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肠道微生物在骨骼肌萎缩中作用的研究进展

郭文雅,向施佳,张小丽,姚丽华,黎玉华*
(江西科技师范大学生命科学学院,南昌 330013)

摘 要:骨骼肌是运动系统关键部分,兼具运动支撑与代谢调节功能。骨骼肌萎缩是因疾病、衰老、神经损伤等多种因素,以肌质量和力量持续下降为特征,引发骨骼肌质量和功能持续减退的病症,对患者生活质量与预后影响较大,是当前研究的热点。肠道微生物是肠道内庞大的微生物群落,其对机体健康的影响备受关注。近年来,肠道微生物在骨骼肌萎缩中的潜在作用逐步显现,二者的关联性成为生物学领域研究热点。本文综述了肠道微生物在骨骼肌萎缩中的研究进展,主要包括肠道微生物与骨骼肌的相互作用机制、肠道微生物在不同类型骨骼肌萎缩中的作用以及干预肠道微生物治疗骨骼肌萎缩的策略等方面,旨在为骨骼肌萎缩相关疾病的研究和治疗提供新的思路和策略。

关键词:肠道微生物;骨骼肌萎缩;肠-肌轴;代谢物;免疫反应
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Research progress on the role of gut microbiota in skeletal muscle atrophy

GUO Wen-Ya, XIANG Shi-Jia, ZHANG Xiao-Li, YAO Li-Hua, LI Yu-Hua*
(School of Life Science, Jiangxi Science & Technology Normal University, Nanchang 330013, China)

Abstract: Skeletal muscle is a fundamental tissue within the locomotor system, indispensable not only for movement and structural support but also as a critical regulator of systemic metabolism. Skeletal muscle atrophy, a debilitating condition characterized by a progressive decline in muscle mass, strength, and function, arises from a multitude of etiological factors including specific diseases, aging, nerve injuries, disuse, and cancer cachexia. This deterioration significantly compromises patients' physical autonomy, metabolic health, and overall quality of life, making it a paramount concern in medical research. Concurrently, the gut microbiota, a complex and dynamic ecosystem of microorganisms residing in the gastrointestinal tract, is increasingly recognized as a central modulator of host physiology, influencing processes from nutrient metabolism to immune and inflammatory responses. The emergent concept of a "gut-muscle axis" posits a bidirectional communication network between the gut microbiota and skeletal muscle homeostasis. This article reviews the research progress of gut microbiota in skeletal muscle atrophy, mainly including the interaction mechanism between gut microbiota and skeletal muscle, the role of gut microbiota in different types of skeletal muscle atrophy, and the strategies for intervening gut microbiota to treat skeletal muscle atrophy, aiming to provide new ideas and strategies for the research and treatment of diseases related to skeletal muscle atrophy. The core of this article provides a detailed elaboration of the primary mechanisms through which the gut microbiota influences skeletal muscle physiology and pathology. These mechanisms are multifaceted: Firstly, microbial metabolites play a pivotal role. Short-chain fatty acids like butyrate, propionate, and acetate, produced by bacterial fermentation of dietary fiber, are crucial mediators. They influence muscle energy metabolism, and help maintain systemic inflammatory homeostasis by preserving intestinal barrier integrity. Other metabolites, including secondary bile acids and metabolites of dietary tryptophan, also significantly impact muscle protein synthesis, mitochondrial function, and inflammatory status. Secondly, immunoregulation is a major pathway. The gut microbiota is essential for the proper development and function of the host immune system. Dysbiosis can disrupt intestinal barrier function, leading to systemic inflammation characterized by elevated pro-inflammatory cytokines, which are potent drivers of muscle catabolism. Furthermore, the microbiota shapes the differentiation and balance of T-cell subsets, which can subsequently influence the inflammatory milieu within the muscle microenvironment, either exacerbating or ameliorating atrophy. The review further

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***通信作者**:E-mail:yuhuali030@163.com

analyzes the specific alterations and roles of the gut microbiota in distinct types of skeletal muscle atrophy, highlighting the interplay between specific pathological contexts and microbial ecology. In Duchenne muscular dystrophy, dysbiosis is characterized by an increase in LPS-producing Gram-negative bacteria, leading to impaired gut barrier, systemic inflammation, and disrupted SCFA metabolism. Interventions like sodium butyrate supplementation have shown promise in improving muscle function in models. In myotonic dystrophy type 1, patients exhibit an altered Firmicutes/Bacteroidetes ratio and a reduction in beneficial *Lactobacillus*, suggesting a link between gastrointestinal symptoms and muscle pathology. In age-related sarcopenia, decreased microbial diversity and reduced SCFA production are associated with chronic inflammation and anabolic resistance. In neurogenic atrophy, distinct microbial shifts are observed, which may contribute to disease progression through heightened neuroinflammation and disrupted energy metabolism. Lastly, in cancer cachexia, microbial dysbiosis is implicated in driving the severe inflammatory response and metabolic wasting. The article also evaluates strategies for intervening in the gut microbiota to prevent or treat skeletal muscle atrophy. These include probiotics, prebiotics to stimulate the growth of beneficial bacteria, and fecal microbiota transplantation to reconstitute a healthy microbial community. Clinical evidence, particularly from studies on elderly sarcopenia, shows that multi-strain probiotic interventions can lead to measurable improvements in muscle strength and reductions in inflammatory markers. The potential of targeted delivery systems, such as engineered probiotics encapsulated in nanomaterials to precisely modulate the gut environment, is also discussed as an emerging frontier. In conclusion, the evidence compellingly supports the gut microbiota as a critical modifier of skeletal muscle health and a key player in the pathophysiology of various muscle atrophies. Targeting the gut-muscle axis presents a novel and promising therapeutic paradigm. Future research should focus on validating these findings in large-scale human trials, elucidating the precise molecular signals involved, and developing personalized microbiota-based interventions to combat muscle wasting and improve patient outcomes.

Key words: gut microbiota; skeletal muscle atrophy; gut-muscle axis; metabolites; immune response

骨骼肌萎缩是骨骼肌纤维体积缩小、数量减少，导致肌肉质量减轻、力量下降及功能减退的一种病理状态，可由多种因素引发，包括营养不良、疾病（如杜氏肌营养不良症、1 型强直性肌营养不良症）、衰老、废用、神经损伤等，这些因素可通过干扰肌肉蛋白质合成与分解代谢平衡，促使肌肉发生萎缩，进而对机体运动、代谢等功能产生负面影响。骨骼肌萎缩是多种疾病的常见并发症，严重影响患者的生活质量。

近年来，随着生物学技术的迅速发展，国内外学者对肠道菌群与骨骼肌萎缩的关系进行了广泛研究，并取得了一定进展，尤其是在肠-肌轴与代谢调节作用方面，已经成为研究的热点。研究表明，肠道微生物群，胃中的细菌、古菌、病毒和真核微生物是年龄相关肌肉衰退的潜在原因[1]。宿主肠道微生物群与宿主的串扰对骨骼肌有不可忽视的影响，但肠道微生物群在骨骼肌萎缩中的潜在角色及作用机制仍不清晰[2]。肠道微生物可能通过复杂的机制参与骨骼肌的代谢和免疫调节，因此，深入研究这一领域有望为骨骼肌萎缩的防治提供新的靶点和策略。

为了更加深入地揭示肠道微生物与骨骼肌萎缩的相互作用机制，同时为骨骼肌萎缩相关疾病的研究和治疗提供新的思路和方向，本文对肠道微生物在骨骼肌萎缩中的作用及其潜在作用机制进行系统的分析与阐述。

1 肠道微生物与骨骼肌的相互作用机制

1.1 肠-肌轴与代谢调节

肠道微生物作为一个庞大而复杂的生态系统，在人体代谢中扮演着关键角色，并与骨骼肌代谢紧密相连，形成了肠-肌轴这一重要的交互途径。肠道微生物的组成受到宿主遗传背景、年龄、饮食、药物等多种因素的精细调控。其中，饮食因素尤为突出，例如膳食纤维的摄入可显著影响肠道微生物的群落结构，富含膳食纤维的食物能够促进有益菌的生长，进而改变肠道微生物的代谢产物谱[3]。

微生物代谢产物，如短链脂肪酸（SCFAs）、次级胆汁酸（SBAs）和硫化氢（H_2S）等，是肠-肌轴调节骨骼肌代谢的关键介质。短链脂肪酸主要由肠道微生物发酵膳食纤维产生，包括乙酸、丁酸和丙酸等[4]。它们在维持肠道屏障完整性方面发挥着不可或缺的作用。在细胞能量代谢层面，短链脂肪酸可作为结肠细胞的重要能量来源，特别是在骨骼肌中，短链脂肪酸能够诱导活性氧（ROS）形成和调节线粒体能量代谢，激活腺苷酸活化蛋白激酶（AMPK）、过氧化物酶体增殖物激活受体γ共激活因子1α（PGC1α）和沉默调节蛋白1（SIRT1）等关键信号通路[4] 。短链脂肪酸还可以激活过氧化物酶体增殖物激活受体（PPARs）家族。PPARs 家族在骨骼肌细胞能量代谢

中发挥关键作用，PPARα调节脂肪酸的β氧化和能量稳态，PPARβ/δ参与能量消耗调节，PPARγ影响细胞能量和脂肪代谢，共同确保骨骼肌细胞的能量供应；PPARs家族还参与肌肉疾病相关过程，与肌肉病理状态下的能量代谢改变密切相关，影响着骨骼肌能量代谢模式。另据报道，肠道菌群失调会破坏肠上皮屏障，使细菌及其产物移位，并引发炎症，进而影响骨骼肌功能。如短链脂肪酸（SCFAs）可调节肠上皮屏障完整性，而肠道菌群失调时会导致脂多糖（LPS）等进入循环系统，激活炎症通路，损害骨骼肌[5]。

此外，次级胆汁酸可间接作用于肠道细胞，通过激活法尼醇X受体（FXR），诱导成纤维细胞生长因子19（FGF19）/FGF15的表达。FXR的激活在代谢调节中具有多方面的作用，它能够降低胰岛素抵抗，有效防止肌肉脂肪沉积，同时调节脂质代谢和炎症反应[6]。在骨骼肌中，FXR信号通路的激活可降低类固醇1c反应蛋白（SREBP1c）、碳水化合物反应蛋白（ChREBP）和PPARα等关键蛋白的表达，这些蛋白在脂肪酸合成、肌肉纤维类型确定以及脂肪酸吸收和氧化等过程中发挥着重要的调控作用，从而维持骨骼肌代谢的稳态平衡[7]。

在动物实验中，无菌小鼠由于缺乏肠道微生物，其骨骼肌出现明显的代谢紊乱，而当将正常肠道微生物移植到无菌小鼠体内，可显著改善其肌肉的氧化代谢能力，增加骨骼肌质量，减少肌肉萎缩标志物的表达，充分证明了肠道微生物在维持骨骼肌正常代谢功能中的关键作用[8]。另有临床研究显示，在20例烧伤面积≥20%的特重度烧伤患者中，血清色氨酸水平显著降低，第三腰椎骨骼肌指数（L3-SMI）较健康志愿者明显下降，提示肠道微生物介导的色氨酸代谢紊乱参与肌肉萎缩[9]。另有动物实验进一步证实，抗生素清除肠道菌群可减轻烧伤大鼠胫骨前肌、趾长伸肌等肌肉质量下降及肌纤维横截面积减小，抑制萎缩标志物MAFbx和MuRF-1表达，而移植烧伤大鼠粪便则加剧受体鼠肌肉萎缩，伴随变形菌门及埃希氏菌-志贺氏菌属丰度升高。补充色氨酸可逆转烧伤大鼠肌纤维萎缩，增加肌肉重量，上调结肠吲哚胺2，3-双加氧酶1（IDO-1）和芳香烃受体（aryl hydrocarbon receptor，AHR）表达[10-12]。此外，抑制结肠IDO-1（如帕马汀处理）可通过阻断色氨酸-犬尿氨酸代谢轴，缓解烧伤诱导的肌肉萎缩[13-15]。这些结果主要来自动物模型（大鼠n=5~8/组），部分结果来自临床研究，但临床样本量较小，动物与临床研究均提示肠道微生物-色氨酸代谢-芳香烃受体通路的关键作用，为烧伤后肌肉萎缩干预提供了潜在靶点，其普适性需更大规模临床研究验证[9]。

上述研究揭示了肠道微生物-色氨酸代谢通路在烧伤后肌肉萎缩中的关键作用，而壳聚糖/海藻酸钠包裹的携带pET28a-T5-CAT-SOD质粒的大肠杆菌Nissle 1917（ECN-pE$(C/A)_2$）系统则通过创新的纳米递送策略，为靶向调控这一代谢轴提供了新的实践方向。ECN-pE$(C/A)_2$系统通过纳米递送策略协同调控肠道-肌肉代谢轴，该系统调节肠道菌群，使产丁酸菌*Lachnospiraceae*_NK4A136和*Odoribacter*丰度增加，抑制肌内脂肪沉积相关的SREBP1c/PPARα异常信号[16]。图1展示了肠-肌轴的调控机制[17]。

1.2　免疫反应调节

在骨骼肌萎缩相关疾病中，肠道菌群可通过调节免疫反应发挥重要作用。肠道菌群与肠道免疫细胞相互作用维持免疫稳态，Toll样受体感知菌群变化，从而引发炎症反应，而炎症与骨骼肌萎缩紧密相关，肠道菌群可通过调控肠道免疫影响骨骼肌萎缩进程。在多种骨骼肌萎缩相关疾病中，肠道菌群变化显著影响免疫，进而推动肌肉萎缩发生发展。如重症肌无力患者肠道菌群多样性降低，菌群失调引发免疫失衡和慢性炎症，从而影响骨骼肌功能[18]；炎症性肌病患者肠道内炎症相关细菌增多、产丁酸细菌减少，破坏免疫平衡，而低剂量IL-2治疗可调节菌群、抑制炎症，改善骨骼肌功能；肌萎缩侧索硬化患者肠道有益菌减少、炎症水平升高，免疫反应异常损害运动神经元和骨骼肌；脊髓损伤患者肠道菌群结构改变，影响肠道屏障和免疫调节，引发全身炎症，损伤骨骼肌，阻碍恢复[19]。

NOD样受体（NLRs）是肠道微生物与免疫系统相互作用的重要参与者。NLRs 是一类多蛋白细胞质复合物，能够感知多种微生物分子和内源性应激信号，激活炎性小体的组装[20]。例如，NLRP3炎性小体在受到刺激时，可产生促炎细胞因子IL-1β和IL-18，这些细胞因子可通过血液循环或旁分泌途径作用于骨骼肌，影响骨骼肌的代谢和功能，加剧骨骼肌萎缩的进程[21]。

在骨骼肌萎缩研究中，肠道微生物与T细胞密切相关。在胃肠道中，微生物群落的组成和代谢产

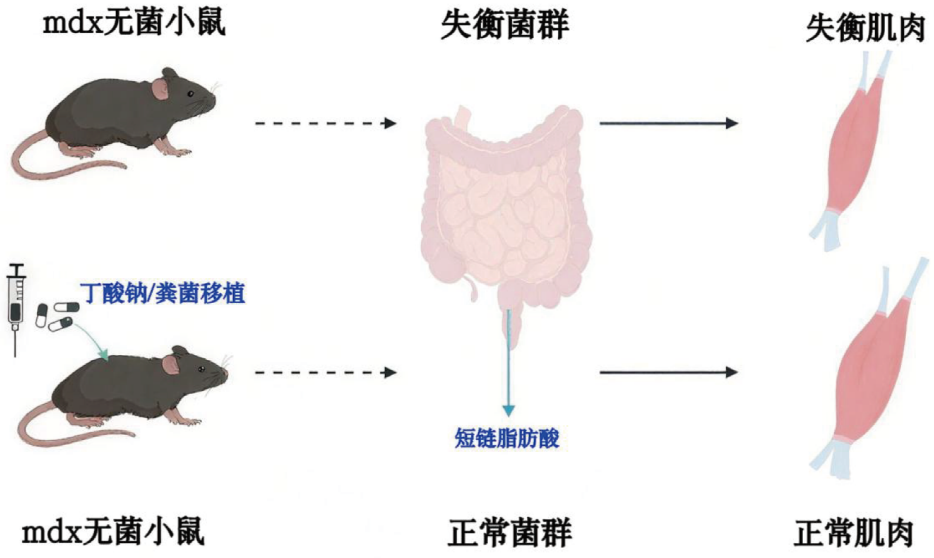

图1 肠-肌轴[17]

肠-肌轴调控机制:mdx无菌小鼠肠道内若为失衡菌群,则可致肌肉失衡;经丁酸钠/粪菌移植干预,肠道恢复正常菌群,借助短链脂肪酸改善,使肌肉回归正常状态。粪菌移植、短链脂肪酸参与肠道菌群-肌肉健康交互调控,揭示肠道菌群干预影响肌肉功能的路径。

Figure 1 Gut-muscle axis regulatory mechanism of the gut-muscle axis

In germ-free mdx mice, an imbalanced gut microbiota can lead to muscular dysfunction. Interventions such as sodium butyrate (NaB) supplementation or fecal microbiota transplantation (FMT) restore a healthy gut microbiota, which improves muscle homeostasis via the action of short-chain fatty acids (SCFAs), thereby normalizing muscle function. FMT and SCFAs are key components in the bidirectional regulation between gut microbiota and muscle health, revealing the pathways through which gut microbiota interventions impact muscle function.

物可调节T细胞向不同亚群(如Th1、Th2、Th17和Treg)的分化。分节丝状菌可促进Th17细胞分化,梭菌属诱导Treg细胞产生。这些T细胞亚群变化经免疫调节等机制影响骨骼肌萎缩进程,肠道微生物或是防治骨骼肌萎缩的潜在靶点[22]。已有研究表明,Treg细胞在骨骼肌的修复和再生中发挥着关键作用。在健康肌肉中,Treg细胞可分泌如IL-10等抗炎细胞因子,调节免疫反应,营造利于肌肉细胞分化和增殖的环境。同时,Treg细胞能分泌双调蛋白,直接作用于肌肉干细胞,刺激其增殖和迁移,助力肌肉组织的修复[23]。

在肠道微生物介导的骨骼肌萎缩研究中,单细胞RNA测序技术可深入解析免疫细胞异质性及动态调控网络。通过对肠道固有层、肠系膜淋巴结及骨骼肌组织的单细胞测序,能精准捕捉NOD样受体(NLRs)激活后,NLRP3炎性小体相关巨噬细胞亚群(如促炎性M1巨噬细胞)的转录特征,以及T细胞亚群(Th17、Treg)的分化轨迹[24,25]。在肌萎缩侧索硬化模型中,低强度脉冲超声可下调小胶质细胞中Hist1h2ap、Fos等增殖基因,阻断G_2/M 检查点通路,显著降低脊髓IL-1β炎症信号。低强度脉冲超声介导的血脊髓屏障开放促进脊髓$CD4^+$ T细胞浸润,激活IL-2/STAT5信号轴,诱导Treg细胞分泌IL-10并抑制巨噬细胞M1极化,形成免疫负反馈调节。跨器官调控显示,低强度脉冲超声通过脊髓-肌肉免疫轴抑制骨骼肌萎缩标志物MAFbx、MuRF-1表达,使模型鼠生存时间延长,证实其在“脊髓免疫-肌肉代谢”轴中的关键调控作用[26,27]。

此外,壳聚糖/海藻酸钠纳米包裹使ECN-pE肠道定植率提升,原位表达的CAT/SOD清除肠道ROS达94%,显著修复肠屏障紧密连接蛋白ZO-1,阻断脂多糖入血引发的全身免疫激活,减少肌纤维炎症浸润。纳米递送系统还通过改善肠道微生态,间接抑制肠道IDO-1活性,阻断色氨酸-犬尿氨酸代谢轴对肌肉萎缩通路的激活(MAFbx/MuRF-1表达降低),形成“肠道菌群-免疫代谢-肌肉功能”跨器官调控网络,缓解炎症性肠病模型中的肌代谢紊乱[16,28]。

综上所述,肠道菌群可通过调节免疫反应和影

响T细胞亚群分化作用于骨骼肌萎缩进程，其中NOD样受体在上述进程中扮演重要角色，而Treg细胞对骨骼肌修复再生有重要意义。

2 肠道微生物在不同类型骨骼肌萎缩中的作用

2.1 肠道微生物在杜氏肌营养不良症(DMD)相关骨骼肌萎缩中的作用

DMD是由肌营养不良蛋白基因突变引发的X连锁隐性疾病，致使肌肉纤维稳定性下降，出现肌肉萎缩和功能丧失，同时伴有线粒体功能障碍、钙稳态失衡、免疫炎症反应等多种病理过程[29]。

在DMD患者中，肠道微生物的组成发生显著改变。研究发现，与健康人群相比，DMD患者肠道中的放线菌门、变形菌门、柔膜菌门和脱铁杆菌门的丰度出现明显变化，其中一些特定的属和种，如*Mucispirillum*属、Deferribacteraceae 科、*Enterorhabdus*属、Coriobacteriaceae科和Rhdospirillaceae 科等，在DMD患者肠道中的分布与健康人存在显著差异[30]。此外，DMD患者肠道中产生LPS的革兰氏阴性菌(如Deferribacteres门、拟杆菌属)增多，这可能与肠道炎症和屏障功能受损密切相关。肠道屏障功能的破坏在DMD疾病进程中起到了关键的推动作用，表现为紧密连接蛋白(Tjp1和Tjp2)表达降低，肠道通透性增加，使得细菌及其产物更容易进入血液循环，引发全身炎症反应，进一步加剧骨骼肌的损伤和萎缩[31]。

在DMD引发的骨骼肌萎缩进程中，肠道微生物扮演着关键角色(图1)。据报道，DMD的mdx小鼠模型存在明显的肠道菌群失调，这一变化致使循环短链脂肪酸(SCFAs)代谢紊乱，血浆丙酸盐和乙酸盐水平显著下降[32]。SCFAs作为肠道微生物的重要代谢产物，其水平降低会干扰肌肉自噬和炎症稳态。补充丁酸钠(NaB)[17]可有效改善mdx小鼠的肌肉力量和运动协调能力，同时抑制促炎因子(Il-6、Tnfa、Cox2)的过度升高，进而缓解骨骼肌萎缩症状，表明调节肠道微生物代谢产物SCFAs的水平对改善DMD相关的骨骼肌萎缩具有重要作用[33]。在DMD患者及mdx小鼠中，肠道微生物与内源性大麻素系统(ECS)存在交互作用，从而影响骨骼肌萎缩。据报道，DMD模型小鼠血浆中内源性大麻素花生四烯酸乙醇胺(AEA)水平显著升高，同时骨骼肌CB1和CB2受体表达上调，ECS过度激活可通过抑制肌肉自噬并加剧炎症反应，加速骨骼肌萎缩进程[34,35]。研究也表明，丁酸钠(NaB)可通过激活GPR109A和PPARγ受体，调控ECS相关基因表达，抑制LPS诱导的炎症因子(Il-6、Cox2)并促进自噬，从而改善肌肉功能[36,37]。

因此，肠道微生物在DMD相关骨骼肌萎缩的发生和发展过程中扮演着重要角色，其作用机制主要是影响代谢产物水平和内源性大麻素系统的活性。

2.2 肠道微生物在1型强直性肌营养不良症(MD1)相关骨骼肌萎缩中的作用

MD1是常染色体显性遗传性神经肌肉疾病，由DMPK基因非编码区CTG重复序列扩增所致，引发基因转录异常及多种蛋白质功能缺陷，患者常出现进行性肌肉无力、萎缩等表现，其中骨骼肌萎缩对患者身体机能影响显著[38]。同时，胃肠道功能障碍在MD1患者中较为常见，例如腹泻与便秘交替、腹痛等诸多胃肠道症状不仅影响生活质量，还可能与肠道微生物失调密切相关，而肠道微生物失调可能进一步加剧骨骼肌萎缩的进程，值得深入探究[39-41]。

研究发现，MD1患者的肠道微生物组成发生了明显的改变[42]。与健康对照组相比，患者肠道中Firmicutes/Bacteroidetes(F/B)比值发生变化[43]，通常表现为Firmicutes相对丰度的改变，且Actinobacteria门(包括*Corynebacterium*、*Rothia* 和DNF00809等属)的丰度相对较低。在属水平上，*Clostridium* CAG352的相对丰度增加，*Lachospiracea*和*Prevotella*的丰度也有所升高，而有益菌*Lactobacillus* 的含量则减少。*Lactobacillus*作为一种益生菌，具有抑制病原菌生长和黏附、促进其清除的作用，其在MD1患者肠道中的减少可能破坏肠道微生态平衡，进而导致骨骼肌萎缩[44]。

目前缺乏明确有效的临床干预方案，补充乳杆菌属等益生菌及调节膳食纤维为潜在策略，但效果尚待进一步研究验证。

2.3 肠道微生物在衰老性骨骼肌萎缩中的作用

衰老伴随的肠道微生物群多样性下降与肌肉质量降低密切相关[45]。据报道，老年人群中肠道微生物Bacteroidetes丰度降低，而Enterobacteriaceae增加，这种失衡与肌肉炎症和胰岛素抵抗相关。补充*Lactobacillus casei*可通过调节mTOR通路，抑制肌肉蛋白质分解，改善老年小鼠的肌肉功能[5,46]。

对衰老加速(SAMP8)小鼠的研究发现，老龄SAMP8小鼠肠道菌群的*Odoribacter* 和*Oscillibacter*等

菌属显著富集,它们与肌肉及线粒体功能呈负相关,却和炎症、衰老特征正相关。而补充干酪乳杆菌代田株(LcS)能调节肠道菌群,提升*Lachnospiraceae*_UCG_006等有益菌的相对丰度,恢复衰老小鼠下降的短链脂肪酸水平,减轻炎症,抑制肌肉蛋白质分解,改善肌肉力量和线粒体功能,缓解骨骼肌萎缩[47]。

此外,短链脂肪酸(尤其是丁酸)水平随年龄增长显著下降,补充丁酸可通过抑制组蛋白去乙酰化酶(HDAC)活性,延缓肌肉萎缩[48]。

2.4 肠道微生物在神经源性骨骼肌萎缩中的作用

脊髓损伤或周围神经病变可导致失神经支配肌肉萎缩。在神经源性骨骼肌萎缩研究领域,脊髓损伤或周围神经病变引发的失神经支配肌肉萎缩备受关注,肠道微生物群在此过程中作用关键。

肌萎缩侧索硬化症(ALS)是一种运动神经元退行性疾病,其肌肉萎缩的直接原因是运动神经元退化导致的神经支配丧失。研究发现,ALS患者肠道菌群显著失调,瘤胃球菌、拟杆菌丰度降低,普雷沃泰氏菌、梭状杆菌等增多,部分亚型(SALS/BALS)患者粪便/口腔中厚壁菌/拟杆菌(F/B)比率异常[49-51]。肠道屏障受损促使脂多糖入血,激活NADPH氧化酶2通路,升高IL-2、IgA等促炎因子,加剧神经炎症与运动神经元退化[52]。此外,患者肠道碳代谢及丁酸通路异常,短链脂肪酸紊乱,可能通过干扰线粒体功能与免疫稳态加速肌肉萎缩。益生菌可调节菌群但对疾病进展无效,补充丁酸酯[53,54]或抑制肉碱棕榈酰转移酶1[55,56]可改善突变超氧化物歧化酶1(SOD1G93A)家族性ALS模型小鼠症状,提示靶向微生物代谢为潜在方向[57-59]。

2.5 肠道微生物在肿瘤恶病质引发的骨骼肌萎缩中的作用

肿瘤恶病质引发的骨骼肌萎缩与肠道微生物群变化密切相关,恶病质患者通常会出现体重减轻、脂肪减少、食欲下降以及全身炎症反应等症状[60,61]。据报道,恶病质患者肠道微生物群中,变形菌门和肠杆菌科增多,韦荣球菌属和乳杆菌属减少[62]。这种变化干扰营养吸收、加剧炎症,促使肌肉质量下降[19,59]。

对动物模型的研究表明,肠道微生物在肿瘤恶病质引发的骨骼肌萎缩中作用关键。在相关小鼠模型中,肠道内乳杆菌属丰度下降,同时肠杆菌科细菌大量繁殖[63]。其中,产酸克雷伯菌作为肠杆菌科的关键物种,在结肠癌小鼠模型中显著增多,这与临床患者数据相符[64]。通过粪菌移植(FMT)将健康肥胖个体的粪便微生物群移植到胃肠道癌症患者体内,虽未改变恶病质特征,但延长了患者生存期[65],提示FMT调节肠道微生物群或对改善肿瘤恶病质状况有益,未来或可成为干预肿瘤恶病质引发骨骼肌萎缩的新方向。

此外,基于益生元和益生菌的有益特性,由菊粉型果聚糖与鲁氏乳杆菌组成的共生方案,可有效纠

表1 肠道微生物在不同类型骨骼肌萎缩中的作用

Table 1 The role of gut microbiota in various types of skeletal muscle atrophy

骨骼肌萎缩类型	杜氏肌营养不良症(DMD)骨骼肌萎缩	1型强直性肌营养不良症(MD1)骨骼肌萎缩	衰老性骨骼肌萎缩	神经源性骨骼肌萎缩	肿瘤恶病质骨骼肌萎缩
肠道菌群改变	产脂多糖革兰氏阴性菌增多,黏液螺旋菌属、脱铁杆菌科等异常,短链脂肪酸代谢紊乱	厚壁菌门/拟杆菌门比值失衡,放线菌门丰度降低,乳杆菌属减少,梭菌属CAG352等增多	拟杆菌门丰度降低,肠杆菌科增加,短链脂肪酸(尤其丁酸)水平下降	瘤胃球菌、拟杆菌丰度降低,普雷沃泰氏菌、梭状杆菌等增多	变形菌门、肠杆菌科增多,韦荣球菌属、乳杆菌属减少
作用机制	肠道屏障破坏,短链脂肪酸干扰肌肉自噬与炎症稳态,内源性大麻素系统过度激活加剧炎症	肠道微生态失衡,有益菌抑菌能力下降,破坏肠道稳态并影响骨骼肌修复	诱发肌肉炎症与胰岛素抵抗,短链脂肪酸缺乏影响肌肉能量代谢及修复	碳代谢及丁酸通路异常,短链脂肪酸紊乱,通过干扰线粒体功能与免疫稳态加速肌肉萎缩	干扰营养吸收、加剧炎症,促使肌肉质量下降
干预措施	补充丁酸钠	补充乳杆菌属益生菌;增加膳食纤维摄入	补充干酪乳杆菌;调节膳食纤维	补充益生菌;补充丁酸酯或抑制肉碱棕榈酰转移酶1	粪菌移植、给予果聚糖+鲁氏乳杆菌、富含纤维的益生元、蛋壳膜
干预效果	改善肌肉力量与运动协调能力,抑制促炎因子,缓解骨骼肌萎缩	改善肠道微生态,减轻炎症,潜在调节骨骼肌萎缩(临床效果待验证)	提升有益菌丰度,恢复短链脂肪酸水平,改善肌肉力量与线粒体功能	调节菌群,改善小鼠肌萎缩侧索硬化症模型肌肉症状	改善肠道微生物失调状况,减轻恶病质相关骨骼肌萎缩
参考文献	[30,36]	[42,43]	[46-48]	[50-52]	[60-62]

正恶病质引发的肠道微生物区系失调[66]；富含纤维的益生元碳水化合物，作为一种新兴的饮食策略，有调节恶病质状态下的肠道微生物区系，对缓解恶病质相关的骨骼肌萎缩具有潜在益处[67]；除了益生元补充剂，蛋壳膜（ESM）同样能够改善肠道微生物失调状况，减轻恶病质相关骨骼肌萎缩[68]。

这些研究表明，调节肠道微生物群及其代谢产物，或为防治肿瘤恶病质相关骨骼肌萎缩提供新策略。

表1总结了肠道微生物在不同类型骨骼肌萎缩中的作用。

3 干预肠道微生物治疗骨骼肌萎缩的策略

鉴于肠道微生物在骨骼肌萎缩中的重要作用，调节肠道微生物组成和功能成为治疗相关骨骼肌萎缩的潜在策略。目前，主要的干预方法包括补充益生菌、益生元以及进行FMT等。

3.1 益生菌

益生菌是一类对宿主有益的活性微生物，补充特定的益生菌菌株可能有助于改善肠道微生物平衡，减轻炎症反应，进而改善骨骼肌萎缩。在动物实验中发现，补充植物乳杆菌能够增加肌肉质量，降低炎症和肌肉萎缩标志物的表达，显示出一定的治疗潜力[69]。另有研究表明，鼠李糖乳杆菌能通过增加短链脂肪酸产量，改善肠道屏障功能，从而减少系统性炎症，缓解肌肉蛋白质分解代谢[70]；长双歧杆菌可通过调控mTOR信号通路，促进肌肉蛋白质合成，同时抑制NF-κB介导的炎症反应，改善肌肉功能[71]。另有临床研究显示，老年肌少症患者肠道中产短链脂肪酸菌（如普雷沃氏菌、粪球菌属）丰度显著降低，而促炎菌属（如肠杆菌科）增加，这种失衡通过加剧慢性炎症和胰岛素抵抗加速肌肉流失。多项临床试验表明，益生菌干预可通过调节肠-肌轴改善老年肌肉功能[72]。一项纳入8项随机对照试验的荟萃分析（n=396）发现，老年人每日补充含乳杆菌和双歧杆菌的多菌株益生菌（如Vivomixx®，1120亿CFU/日）12~16周后，握力显著提升，步速显著提高，且血清促炎因子IL-6下降。这一效果与干酪乳杆菌的核心作用机制直接相关，干酪乳杆菌通过抑制肠道有害菌（如肠杆菌科）、促进短链脂肪酸（如丁酸）生成，降低系统性炎症，从而缓解肌肉蛋白质分解[73]。补充干酪乳杆菌代田株（LcS）联合亮氨酸和ω-3脂肪酸，使老年受试者握力显著提升，其机制与恢复短链脂肪酸水平、抑制肌肉萎缩基因（MuRF1/Atrogin-1）表达相关。这些证据凸显了肠道微生态干预作为肌肉萎缩防治新策略的临床潜力[74]。

然而，不同的益生菌菌株对肠道微生物群落和宿主的影响可能存在差异，因此需要进一步筛选和验证有效的益生菌菌株，并深入研究其作用机制。

3.2 益生元

益生元是一类能够选择性地促进肠道有益菌生长和代谢的物质，通过调节肠道微生物的组成和代谢产物，间接影响骨骼肌的功能。常见的益生元包括膳食纤维、低聚果糖、菊粉等。

膳食纤维可被肠道微生物发酵产生短链脂肪酸等有益代谢物，从而改善肠道屏障功能，调节免疫反应，促进线粒体生物发生，对骨骼肌萎缩起到一定的缓解作用[75]。低聚果糖能增加肠道中双歧杆菌等有益菌的数量，提升肠道有益菌的活力，抑制有害菌生长，优化肠道微生态环境，进而改善骨骼肌的营养供应和代谢环境，缓解骨骼肌萎缩[76]。菊粉被肠道微生物利用后，不仅能促进有益菌增殖，还可调节机体的能量代谢和炎症反应，减少炎症因子对骨骼肌的损伤，有助于维持骨骼肌的质量和功能[77]。另有临床试验结果显示，与老年受试者对照组相比，菊粉补充组老年受试者的肌肉氧化代谢能力提升，IIA型肌纤维比例增加，表明肠道微生物调控可直接作用于肌纤维组成，改善肌肉功能[73]。

未来的研究需要进一步探索不同类型益生元的作用效果和最佳使用剂量，以及它们与益生菌之间的协同作用机制。

3.3 粪菌移植

粪菌移植是一种将健康供体的粪便微生物群移植到患者肠道内的治疗方法，旨在重建患者的肠道微生物生态系统。据报道，将正常肠道微生物群移植到mdx小鼠体内后，炎症性肌肉反应减轻，肌肉纤维横截面积减小、纤维浸润、脂质和碳水化合物代谢异常以及肌肉收缩力下降等病理和功能缺陷得到改善，为FMT治疗骨骼肌萎缩相关疾病提供了有力证据[78,79]。然而，FMT的安全性、有效性和标准化操作流程仍需要进一步深入研究和完善，同时需要明确适合进行FMT的患者人群和疾病阶段。

4 结论与展望

综上所述,肠道微生物在骨骼肌萎缩的发生发展过程中扮演着重要的角色,其与骨骼肌之间通过复杂的信号通路和分子机制相互影响。在多种肌营养不良症及其他相关疾病中,肠道微生物的组成和功能失调与骨骼肌萎缩的严重程度密切相关,为深入理解这些疾病的发病机制提供了全新的视角。

然而,目前该领域的研究仍存在诸多挑战与不足。尽管大量动物实验为肠道微生物与骨骼肌萎缩的关联提供了有力证据,但在人体临床试验方面仍相对匮乏,需要更多大规模、多中心的临床研究进一步验证动物实验结果的可靠性和适用性,从而为基于肠道微生物的治疗策略在临床实践中的应用提供坚实的依据。

未来的研究方向应聚焦于以下几个关键领域:一是深入探究肠道微生物与骨骼肌之间的分子信号转导机制,明确不同微生物代谢物和免疫调节因子在其中的具体作用靶点和信号转导途径,为开发精准的治疗药物奠定基础;二是进一步挖掘潜在的益生菌、益生元和微生物代谢物等,通过优化筛选方法和开展联合治疗研究,提高治疗效果;三是加强对肠道微生物群落的动态监测和调控技术的研发,以便能够实时评估肠道微生物的变化,并及时采取有效的干预措施,实现个性化的治疗。

随着对肠道微生物在骨骼肌萎缩中作用机制的不断深入理解和研究技术的持续创新,有望开发出一系列基于肠道微生物调节的新型治疗方法,为改善骨骼肌萎缩患者的预后和生活质量提供新的思路和策略。

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