理变化也引起了人们的极大关注，因为它们很大程度上可能会导致疾病的发生[93]。胆汁酸通过肝脏中的多步酶解合成，与甘氨酸或牛磺酸共轭后形成初级胆汁酸，释放到十二指肠中[94]。在十二指肠中，初级胆汁酸可以调节肠道微生物群的组成，并在微生物胆汁酸代谢的影响下，进行结合和酶转化，进而影响其在特定胆汁酸受体上的信号转导特性。重要的是，回肠FXR介导的负反馈机制可以调节肝脏中的胆汁酸合成[94]。FXR和其他特异性胆汁酸受体[如Takeda G蛋白偶联受体5（TGR5）]参与多种分子机制，包括脂质[95]、葡萄糖稳态[96]以及能量和免疫的改变[97]。

Puri等[98]对活检证实的脂肪肝患者的血浆胆汁酸图谱进行了研究，结果表明，与MASLD和（或）对照组相比，MASH患者的总结合初级胆汁酸水平明显升高。此外，胆汁酸的组成也存在显著差异，关键胆汁酸的增加也可导致脂肪变性（牛磺胆酸盐）、小叶炎症（甘胆酸盐）、门静脉炎症（牛磺胆酸盐）以及肝细胞气球样变（牛磺胆酸盐）。这些改变又可能与多种分子和（病理）生理机制有关，如肠道FXR信号、黏液和抗菌肽合成的减少以及肠道血管屏障完整性的降低[99]。

目前靶向调控胆汁酸的机制似乎是治疗MASLD患者最有前景的方法之一[100]。奥贝胆酸（OCA）是一种有效的FXR选择性激动剂，因此，它对胆汁酸的调节有显著影响，从而减少脂质吸收以及肝纤维化[100]。触发这种核受体会增加肝细胞内胆汁酸的转运，并抑制胆固醇的合成，降低肝细胞内胆汁酸的浓度[100–101]。在这方面，两项随机对照试验表明，临床OCA治疗可改善肝脏脂肪变性，与安慰剂相比，MASLD/MASH患者的肝脏组织学状况有所改善[99–100]。

研究还表明，奥贝胆酸会影响肠道通透性、微生物群丰度和细菌易位[102]。而各种基于动物模型的研究也描述了肠道微生物群在调节OCA和FXR方面的相关性[103]。Liu等[85]对患有MASLD和抗生素引起的菌群失

调的小鼠进行了宏基因组和代谢组分析，以评估微生物群在OCA治疗中的作用。研究人员发现，OCA治疗可以增加负责胆汁酸平衡的微生物群（嗜黏蛋白阿克曼菌、脆弱拟杆菌、嗜热链球菌以及双歧杆菌属）。这些菌属的增加受初级胆汁酸（胆酸和脱氧胆酸）水平降低以及结合胆汁酸（牛磺脱氧胆酸和牛磺熊去氧胆酸）水平升高的影响[85]。因此，在某种程度上，OCA可通过调节肠道微生物群达到良好疗效。

例如，肠道微生物群对胆汁酸的调节甚至会影响到肝细胞癌的发病。目前已证实MASLD患者，尤其是MASH患者的肝细胞癌的发生概率会增加[104]。众所周知，肠道微生物组通过降低肠细胞对FXR的抑制，参与次级胆汁酸代谢和抑制初级胆汁酸合成，导致由微生物组调节的次级胆汁酸的产生减少。这一过程会诱导肝窦内皮细胞合成趋化因子CXCL16，增加肝C-X-C趋化因子受体6^+（$CXCR6^+$）数量，促进自然杀伤T细胞的活化，肝脏抗肿瘤免疫会因此得到改善[105]。

在最近一项多中心三期试验中发现，使用强效激动剂OCA靶向作用FXR可显著改善肝纤维化以及MASH活性。研究人员观察到ALT和AST呈剂量依赖性下降，MASH的主要组织学特征也有所改善。然而，由于OCA对非酒精性脂肪性肝炎（NASH）的缓解程度有限（仅有11%~12%接受治疗的患者病情有所改善，而接受安慰剂治疗的患者中这一比例为8%），因此美国食品和药物管理局（FDA）并未批准该疗法[106]。在近期进行的ALPINE 4试验中，一种成纤维细胞生长因子19（FGF19）类似物aldafermin在MASH治疗上展示出良好的有效性、安全性和耐受性。Aldafermin可以减少胆汁酸的生成、增加胰岛素敏感性，和减少脂肪的生成[107]。

2.4. 短链脂肪酸

肠道微生物可将食物纤维转化为短链脂肪酸，如乙酸盐、丙酸盐和丁酸盐等化合物[108–110]。释放至肠道后，60%~70%的短链脂肪酸用于满足结肠细胞和肠细胞的能量需求，小部分（5%~15%）的短链脂肪酸会进入血液循环，帮助改善宿主免疫以及胰岛素敏感性[85]。短链脂肪酸可以触发G蛋白偶联受体41（GPR41）和GPR43，进而较大程度上影响肝脂肪变性、食欲、胰岛素抵抗和炎症反应，而所有这些均可能导致MASLD和MASH的恶化[111]。

短链脂肪酸影响脂肪肝的确切机制尚不十分清楚。但从各种临床研究中对其普遍治疗潜力进行推测后发现，一些益生菌能够抑制炎症并刺激脂质代谢的变化。研究认为，这些影响至少部分是由于肠道中短链脂肪酸的增加所致[112]。

短链脂肪酸可以减少脂肪组织中脂肪蓄积，对保护结肠黏膜的肠道屏障非常重要[113]。在三种主要的短链脂肪酸中，丁酸盐效果最为显著。据报道，丁酸盐可通过诱导紧密连接蛋白（尤其是黏蛋白），改善肠道屏障[114–117]，丁酸盐可以在生理浓度下降低菊粉的渗透能力[118]。丁酸盐可通过单磷酸腺苷活化蛋白激酶（AMPK）的活化来调节炎症细胞因子和促进紧密连接的组装，还能通过减少肝损伤和纤维化改善胰岛素敏感性并抑制MASLD的发展[3,119]。

此外，丁酸盐可增强过氧化物酶体增殖物激活受体（PPAR）依赖性信号传导。众所周知，PPAR对新陈代谢和炎症有改善作用[120–121]。有趣的是，短链脂肪酸无法降低PPARγ基因缺陷小鼠肝脏中的脂肪含量。因此，PPARγ在短链脂肪酸介导的对代谢综合征有益影响中起关键作用[122]。研究发现，丁酸盐可诱导抑制组蛋白去乙酰化酶蛋白（HDACPs）的表达，随后的表观遗传修饰也可能增强胰高血糖素样肽-1受体（GLP-1R）的表达[123]，下调核因子-κB（NF-κB）的转录，在一定程度上减轻炎症和纤维化[124–125]。

总体而言，短链脂肪酸对MASLD治疗潜力的评价才刚刚开始。它们对脂肪酸代谢和炎症等分子机制的影响，为这些物质发展成为有效和廉价的MASLD调节剂带来了希望。

2.5. 抗生素通过影响微生物群作为炎症和纤维化调节剂

抗生素调节肠道共生菌群的丰度，可能会导致菌群失调和细菌耐药性。此外，抗生素治疗可以减少肠道炎症和渗漏[126]。但抗生素也可以促进有益细菌的生长。最近有报道称，利福昔明（一种不可吸收抗菌药）可调节肠道通透性，防止细菌易位，表现出抗炎特性，在MASH或肝硬化患者中发挥免疫调节作用[127]。根据这些观察结果，我们开展了多项小鼠研究和小型临床试验，以确定利福昔明在MASLD治疗方面的潜在疗效。Jian等[128]在蛋氨酸和胆碱缺乏（MCD）饮食诱导的MASH小鼠中，对利福昔明的疗效进行了研究，结果显示利福昔明可显著改善肝脏脂肪变性、肝小叶炎症和纤维化。最后，Enomoto等[129]在胆碱缺乏-特殊氨基酸（CDAA）饮食诱导的大鼠模型中，对利福昔明和鲁比前列酮联合用药疗效进行了研究，研究结果证明这种组合的联合治疗明显降低了巨噬细胞扩增，减少了促炎反应和肝纤维化。

很少有临床观察或小型试验能将这些发现应用于临床

患者。在最近的一项在酒精相关性肝病（GALA-RIF）患者中进行的双盲、安慰剂对照的II期试验中[130]，研究人员发现利福昔明可能是肝纤维化的有效治疗方法。这些数据表明利福昔明可能会减少酒精相关性肝病（ALD）肝纤维化进展。Abdel-Razik等[131]也对50例患者进行了一项双盲随机对照研究。总的来说，研究人员发现，与安慰剂组相比，利福昔明治疗组患者的肝酶指标有所改善，促炎细胞因子减少，MASLD-肝脏脂肪评分有所改善。不过，一些研究人员在较小的队列中发现，利福昔明对MASH患者并无益处[132]。此外，利福昔明能否在改善MASLD的脂肪变性的同时防止肝脏纤维化，这一问题仍需探究。

使用其他抗生素进行MASLD治疗的相关研究很少。Chong等[73]报道，补充甲硝唑和菊粉显著降低了链球菌属、戴阿利斯特杆菌属和罗氏菌属的细菌丰度。此外，甲硝唑-菊粉治疗搭配极低热量饮食显著降低了肝脏ALT和AST水平。

总体来看，小鼠试验和一些人体试验表明，抗生素（尤其是利福昔明）可能具有治疗MASLD的潜力。其可能通过包括保护细胞、预防细菌易位和抗炎特性等潜在机制，改善MASH患者的实验室和纤维化生物标志物。然而，一些研究显示利福昔明或其他抗生素并没有显著的治疗效果，并且报道的试验规模较小，因此，需要进一步的研究（特别是更大的研究人群），以进一步确定利福昔明或其他抗生素在治疗MASLD和（或）MASH方面的潜力。

3. 个性化治疗——微生物组视角

3.1. 肠道微生物群作为肝脏疾病分析的非侵入性工具

临床和临床前研究已证明，肠-肝轴与维持人体多系统平衡息息相关。菌群失调已被报道会触发多种病理生理相关机制，从内毒素积累[120]到慢性炎症[133]，甚至肝癌的发生[134]。然而，微生物群组成会发生非常多样化的变化，从而开辟出预后和（或）对治疗反应不同的患者亚组。目前，尚不确定哪些患者能从微生物组调节中获益，且治疗方法也无法实现因人而异。因此，识别特定亚组并且靶向干预这些机制及其背后的微生物群变化，对慢性肝病的个性化治疗具有重要意义。

关于预后亚组，Loomba等[135]的研究表明，年龄和BMI结合宏基因组测序获得的肠道微生物标记物，可以高效地鉴别晚期纤维化的MASLD患者。在他们的研究[135]中，MASLD患者的粪便微生物群主要以厚壁菌门和拟杆菌门为主，其次是变形菌门和放线菌门。然而，随着MASLD患者肝纤维化程度的增加，变形菌的数量显著增加，而厚壁菌门的数量有所下降。

另一方面，一项由88例酒精性肝炎患者组成的国际多中心队列研究显示，溶血素（一种由粪肠球菌表达和分泌的双亚基组成的毒素）是造成肝细胞死亡以及肝损伤的原因之一[136]，且该毒素的存在与疾病的严重程度相关。研究中，噬菌体介导的靶向实验表明了利用噬菌体对肠道微生物群进行治疗性编辑的可行性[136]。虽然可能需要更大规模的临床试验来探索这些结果之间的因果关系，并在实际环境中评估治疗效果，但这项研究证明了噬菌体作为一种可能的治疗策略的潜在效果和安全性[136]。

3.2. 药物微生物学及其在药物疗效中的作用

药物微生物群学是一门新兴的研究领域，旨在探索微生物群变异与药物反应和处置（即吸收、分布、代谢和排泄）之间的相互作用[137–139]。微生物群的可塑性及其组成可被改变和调节的能力，使其成为提升药物安全性和有效性的一个有趣靶点。最近的一项研究聚焦于T2D患者的疾病以及肠道微生物组药物特征，使用鸟枪法宏基因组分析后发现二甲双胍治疗的T2D患者中肠杆菌属（*Escherichia* spp.）丰度增加，*Intestinibacter*菌属丰度下降[140]。这些结果与Bryrup等[141]的研究结果相似，他们报道称，*Intestinibacter*菌属和梭菌属的丰度的减少，以及肠杆菌属/志贺菌属比例和沃氏嗜胆菌丰度的增加与二甲双胍的治疗直接相关。所有这些发现均表明二甲双胍治疗可对肠道微生物群产生巨大影响。值得注意的是，在首尔国立大学的一项研究中，研究人员发现，与对照组相比，二甲双胍治疗显著增加了嗜黏蛋白阿克曼菌以及耳蜗形梭菌的丰度，这与肠黏膜厚度和肠黏蛋白丰度的增加以及代谢疾病生物标志物（如总胆固醇和体重）的总体改善相关[142]。

肠道微生物群与外源性药物相互作用的另一个重要例子是对免疫疗法的反应。肠道微生物组可以调节宿主局部以及全身免疫系统。许多生理功能受到微生物群的影响，尤其是免疫、代谢和炎症。有大量证据表明，肠道微生物组影响癌症免疫治疗的疗效，尤其是在免疫检查点抑制剂方面[143–146]。

例如，过去几十年来大量证据表明，微生物组是肝脏疾病进展的不同方面的关键因素，菌群失调也是促进HCC进展的关键因素[34,111,134,147]。菌群紊乱进而导致细菌代谢物的改变，如有促癌作用的次级BA或DCA[17]，这会进一步导致肠道渗漏，并通过TLR4信号增加

炎症发生的概率[148–149]。

此外，免疫检查点抑制剂（ICI），如以程序性死亡受体-1（PD-1）/程序死亡配体1（PD-L1）为靶点的抑制剂，已被证明对肝细胞癌以及许多其他肿瘤实体都非常有效[150]。然而，近30%符合突破性治疗条件的患者对治疗应答不良[151]。最近的一项研究表明，在晚期黑色素瘤的一线治疗中，来自健康供体的FMT与抗PD-1免疫疗法联合应用是安全的，并且有望在HCC中进行类似的研究[152]。由于肠-肝轴在人类生物学中的内在作用，药物微生物组学在治疗脂肪肝和全身性病症方面前景广阔。目前，人们正在努力开发准确的综合微生物组预测指标，以便促使肠道微生物组成为肿瘤免疫治疗应答临床生物标志物[153]。在HCC治疗中，预测模型可对ICI疗法无应答者进行较好识别[154]。然而，由于与肠道微生物群有关的ICI疗效的研究证据有限且样本数量较少，因此需要进行更多的研究以提高这些模型的准确性，从而发挥其在个性化治疗方面的潜力。目前当务之急是将这种方法应用到慢性肝病的治疗中，因为更有效的治疗方法可以使患者的预后和整个卫生系统受益。更大样本量和进一步的研究可能允许在临床环境中使用微生物组生物标志物来帮助诊断和预测脂肪性肝病和肠道-肝脏相关病变患者的预后（图2）。

4. 总结

在MASLD发展为MASH、肝硬化或HCC的过程中，肠道微生物及其产物的影响愈加重要。其主要机制包括影响肠道通透性、炎症信号传导以及SCFA的生成。鉴于微生物群在MASLD病理生理学中的核心作用，微生物群已成为一个有前景的治疗靶点，尤其是在目前仍缺乏替代药物的情况下。目前已对益生菌、益生元、合生元、抗生素和FMT等几种疗法进行了研究，并在较小规模的研究中看到曙光。然而，仍需要进行进一步研究，特别是更大规模的临床试验，了解该类方法在MASLD和MASH的（辅助）治疗过程中是否具备低风险、安全且廉价的潜力。

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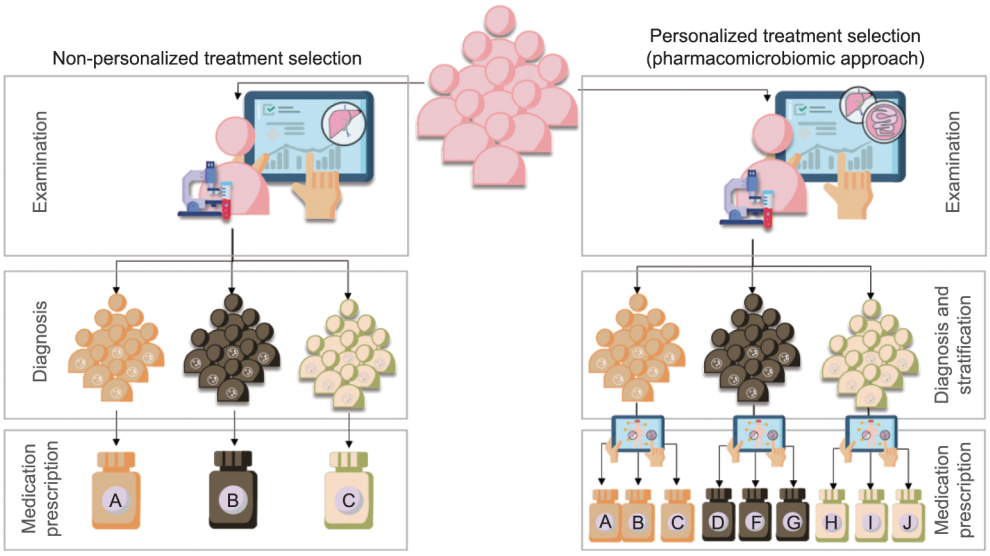

图2. 数据驱动患者分层示意图，将经典生物标志物的标准治疗实验室测试与肠道微生物群生物标志物的前沿知识相结合。准确的模型为开始治疗和选择药物的决策过程提供支持，并提供在当前生物标志物情况下可能出现的预后情况的信息。

gut-liver axis).

Compliance with ethics guidelines

Ernesto Saenz, Nathally Espinosa Montagut, Baohong Wang, Christoph Stein-Thöringer, Kaicen Wang, Honglei Weng, Matthias Ebert, Kai Markus Schneider, Lanjuan Li, and Andreas Teufel declare that they have no conflict of interest or financial conflicts to disclose.

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