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骨骼肌卫星细胞介导的肌肉再生在年龄相关肌少症治疗中的作用*

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摘要　年龄相关肌少症是一种与衰老相关的进行性全身性骨骼肌疾病，主要表现为肌肉质量、力量和身体功能的显著下降，而非正常衰老的必然结果。该病患病率高，伴随全球老龄化加剧，预计未来发病率将持续上升，构成重大公共卫生挑战。年龄相关肌少症不仅会显著增加身体残疾的风险，还对患者的生活质量、独立性及总体生存率产生深远影响。因此，亟需开发有效防治策略，以减轻其对社会和个体健康的双重负担。骨骼肌再生作为维持肌肉健康的关键生理过程，其功能障碍是导致年龄相关肌少症的重要原因之一。骨骼肌卫星细胞（muscle satellite cells，MSCs），即骨骼肌干细胞，是生成新肌纤维的核心细胞群，在肌肉再生及维持肌肉质量和功能中扮演着不可或缺的角色。MSCs的数量减少或功能异常与肌少症的发生发展密切相关。MSCs内在机制的改变（如Notch、Wnt/β-Catenin、mTOR等信号通路，转录因子和表观遗传修饰等）、微环境的变化（包括骨骼肌纤维及其分泌的细胞因子构成的直接微环境和细胞外基质蛋白和大量细胞构成的间接微环境）、线粒体功能障碍以及慢性炎症等因素，均可导致MSCs功能失调，进而引发年龄相关肌少症。目前，临床上尚缺乏针对该疾病的有效药物，主要依赖营养干预和运动疗法。在确保能量充足的基础上摄入足量蛋白质是防治年龄相关肌少症的关键，膳食补充剂、热量限制等辅助疗法也为改善年龄相关肌少症提供了新的可能性。运动可以通过机械应力、肌肉因子、远程细胞因子、免疫及表观遗传调控靶向MSCs，促进肌肉再生，改善年龄相关肌少症。对于行动受限、健康状况不佳或严重肌少症患者，传统方法可能难以满足需求。然而，新兴的治疗策略，如miRNA模拟物或抑制剂的应用、肠道菌群移植以及干细胞疗法等，为基于MSCs的干预提供了新的方向。本文总结MSCs介导的肌肉再生在年龄相关肌少症中的作用及机制进展，系统探讨通过调控MSCs介导的肌肉再生进而改善肌肉质量和力量的年龄相关肌少症的靶向治疗策略，旨在为年龄相关肌少症的防治提供理论依据和未来研究方向。

关键词　年龄相关肌少症，骨骼肌卫星细胞，衰老，运动，营养
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年龄相关肌少症是一种与衰老密切相关的进行性全身性骨骼肌疾病，其特征为肌肉质量、力量及身体功能的显著衰退，虽与年龄增长相关，但并非正常衰老的必然表现，属于原发性肌少症范畴[1]。目前，该疾病的诊断标准及症状尚未形成全球统一的医师共识[2]。欧洲肌少症工作组、亚洲肌少症工作组和中国专家组提出的诊断标准存在差异（表1）[1, 3-5]。根据欧洲肌少症工作组的定义，60岁以上人群中肌少症的患病率为10%~27%，其中2%~9%为严重病例[6]。而亚洲肌少症工作组的数据显示，65岁以上人群的患病率高达41.0%[7]。无论采用何种标准，年龄相关肌少症的患病率均居高不下。随着全球人口老龄化趋势的加剧，预计未来其患病率将进一步攀升，成为一项严峻的公共卫生挑战。

年龄相关肌少症不仅显著增加身体残疾的风险，还对患者的生活质量、独立性及总体生存率产生深远影响。一项针对60岁以上社区老年人的研究表明，肌少症患者与非肌少症患者的预估寿命相近（分别为22.7岁和22.5岁），但肌少症患者的预估残疾寿命占其总寿命的比例是非肌少症患者的3倍[8]。此外，对14 585名65岁以上人群的数据分

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析显示，严重肌少症与生活质量下降密切相关，这一现象可通过肌少症相关的残疾状态得到解释[9]。然而，目前针对该疾病的临床药物仍极为有限，主要依赖运动锻炼和营养干预等非药物手段。因此，开发有效的防治策略以减轻其对社会和个体健康的双重负担，已成为当前亟待解决的重要课题。

Table 1 Diagnostic criteria for age-related sarcopenia

表1 年龄相关肌少症诊断标准

	握力/kg		四肢肌肉质量指数/(kg•m^{-2})		躯体功能			参考文献
	男	女	男	女	6 m步速/(m•s^{-1})	5次椅子站坐试验/s	SPPB分数	
EWGSOP2	<27	<16	<7.0（DXA或BIA）	<5.5（DXA或BIA）	<0.8	≥15	≤8	[1]
AWGS 2019	<28	<18	<7.0（DXA）<7.0（BIA）	<5.4（DXA）<5.7（BIA）	<1.0	≥12	≤9	[3]
老年人肌少症防控干预中国专家共识（2023）	<28	<18	<7.0（DXA）<7.0（BIA）	<5.4（DXA）<5.7（BIA）	<1.0	—	—	[4]
中国肌肉减少症诊疗指南（2024版）	<28	<18	<7.0（DXA）<7.0（BIA）	<5.4（DXA）<5.7（BIA）	<1.0	≥12	≤9	[5]

EWGSOP：欧洲肌少症工作组（European Working Group on Sarcopenia in Older People）；AWGS：亚洲肌少症工作组（Asian Sarcopenia Working Group）；DXA：双能X线吸收法（dual energy X-ray absorptiometry）；BIA：生物电阻抗分析法（bio-electrical impedance analysis）；SPPB：简易体能测试量表（short physical performance battery）。肌少症的定义基于3个主要标准：a. 肌肉力量降低；b. 同时伴有肌肉质量和数量受损；c. 患者身体机能下降。通过第一个标准为“肌少症可能”，通过第二个标准确认诊断。如果患者满足所有3个标准，则被诊断为“重度肌少症”。

肌少症可分为继发性与原发性两类。继发性肌少症通常由明确诱因引发，如长期卧床导致的肌肉废用、失重或微重力环境、肿瘤恶病质等；而原发性肌少症则主要与年龄相关，无明显诱因。其发病机制复杂，涉及蛋白质代谢异常、运动神经元退化、合成代谢激素减少、线粒体功能障碍、纤维化及脂肪浸润、慢性炎症和遗传因素等多种病理过程。随着研究的深入，年龄相关肌少症的病理生理途径逐渐被揭示，特定生物标志物和潜在防治靶点也日益明确[10-11]。

衰老过程中，肌肉质量、力量及身体运动能力会出现不同程度的下降。肌肉质量与力量在18~30岁达到峰值，随后从30岁起每10年减少约3%~8%，60岁后下降速度加快，且男性较女性更为显著。由于肌肉细胞更新周期长达约10年，肌肉退化与再生失衡最终导致肌肉萎缩，表现为肌肉质量与力量的显著下降。年龄相关肌少症的重要病因之一是肌肉再生功能障碍。骨骼肌作为一种高度异质性的组织，由多核肌纤维、骨骼肌卫星细胞（muscle satellite cells，MSCs）及非成肌细胞组成。其中，MSCs是肌肉再生的中坚力量，是新肌纤维生成的主要来源，在维持肌肉质量和功能中发挥不可替代的作用[12]。然而，随着年龄增长，MSCs的自我更新及成肌能力逐渐下降，直接导致年龄相关肌少症的发生[13]。因此，本文聚焦于MSCs介导的肌肉再生在年龄相关肌少症中的作用，系统探讨以MSCs为靶点的治疗策略及其研究进展，结合临床及临床前研究，为年龄相关肌少症的干预提供科学依据和可行性方案。

1 MSCs在肌肉再生中的功能及特征

肌肉再生是维持肌肉质量和功能的关键生理过程，而年龄相关肌少症常伴随这一过程的显著受损[14-15]。骨骼肌再生是一个高度协调的复杂过程，主要由MSCs主导，并依赖多种细胞的动态协作。MSCs，又称骨骼肌干细胞，是一类具有高核质比的小型梭形细胞，位于肌纤维基底膜与肌浆膜之间，是新肌纤维生成的主要来源[16]。MSCs通过持续的自我更新维持骨骼肌的完整性，对肌肉质量的保持及损伤后的修复至关重要。因此，MSCs功能障碍被认为是年龄相关肌少症发生和发展的关键因素之一。

在正常成年个体中，MSCs的数量保持相对稳定。MSCs通过自我更新补充驻留干细胞库，从而支持肌肉在多种损伤后的再生能力[17-18]。通常情况下，MSCs处于静止状态，可逆地退出细胞周期，但仍保留重新进入增殖阶段的能力。这种静止状态由细胞自主性因子及MSCs微环境提供的外部信号

共同维持[17，19]。一旦MSCs的自我更新能力受损，将导致干细胞池耗竭，进而削弱肌肉再生能力。

在肌肉损伤或其他刺激下，MSCs会进行不对称分裂，一方面维持母细胞的干性，另一方面生成定向分化的后代。这些后代细胞被激活后，经历增殖、分化，最终形成成熟的肌纤维，以修复受损组织。肌纤维生成包括多个步骤：MSCs首先被激活进入细胞周期，随后增殖成为成肌细胞并进一步分化为肌细胞；肌细胞融合形成肌管，最终发育为成熟肌纤维；在此过程中，残留肌纤维的基底膜引导MSCs与肌纤维融合，促进肌纤维的定向再生[20-21]。此外，受损组织的MSCs储备可通过未分化的骨髓干细胞从血管系统迁移补充。肌肉再生完成后，微环境信号会促使MSCs恢复静止状态[22-23]。

MSCs的静止与激活受到多种转录因子的精确调控，这些因子可作为MSCs状态的标志物（图1）。其中，配对盒7（paired box 7，Pax7）是MSCs的典型标志物，静止期MSCs高表达Pax7但不表达成肌调节因子，激活后，MSCs逐渐失去Pax7表达并开始表达成肌调节因子。在肌肉生成的不同阶段，多种成肌调节因子依次发挥作用。例如，MSCs向成肌细胞转化时表达成肌调节因子（myogenic regulating factors，MRFs）——成肌决定因子（myogenic determining factor，MyoD）和成肌因子5（myogenic factor 5，Myf5）[21]。MyoD作为成肌分化的主控基因，其低表达标志着MSCs未分化状态，而高表达则提示细胞进入分化阶段[24]。MyoD在分化早期诱导成肌蛋白（myogenin，MyoG）和MRF4的表达[25]。此外，肌细胞增强因子2（myocyte enhancer factor 2，Mef2）家族在MSCs分化中具有冗余作用，缺乏Mef2a、Mef2c和Mef2d的MSCs虽能正常增殖，但无法完成分化[26]。在成熟肌纤维中，具有时空调控表达模式的肌球蛋白重链（myosin heavy chain，MHC）会表达[21]。研究还发现，Gli因子家族在MSCs群体中具有特异性表达模式：Gli1阳性MSCs更易进入增殖和分化状态[27]，Gli2在MSCs激活期间表达，而Gli3则对维持静止状态至关重要[28-29]。这些发现表明，MSCs的干性维持及分化调控涉及复杂的分子网络。

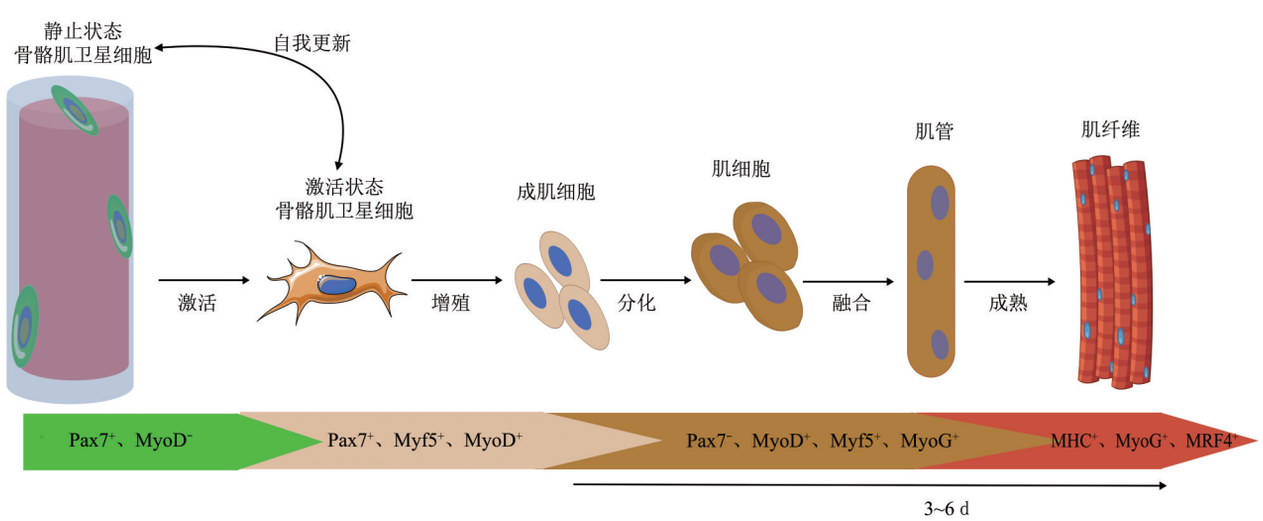

Fig. 1　Quiescence and activation of MSCs

图1　MSCs的静止和激活

Pax7：配对盒7（paired box 7），MyoD：成肌决定因子（myogenic determining factor），Myf5：成肌因子5（myogenic factor 5），MyoG：成肌蛋白（myogenin），MHC：肌球蛋白重链（myosin heavy chain），MRF4：成肌调节因子4（myogenic regulatory factors 4）。+：阳性；−：阴性。

2　MSCs介导的肌肉再生对年龄相关肌少症的作用及机制

肌纤维作为骨骼肌的主要功能单位，其大小和质量直接决定了肌肉的整体功能与力量[30]。年龄相关肌少症的发生与MSCs成肌能力减弱及肌纤维退化加速密切相关[31]。衰老会通过MSCs数量和功能变化导致肌肉再生能力下降。衰老过程中，

MSCs数量减少和功能下降是导致肌肉再生能力衰退的关键因素。研究表明，与年轻人（18~40岁）相比，老年人（70~86岁）的MSCs数量显著减少，尤其是II型肌纤维中的MSCs[32]。此外，衰老骨骼肌中MSCs的不对称分裂能力显著降低，导致其自我更新能力受损[15]。MSCs数量的减少及其功能下降被认为是衰老骨骼肌质量和功能衰退的重要原因[33]。老年个体的MSCs难以维持静息状态，转而进入衰老状态，其增殖与分化能力显著减弱[34]。这种功能丧失导致MSCs依赖性的肌肉再生能力下降，进而引发年龄相关肌少症。

2.1 MSCs内在因素对肌肉再生的影响

MSCs的静止与激活状态之间的平衡对其功能和肌肉稳态的维持至关重要，这一过程受多种内在因素调控，包括细胞周期调节剂、转录因子和表观遗传修饰等。

MSCs功能的维持受到多种信号通路的调控，通过调节肌肉再生，成为年龄相关肌少症的可能干预靶点。其中，Notch信号通路在MSCs的生命周期中发挥重要作用。Notch是一种膜蛋白受体，与配体相互作用后被切割，易位入核，激活下游靶基因。静息态MSCs具有高Notch活性，维持Pax7表达并抑制MyoD和MyoG；MSCs激活后Notch活性下降，促进MyoD表达，加速细胞增殖；成熟肌纤维中Notch保持低活性，以为静息态MSCs提供配体，并通过细胞间相互作用维持MSCs静止[35]。衰老骨骼肌中Notch信号失常，导致MSCs增殖减少，肌肉再生能力下降[36]。Notch配体以旁分泌或自分泌的形式与肌纤维上的Notch受体结合，诱导肌肉萎缩[37]。抑制Notch信号可减轻肌肉萎缩，为年龄相关肌少症治疗提供潜在策略[38]。Wnt/β-Catenin信号通路是MSCs分化的关键调控者。适度激活该通路可促进MSCs增殖，提高肌肉质量与力量，抑制骨骼肌萎缩[39]。然而，过度激活会损伤MSCs功能，抑制肌肉再生[40]。因此，Wnt信号的精确调控可能为年龄相关肌少症的治疗提供新方向。此外，哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路通过控制肌源性基因表达影响MSCs的增殖与分化。小鼠敲除mTOR后，Pax7及MyoD表达水平显著下降，MSCs的增殖和分化均被抑制[41]。mTOR复合物1的活化是MSCs激活的必要因素，其缺乏极大地影响了肌肉的再生能力[42]。mTOR复合物2虽不是肌纤维生成所必要的，但在MSCs的长期维持中发挥作用[43]。这些结果表明，mTOR信号在MSCs介导的肌肉再生起着重要作用，可能是年龄相关肌少症治疗的潜在靶点。

在肌肉骨骼系统的许多控制基因中，转录因子叉头盒蛋白O（forkhead-box-protein O，FOXO）3在MSCs稳态中起重要作用[44]。静止态MSCs中FOXO3高表达，MSCs激活态时FOXO3表达下调[45]。García-Prat等[46]将静止MSCs细分为具有干特性的真正静止态MSCs（可保存到晚年，极度衰老时才会启动）和致力于肌源性分化的启动静止态MSCs，FOXO的激活促进MSCs向真正静止态转化，而失活则推动其向启动静止态MSCs转变，促进其分化。这就解释了FOXO3缺失小鼠在肌肉损伤后，自我更新的MSCs数量减少但肌肉恢复能力增强的疑问[45]。总之，抑制FOXO3启动了MSCs分化，而激活FOXO3则保留了干细胞的命运，使FOXO3在干细胞再生中发挥保护作用，使其成为肌少症的潜在治疗靶点。此外，还有其他途径包括JAK/STAT、p38 MAPK和成纤维细胞生长因子受体1等，在老年MSCs中被激活，导致MSCs自我更新能力受损，影响肌肉再生，这意味着可通过它们调节MSCs，改善肌少症[47]。

表观遗传修饰已被证实在骨骼肌功能障碍中起着重要作用。Li等[48]对50名肌少症老年人（≥65岁）和50名年龄和性别匹配的非肌少症个体的全血样本中骨骼肌功能相关的DNA甲基化水平进行分析发现，作为纤维细胞的调控因子，成纤维细胞生长因子2（fibroblast growth factor 2，FGF2）的低甲基化水平与肌少症风险和严重程度相关，FGF2甲基化可作为筛查和评估肌少症的替代生物标志物。肌肉损伤导致MSCs的DNA甲基化产生长期变化，在驻留MSCs中得到了稳定的维持，这意味着对先前生理事件的分子记忆，这种记忆为肌少症的干预提供了潜在靶点[49]。此外，N6甲基腺苷甲基化在FOXO3依赖性萎缩中也具有重要的生物学意义[50]。最近，乳酸介导的组蛋白乳酸化被鉴定为一种促进基因转录的新型表观遗传修饰，乳酸通过激活H3K9乳酸化促进肌生成[51]。这些发现为年龄相关肌少症的筛查和干预提供了新思路。

由此可见，MSCs内在因素的变化对其数量和功能的维持至关重要，在肌少症治疗中的地位不言而喻。细胞周期调节剂wnt/β-Catenin信号通路的适度激活启动MSCs增殖、转录因子FOXO3维持MSCs细胞稳态、表观遗传修饰对MSCs介导的肌

肉再生的影响对肌少症的治疗有重要意义，特别是表观遗传修饰在肌少症的筛查、评估和防治中的作用，但要将其应用到临床仍需要深入研究。

2.2　MSCs微环境对肌肉再生的影响

MSCs的功能受到MSCs微环境的广泛调节，通过MSCs微环境细胞间相互作用响应肌肉损伤、衰老等刺激变化。MSCs微环境包含丰富的细胞外基质蛋白和大量细胞（即毛细血管内皮细胞、纤维-脂肪细胞祖细胞和免疫细胞等）及分泌因子。

骨骼肌纤维通过直接接触或分泌细胞因子调控MSCs功能。在衰老情况下，骨骼肌老化首先伴随着MSCs池的缩小，这与肌细胞因子FGF2表达增加有关。从机制上讲，FGF2会使MSCs脱离静止状态，产生自发的有丝分裂活动，同时恢复静止的能力受损，导致MSCs池耗尽[52]。同时，随着年龄增长，骨骼肌纤维中生长分化因子11表达增加，抑制邻近的MSCs增殖，影响肌肉再生[53]。MSCs微环境中分泌因子的年龄变化，会使MSCs出现老化表型，降低肌肉再生能力，而免疫细胞是细胞因子和其他分泌因子的重要来源。将富含免疫细胞的老年骨髓细胞移植到年轻动物体内会减少MSCs数量，并促进MSCs纤维化；相反，将年轻的骨髓细胞移植到老年受者体内能抑制MSCs纤维化，预防年龄相关肌少症的发生[54]。可见，微环境中分泌因子能通过MSCs介导肌肉再生能力，是肌少症干预的潜在靶点。

除了直接微环境外，细胞外基质蛋白作为MSCs微环境的主要成分是决定MSCs命运的另一个关键因素。细胞外基质可以为MSCs提供结构支撑并调控其功能。衰老过程中，细胞外基质成分失调与肌少症的肌肉再生受损有关[55]。细胞外基质蛋白主要由骨骼肌中的纤维-脂肪形成祖细胞产生，并表现出与年龄相关的差异。纤维-脂肪形成祖细胞能够与MSCs相互作用，这种细胞间通讯由FGF7-FGFR2介导，外源性FGF7促进了MSCs的增殖，从而有利于肌肉再生，并抵抗年龄相关肌少症[56]。现已证明，抑制纤维-脂肪形成祖细胞向脂肪细胞分化，减少肌内脂肪组织的堆积，可以改善肌少症[57]。这些结果进一步强调了MSCs微环境对肌少症的治疗潜力。

综上，MSCs微环境随年龄变化会影响MSCs的细胞命运，如何逆转年龄老化带来的微环境变化实现肌肉再生，如何通过微环境中细胞之间的串扰抵抗年龄相关肌少症是下一步研究的工作重点。

2.3　线粒体功能障碍与MSCs成肌能力

静止状态下，MSCs通过启动线粒体自噬来维持细胞活力，从而保持其肌肉再生潜力[54]。随着年龄增长，线粒体自噬受损，导致功能障碍的线粒体积累，再加上由于电子传递链功能受损导致线粒体能量代谢受限，使得骨骼肌线粒体功能下降[58]。线粒体质量和数量下降与骨骼肌细胞稳态失调有因果关系，并且是导致年龄相关肌少症的因素之一[59]。线粒体功能障碍是MSCs成肌能力受损的重要因素。由于衰老或遗传损伤，MSCs中线粒体分裂活动减少，电子传递链失调，使氧化磷酸化和线粒体吞噬效率低下，氧化应激增加，引起MSCs增殖减少和功能丧失，最终导致肌肉再生障碍[60]。

鉴于线粒体功能障碍是肌肉失衡和功能衰退的驱动因素，有人提出将线粒体移植作为肌肉生物能量重编程和恢复的一种治疗策略[61]。该策略背后的原理在于，移植的线粒体可以支持能量产生和ATP储存，还可以通过替换受损的线粒体DNA来挽救细胞功能[62-63]。将小鼠骨骼肌的肌原纤维间线粒体移植到成肌细胞也已被证明可以诱导成肌细胞生物能学的改善[63]。在不损伤常驻干细胞的情况下诱导小鼠腓肠肌损伤，随后注射外源性线粒体，骨骼肌质量和功能恢复加快，表明将线粒体整合到MSCs中，可促进创伤性肌肉再生[64]。可见，将线粒体输送到受损组织部位并将其纳入MSCs是一种缓解与年龄相关肌少症的新方法。

2.4　慢性炎症对MSCs分化的影响

肌肉再生的所有阶段都受到急性炎症和免疫细胞的严格调控，炎症反应的变化会改变肌肉再生的进程。事实上，抑制炎症会破坏肌肉修复，强烈的初始炎症反应会导致骨骼肌再生加速，表明炎症因子也支持MSCs的活动[65-66]。研究发现，M1巨噬细胞和M2巨噬细胞在调节骨骼肌再生中发挥核心作用[67]。M1巨噬细胞具有促炎作用，是肌肉再生早期的主要巨噬细胞类型，它们清除创伤造成的肌肉碎片，并分泌细胞因子，如肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）和白介素（interleukin，IL）-6，从而增强炎症状态[68-69]。TNF-α吸引MSCs到受伤的肌肉部位，并通过激活转录因子核因子κB（nuclear factor-κB，NF-κB）促进MSCs增殖。此外，TNF-α激活p38信号通路并刺激MSCs分化[70]。而M2巨噬细胞具有组织愈合作用。M2巨噬细胞产生抗炎细胞因子，包括IL-4、IL-10和IL-13，以抑制损伤部位的局部炎症

反应。M2巨噬细胞产生的抗炎微环境转换支持MSCs的分化和新形成的肌纤维的成熟。M2巨噬细胞的缺失会导致肌肉生长延迟，并阻碍肌肉分化和再生[71]。可见，骨骼肌再生过程中巨噬细胞表型的转变及其相应的细胞因子释放是肌肉正常再生的关键因素。

但是慢性炎症损害了MSCs在肌肉再生中的功能。衰老通常与血浆促炎效应物水平轻微升高的慢性状态有关，这种情况通常被称为低度炎症，其特征是促炎细胞因子TNF-α、IL-6和NF-κB过度活化，这会损害MSCs的功能，进而影响肌肉再生过程[72]。有调查显示，膳食引起的炎症可能与肌少症有关，在中国社区居住的老年人中，摄入更多促炎饮食与肌少症之间的关联主要是由于饮食能量、蛋白质和抗炎食物的摄入量低，而不是由于摄入大量促炎食物，使得机体处于低度炎症水平[73]。通过孟德尔随机分析发现，循环炎症因子IL-10、IL-6、血管内皮生长因子A和TNF-β等与肌少症之间存在因果关系[74-76]。对炎症生物标志物在肌少症不同阶段中的变化特征进一步分析，脑源性神经营养因子、IL-8、可溶性肿瘤坏死因子受体1和2等炎症因子与肌少症严重程度呈正相关[77]。这意味着，炎症因子水平可用来监测年龄相关肌少症的发生发展，并可能作为潜在的干预靶点。

抗炎疗法，包括使用细胞因子抑制剂和非甾体抗炎药，已显示出增强肌肉再生和减少与肌少症相关的肌肉损失的潜力[78]。然而，非甾体抗炎药对老年人具有副作用，如胃肠道和心血管并发症，对其在临床实践中的广泛使用构成了挑战[79]。除了传统抗炎药物，补充抗炎菌株CNRZ160也可以抑制老年大鼠轻度炎症引起的肌少症[80]。小麦幼苗提取物可以作为一种膳食抗炎因子增加肌肉质量，预防肌肉萎缩，改善老年小鼠肌少症[81]。

综上所述，MSCs介导的肌肉再生在年龄相关肌少症中起核心作用。通过调控MSCs内在因素、改善微环境、恢复线粒体功能及抑制慢性炎症，可能为肌少症的治疗提供新策略。然而，这些干预手段的临床应用仍需进一步研究。

3 以MSCs为靶点治疗年龄相关肌少症

3.1 营养

优化营养是改善年龄相关肌少症的首选策略。充足的蛋白质摄入为肌肉修复和生长提供了必需的基础成分[82-83]。研究表明，老年肌少症患者摄入1.2~1.5 $g \cdot kg^{-1} \cdot d$蛋白质可改善身体质量指数，而补充乳清蛋白和维生素D则能进一步提升步行速度[84]。乳清蛋白、亮氨酸和维生素D的联合补充还可增加肌少症患者的四肢肌肉质量[85]。特定氨基酸不仅能够刺激肌肉蛋白质合成，还能增强MSCs的活性。例如，亮氨酸已被证明能够促进MSCs的增殖，并通过mTORC1-MyoD信号轴增强其分化能力[86-87]，而亮氨酸缺乏则会抑制MSCs的增殖及新肌纤维生成[88]。亮氨酸的代谢产物β-羟基-β-丁酸甲酯（HMB）在血清饥饿的成肌细胞中同样具有促进增殖和MyoD表达的作用，还可以加速细胞融合[89]，并通过NF-κB途径抑制细胞凋亡[90]。其他必需氨基酸，如甲硫氨酸，也被确定为细胞增殖的调节因子，补充甲硫氨酸可以降低Myf5阳性MSCs密度，同时增加Pax7阳性细胞密度[91]，去除甲硫氨酸培养72 h会显著降低细胞MyoD1和MyoG的表达，而重新补充甲硫氨酸则能恢复其表达水平，表明甲硫氨酸在细胞分化中的重要作用[92]。谷氨酰胺在成肌细胞增殖阶段是仅次于葡萄糖的第二大消耗营养素，它通过激活mTOR信号促进MSCs的增殖与分化[93]，老年小鼠MSCs中的谷氨酰胺水平下降，补充后肌肉再生能力显著改善[94]。除了蛋白质，脂肪摄入对肌肉生长也具有重要影响。ω-3、ω-6多不饱和脂肪酸的补充对肌少症的改善也具有一定意义[88]，ω-3能激活MSCs并调节其分化[95]，而ω-6在体内可以转化ω-3，从而提高肌肉再生能力[96]。然而，有研究显示，饮食中ω-3多不饱和脂肪酸水平与肌少症呈负相关，而ω-6水平与肌少症无显著关联，肌少症患者的膳食ω-6水平略低于对照组，仍需进一步研究以明确多不饱和脂肪酸的最佳比例[97]。这些研究表明，膳食营养素在调控MSCs命运中具有重要作用，对年龄相关肌少症的防治具有重要意义。

膳食补充剂等辅助疗法也有助于预防肌少症。天然膳食成分如柠檬桃金娘提取物及其活性化合物木麻黄素可促进骨骼肌MSCs的激活[98]。绿茶提取物儿茶素和可可黄烷醇均能提高老年小鼠胫骨前肌和比目鱼肌中Pax7阳性MSCs的比例，增加MSCs密度[99]。姜黄素不仅能维持老年肌少症小鼠急性损伤后比目鱼肌中的成熟肌纤维水平，增加MyoD阳性MSCs数量，还能通过多种途径维持MSCs的数量和功能，具有治疗肌少症的潜力[100-101]。此外，柑橘甲基化黄酮可促进体外培养的肌少症原代MSCs细胞分化，并增加成肌调节因

子MyoD和MyoG的表达[102]。这些发现表明，膳食补充剂通过调控MSCs功能为改善肌少症提供了新途径。

热量限制可能是预防年龄相关肌少症对老年人产生不利影响的另一种方法。短期热量限制可促进MSCs扩增，增加肌肉弹性，有利于损伤后肌肉再生[103]。热量限制通过促进MSCs分化延缓与年龄相关的肌肉萎缩[104]，并在预防和在缓解年龄相关肌少症方面发挥了积极作用[105]。值得注意的是，热量限制应在保证蛋白质摄入充足的前提下进行。

综上所述，在确保能量充足的基础上摄入足量蛋白质是防治年龄相关肌少症的关键。此外，膳食补充剂、热量限制等辅助疗法也为改善年龄相关肌少症提供了新的可能性。

3.2　运动

运动是一种结构化、重复性的身体活动，主要包括有氧耐力训练（如步行、慢跑、骑自行车）和无氧抗阻训练（如杠铃卧推、杠铃过顶深蹲、哑铃弯举）。运动被广泛认为是增强肌肉功能、缓解多种慢性疾病（如糖尿病、心血管疾病、肌少症、呼吸系统疾病和关节炎）的有效方法。运动诱导的组织再生为对抗损伤或衰老提供了一种新方法，并为“运动模拟物”的开发奠定了理论基础（图2）。

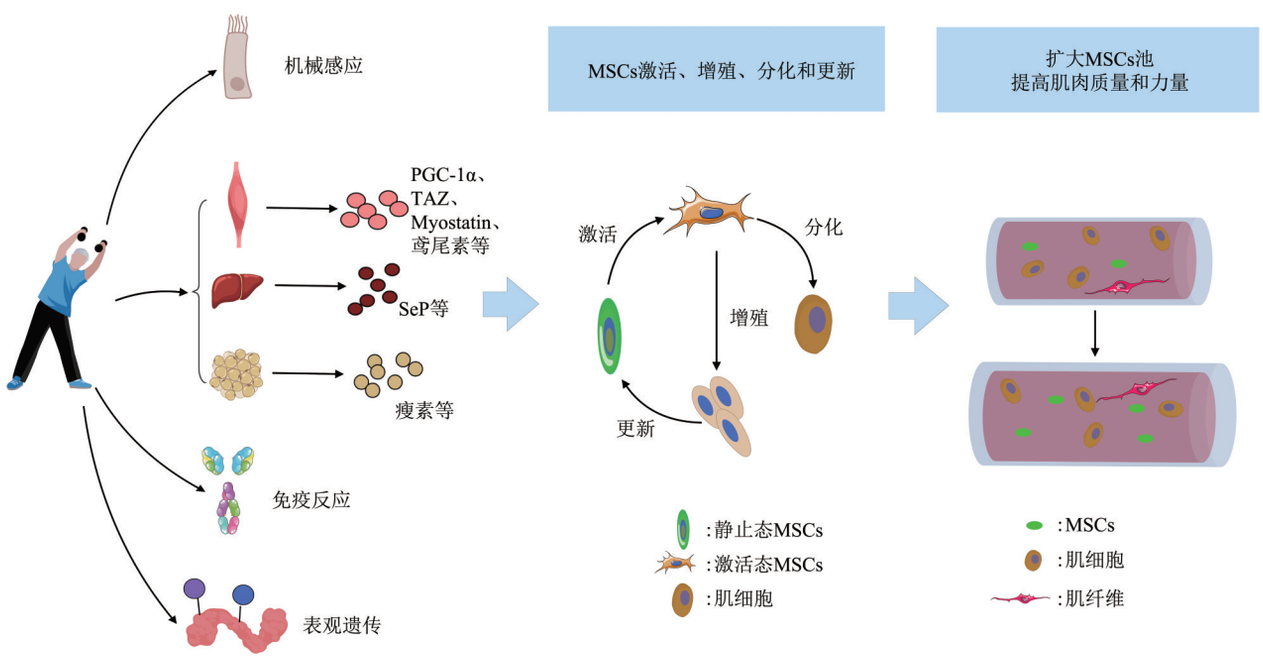

Fig. 2　Exercise stimulates tissue regeneration through MSCs to fight age-related sarcopenia

图2　运动通过MSCs诱导组织再生对抗年龄相关肌少症

PGC-1α：过氧化物酶体增殖激活受体激活因子1α（peroxisome proliferator-activated receptorycoactivator-1α），TAZ：具有PDZ结合基序的转录共激活因子（transcriptional co-activator with PDZ-binding motif），Myostatin：肌肉生长抑制素，SeP：肝因子硒蛋白P（selenoprotein P），MSCs：骨骼肌卫星细胞（muscle satellite cells）。

运动会对肌肉纤维产生机械应力，从而触发参与肌肉再生的多种信号通路的激活。研究表明，终身休闲锻炼可以保留老年人MSCs数量和神经支配特征，抵消衰老带来的负面影响[106]。运动可增加MSCs丰度，特别是抗阻训练可以激活MSCs、增加肌肉蛋白质合成并增强肌肉力量和质量[107-108]。运动过程中，骨骼肌中的Pax7$^+$细胞耗竭，同时未分化骨髓干细胞短暂释放以补充MSCs库。抗阻运动后24~72 h内，可以观察到肌肉中Pax7$^+$细胞的长期扩增[108]。尽管50岁后MSCs储备较低，但运动诱导的Pax7$^+$细胞扩增仍然显著[108]。MSCs已被确定为机械敏感细胞，其纤毛蛋白ADP-核糖化因子样蛋白3的缺失会损害纤毛功能并抑制肌生成程序的启动信号[109]。这说明MSCs纤毛可作为机械传感器，激活MSCs并促进运动诱导的肌肉肥大。

运动通过多种途径诱导MSCs激活，其中肌肉

因子是运动产生有益影响的关键介质，如过氧化物酶体增殖激活受体激活因子1α（peroxisome proliferator-activated receptorycoactivator-1α，PGC-1α）、具有PDZ结合基序的转录共激活因子（transcriptional co-activator with PDZ-binding motif，TAZ）、肌肉生长抑制素（Myostatin）和鸢尾素等。PGC-1α调节运动时的广泛转录程序，肌纤维中的PGC-1α可调节肌源性和脂肪源性祖细胞之间的平衡，影响肌肉再生[110]。PGC-1α通过纤连蛋白重塑MSCs微环境，使其更易于激活和增殖[111]。在衰老过程中PGC-1α的短亚型PGC-1α4转录水平和核定位减少，而通过腺相关病毒（adeno-associated virus，AAV）递送核定位PGC-1α4可改善肌少症和衰老相关的代谢功能障碍[112]。TAZ是一种新型转录共激活因子，通过Pard3-p38 MAPK-TAZ信号轴刺激运动诱导的MSCs激活，表明TAZ可能是改善肌肉老化表型的重要靶点[113]。肌肉生长抑制素属于转化生长因子β家族成员，通过自分泌或旁分泌信号抑制成肌基因转录，负向调节骨骼肌发育。研究发现，微重力环境会诱导MSCs中肌肉生长抑制素的表达，而使用肌肉生长抑制素抗体可维持MSCs的存活和分化[114-115]。这表明耐力运动可以通过抑制肌肉生长抑制素表达激活MSCs，增强肌肉再生能力，是防治年龄相关肌少症的潜在策略[116]。鸢尾素主要由骨骼肌分泌，作为肌动蛋白和促肌生成因子具有多种健康益处。有氧运动通过鸢尾素改善年龄相关肌少症，但在鸢尾素基因敲除的老年小鼠中效果不明显[117]。这主要归因于，鸢尾素可以在分子水平上促进MSCs激活[118]，而衰老肌肉组织中鸢尾素mRNA和蛋白质水平下调，腹腔注射鸢尾素可增加肌肉的重量和力量，改善老年肌少症[119]。此外，有氧运动可抑制衰老MSCs分泌结缔组织生长因子，增强骨骼肌再生并预防纤维化，有效逆转了老年小鼠耐力下降和肌肉萎缩[120]。

除了肌肉因子外，运动还可以通过远程调控细胞因子参与骨骼肌再生。瘦素由脂肪细胞产生，可诱导MSCs退出静止状态，对肌肉再生具有积极作用[121]。血清瘦素水平越高，老年人患肌少症的风险越低[122]。最近还发现，衰老过程中肝因子硒蛋白P水平升高[123]，而肝因子硒蛋白P缺乏可增强小鼠骨骼肌的反应性，改善久坐不动引起的肌肉萎缩[123-124]。这表明肝因子硒蛋白P抑制剂可作为运动模拟物，用以治疗年龄相关肌少症。

运动裨益的另一种方式是通过直接或间接作用影响免疫系统，调控肌肉再生。运动可调节衰老肌肉中促炎和抗炎细胞因子的水平，这些细胞因子是MSCs响应损伤的关键因素之一。有研究显示，运动诱导的IL-6释放可增加骨骼肌中调节性T细胞的丰度，而调节性T细胞的消耗会消除运动响应所需的肌肉特异性基因表达，影响肌肉再生[125]。巨噬细胞释放的金属蛋白酶通过抑制Notch信号转导诱导MSCs激活，促进肌肉再生[126]。单核细胞的先天免疫记忆程序使其在二次刺激下产生更多细胞因子[127]。研究发现，受损MSCs在二次损伤后修复速度更快、效率更高[128]，表明运动可通过诱导先天免疫记忆程序来改善衰老过程中的肌肉性能，抵抗年龄相关肌少症。

运动还可以通过表观遗传靶向MSCs，在年龄相关肌少症防御中发挥重要作用。Sirtuins是衰老的关键表观遗传调节因子，衰老过程中沉默信息调节因子1（silence infor-mation regulator 1；sirtuin 1，SIRT1）活性和表达降低，导致MSCs的肌肉修复功能下降，引发肌少症。运动可增加Sirtuin蛋白（SIRT1和SIRT3）表达，MSCs以SIRT1依赖的方式修复肌肉，从而增强肌肉质量[129]。最近研究发现，运动以甲基转移酶样蛋白3（methyltransferase like 3，Mettl3）介导的m6A依赖方式提高MSCs中*MyoD* mRNA的稳定性，甲基供体甜菜碱可能作为运动的替代品，通过上调m6A甲基化水平促进骨骼肌生长，对肌少症具有潜在的治疗作用[130]。

将运动与其他治疗干预措施（如营养补充剂或药物）结合，可能在促进肌肉再生，改善年龄相关肌少症方面产生协同效应[131]。例如，低剂量白藜芦醇（12.5 mg/kg/d）单独使用不会增加MSCs数量或肌肉质量，但与运动联合干预比单纯运动更能改善年龄相关肌少症[132]。褪黑素与运动训练联合干预通过抑制细胞衰老和减轻线粒体功能障碍保护MSCs池，缓解肥胖相关肌少症引起的骨骼肌功能障碍[133]。

综上所述，运动是肌少症干预的重要手段。然而，坚持锻炼计划可能具有挑战性，尤其是对于行动不便或健康状况不佳的老年人。运动与营养或药物干预的最佳组合仍需进一步研究，以确定对不同患者群体最有效的方案。此外，虽然运动是对抗肌少症的有力工具，但对于严重肌少症可能还需要额外的干预措施。

3.3　其他治疗手段

微RNA（miRNA）是小型非编码RNA，通过靶向信使RNA进行降解或翻译抑制来调节基因表达。几种miRNA已被确定为MSCs功能和肌肉再生的关键调节剂。例如，miR-203a-3p的下调抑制了人类骨骼肌细胞的增殖[134]。miR181a的过表达下调了C2C12成肌细胞的肌肉生成[135]。miR-455-3p模拟物增加了C2C12成肌细胞的肌管形成[136]。Dai等[137]通过生物信息学分析确定miR-467a-3p和miR-874-5p可以分别介导MSCs的干性和肌肉生成，随后构建了分层可注射水凝胶，在体内持续释放间充质干细胞衍生的细胞外囊泡，靶向MSCs递送miRNA拮抗剂antagomiR-467a-3p和antagomiR-8745p，抑制miRNA发挥作用，实现了多次注射改善肌少症的效果。使用miRNA模拟物或抑制剂对miRNA表达进行治疗性调节，为增强肌肉再生和治疗年龄相关肌少症提供了一种新方法。然而，需要进行大量研究来探索其潜在的临床应用。

肠道菌群失调会破坏肠道屏障功能，引发血液中代谢物水平的变化，最终影响肌肉代谢，并可能在肌少症的发展中起关键作用。有研究发现，代谢物丁酸盐水平的降低以及肠道微生物失调可能是导致骨骼肌衰老过程中MSCs数量减少和随后损伤的主要因素[138]。肠道菌群可能通过“肠-肌肉”轴参与肌少症的发展。其中，基于益生菌的治疗策略可能是保持所有年龄段健康或疾病个体肌肉功能的最佳方法[139]。最近，来自年轻捐赠者的粪便微生物群移植也因其益生菌的良好功能特性而受到广泛关注，并显示出对与年龄相关的行为功能障碍的保护作用[140]。据报道，年轻供体的粪便菌群移植可以重塑肠道菌群，减轻代谢物失调，维持肠道屏障完整性，改善肌肉线粒体功能障碍，增加老年大鼠MSCs数量，下调MyoD、MyoG和胰岛素样生长因子1水平，上调肌肉萎缩盒F基因、肌肉环状指基因和肌肉生长抑制素，触发MSCs增殖和分化，改善肌肉萎缩，促进肌肉再生，最终减轻老年大鼠的肌少症[141]。可见，年轻供体的粪便菌群移植可能成为年龄相关肌少症的一种新治疗策略。

肌少症的另一种治疗选择是补充激素。众所周知，雌激素缺乏会降低绝经后妇女的骨骼肌质量和力量，肌肉质量的维持有赖于MSCs，而MSCs受雌激素调节[142]。最近研究显示，雌二醇通过促进MSCs循环来保持MSCs池[143]。补充17β-雌二醇对肌少症具有积极作用，是肌少症的潜在治疗药物[144]。雄性激素中，睾酮可增加慢性病患者的肌肉质量和肌肉力量[145]。临床上，睾酮凝胶副作用少，是对肌肉健康和安全性影响累积证据最多的药物[146]。在男性受试者（≥65岁，*n*=790）中，每天使用1%睾酮凝胶，持续12个月，可使6 min步行距离更长[147]。年轻女性补充睾酮后，股外侧肌肌纤维横截面积增加，II型肌纤维MSC数量增加[148]。一项系统综述提到，睾酮在瘦体重、最大自主力量、爬楼梯能力、有氧能力、血红蛋白和自我报告功能方面，显示出与剂量相关的改善，但在步行速度改善方面并不一致[149]。因此，需要大规模临床随机试验，确定睾酮在年龄相关肌少症治疗上的长期疗效和安全性。

干细胞疗法是另一种有前途的利用MSCs以外的干细胞群来增强肌肉再生的方法。间充质干细胞可以分化为成肌细胞，并分泌促进MSCs活性和肌肉修复的旁分泌因子[150]。间充质干细胞注射可激活MSCs，减轻肌肉萎缩，改善年龄相关肌少症小鼠的骨骼肌功能障碍[151-152]。将磁化后的间充质干细胞局部注射到小鼠骨骼肌中，组织炎症降低，提示磁化干细胞可能有助于有效治疗肌少症[153]。但干细胞疗法也存在风险，因此干细胞的临床应用需要谨慎评估。

4　临床研究

基于MSCs治疗年龄相关肌少症的临床研究主要集中在运动和营养及两者联合干预。近年来，多项治疗肌少症的临床试验表明，运动是抵抗肌少症的有效策略之一[154]。在肌少症干预中应用较多的运动是抗阻运动，一项随机对照试验发现，16周抗阻训练对老年肌少症患者肌肉质量的保持具有积极作用[155]。外周肌肉抗阻训练增加了老年肌少症妇女的肌肉力量，并阻止了与年龄相关的呼吸功能下降[156]。除了世界卫生组织推荐的抗阻运动，步行是日常生活中最简单、最经济也最容易坚持的一种运动，尤其适合中老年人。临床研究探索了基于计步器的步行计划加上12周的阻力训练的有效性，佩戴计步器行走7 500步/d，5 d/周，加上2次/周阻力训练，可以有效改善老年肌少症患者的心肺功能和身体活动能力[157]。随着科技的不断发展，人工智能在老年疾病治疗康复中的应用逐渐增多，结合ChatGPT-4和可穿戴设备的康复系统可能会提高专业康复服务的可用性和效率，从而提高同时患有肌少症和骨关节炎的人群的治疗效果[158]。

基于MSCs进行的年龄相关肌少症的营养干预首当其冲的是充足的蛋白质摄入。老年人肌少症防控干预中国专家共识（2023）建议，老年肌少症患者摄入1.2~1.5 $g\cdot kg^{-1}\cdot d^{-1}$蛋白质，优质蛋白质比例最好能达到50%，并均衡分配到一日三餐中[4]。临床研究显示，高蛋白（乳清、豌豆和胶原蛋白）摄入增强了老年男性肌原纤维蛋白合成，对克服年龄相关的合成代谢抵抗有益，对肌少症的治疗有意义[159]。高植物蛋白/肽营养补充剂可以通过改善肌肉质量和力量，缓解老年肌少症患者的骨关节炎症状[160]。虽然维生素D可以预防糖尿病前期肌少症的形成[91]，但是维生素D一直是一种有争议的治疗方法。老年人肌少症防控干预中国专家共识（2023）不推荐老年肌少症患者常规补充维生素D，建议结合血清25（OH）D的浓度进行补充，当血清25（OH）D<50 nmol/L时可予以补充维生素D[4]。近来，肠道菌群是治疗肌少症的研究热点。益生菌补充剂可以提高老年肌肉减少症患者的握力，减弱肌肉衰退，改善与肌少症相关的生活质量[161]。一种获得专利的膳食补充剂（丁酸羟甲基酯、肌肽、镁、丁酸酯、乳铁蛋白）通过调节肠道通透性，改善肌肉质量和功能，治疗年龄相关性肌少症[162]。可见，肠-肌轴正逐渐成为肌少症的一个新的干预靶点。运动结合营养的联合干预措施对肌少症的预防和治疗具有协同效应。有研究显示，家庭无监督的抗阻运动和多成分补充剂（乳清、胶束酪蛋白、肌酸、维生素D和ω-3脂肪酸）结合改善了久坐不动老年男性的瘦体重、力量和整体肌肉质量，有助于肌少症的预防[163]。但对于卧床行动不便的老年人，运动是一种奢望，肌肉电刺激成为了运动的替代疗法。一项随机对照试验显示，补充乳清蛋白、ω-3脂肪酸和多酚，结合肌肉电刺激，可增加行动不便老年人的肌肉力量，对肌少症的防治具有一定效果[164]。

基于MSCs治疗年龄相关肌少症的药物进入临床研究的有限，其中靶向肌肉生长抑制素信号转导已成为增强肌肉再生的一种有前途的策略[165]。目前，肌肉生长抑制素抑制剂比马格鲁单抗正处于临床试验阶段，有研究显示，16周比马格鲁单抗临床干预有利于改善老年肌少症患者的肌肉质量和力量，增强行走速度较慢患者的活动能力[166]。Rooks等[167]的随机临床试验发现，在患有肌少症的老年人中，接受比马格鲁单抗治疗的参与者与安慰剂治疗的参与者之间没有显著差异。初步结果表明，比马格鲁单抗在改善老年肌少症肌肉功能方面，其临床结果并不一致，这就需要对其可靠性和有效性进一步探究。二甲双胍是治疗糖尿病的常用的处方药，具有脱靶效应，可能对老年肌肉健康具有影响。临床研究发现，二甲双胍急性暴露会影响健康老年人肌肉I型肌纤维MSCs含量，影响其MSCs动力学。对肌少症患者进行随机双盲试验显示，二甲双胍可以增强患者的握力，防止与年龄相关的肌肉衰退，改善与肌少症相关的生活质量[168]。此外，还有一些药物虽然对MSCs的作用不详，但对肌少症的治疗显示出一定疗效。20-羟基蜕皮激素是一种多羟基化的植物类固醇，在许多疾病动物模型中表现出药理作用，包括衰老/肌少症。目前BI0101（20-羟基蜕皮激素的纯化试验药）的临床1期研究在健康的年轻人和老年人中进行了评估，显示出其良好的安全性和药代动力学特征，这为随后的年龄相关肌少症2期临床试验的剂量选择奠定了基础[169]。

5 总结与展望

年龄相关肌少症是一种复杂且多因素交织的临床疾病，其特征是肌肉质量、力量及功能的进行性下降，且常与其他慢性疾病及老年综合征共存，导致每位患者的干预需求具有高度个体化特征。MSCs作为肌肉再生的核心驱动者，其数量减少与功能衰退与年龄相关肌少症的发生发展密切相关。MSCs的内在调控机制及其所处微环境的动态变化共同决定了肌肉再生的效率，并在年龄相关肌少症的筛查、评估及防治中占据关键地位。线粒体功能障碍是肌肉失衡和功能衰退的重要驱动因素，而线粒体移植作为一种新兴策略，通过将功能性线粒体递送至受损组织并整合入MSCs，为缓解年龄相关肌少症提供了新思路。此外，炎症调控在肌肉再生中扮演双重角色：急性炎症促进修复，而慢性炎症则损害MSCs功能。尽管基于炎症调控的抗炎疗法在临床试验中尚未取得理想效果，且长期使用非甾体抗炎药可能引发副作用，但其潜在价值仍值得进一步探索。

目前，营养干预和运动被确定为年龄相关肌少症的主要临床治疗手段。在保证能量摄入充足的基础上，增加蛋白质摄入并结合适度的运动计划，已被证实是防治年龄相关肌少症的有效策略。然而，对于行动受限、健康状况不佳或严重肌少症患者，传统方法可能难以满足需求。因此，基于MSCs的

创新治疗策略，如miRNA模拟物或抑制剂干预、肠道菌群移植及干细胞疗法，为年龄相关肌少症的治疗开辟了新的希望。miRNA调控技术的突破性进展，尤其是2024年诺贝尔生理学或医学奖对miRNA研究的肯定，为其临床转化提供了强劲动力。肠道微生物群通过“肠-肌”轴参与肌少症的发展，粪便菌群移植可能成为调节MSCs功能、改善肌肉再生的新途径。此外，干细胞疗法通过直接补充或激活MSCs，为年龄相关肌少症的肌肉再生干预带来了新曙光。

尽管这些新兴疗法展现出巨大潜力，但其有效性和安全性仍需在临床试验和现实环境中进一步验证，特别是在多病共存的老年人群中。未来的研究应聚焦于MSCs在年龄相关肌少症中的病理学特征，结合系统性肌肉再生研究与多维度干预策略（如运动、营养及靶向治疗），为年龄相关肌少症的全面防治提供创新性解决方案。通过多学科协作与技术创新，有望显著改善老年人群的身体机能与生活质量，为应对全球老龄化挑战提供科学依据与实践指导。

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The Role of Skeletal Muscle Satellite Cells-mediated Muscle Regeneration in The Treatment of Age-related Sarcopenia*

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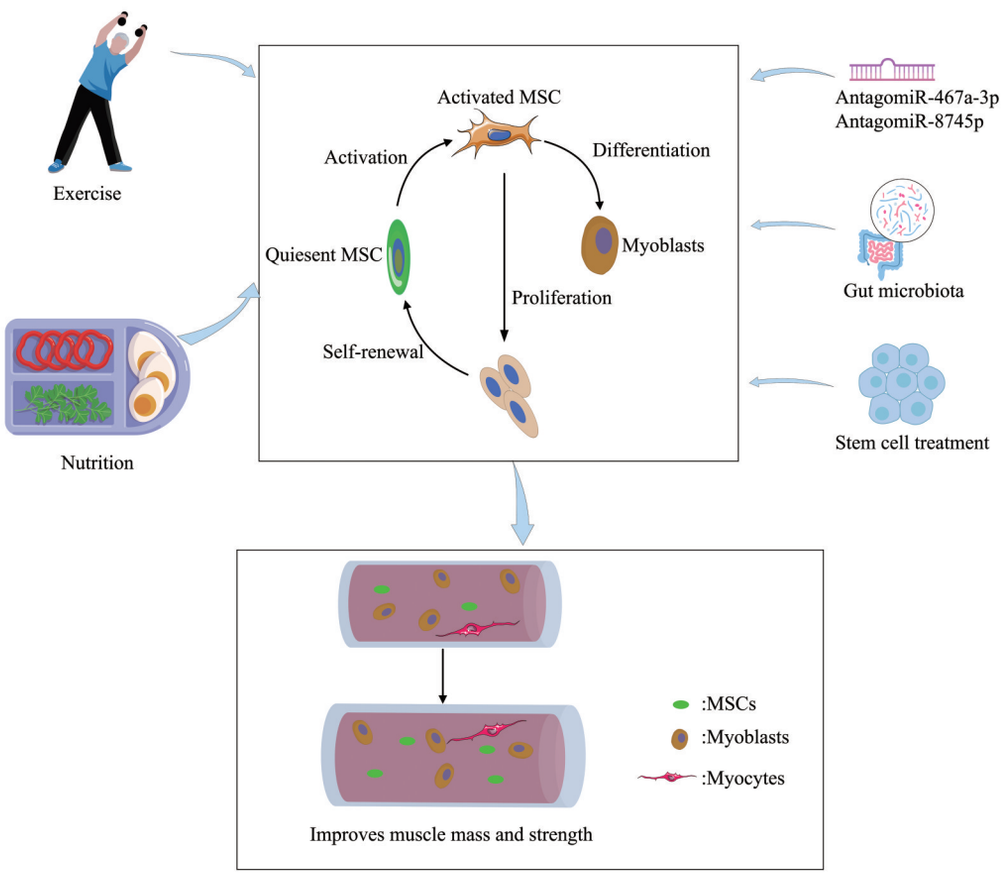
Graphical abstract



Abstract Age-related sarcopenia is a progressive, systemic skeletal muscle disorder associated with aging. It is primarily characterized by a significant decline in muscle mass, strength, and physical function, rather than being an inevitable consequence of normal aging. Despite ongoing research, there is still no globally unified consensus among physicians regarding the diagnostic criteria and clinical indicators of this condition. Nonetheless, regardless of the diagnostic standards applied, the prevalence of age-related sarcopenia remains alarmingly high.

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With the global population aging at an accelerating rate, its incidence is expected to rise further, posing a significant public health challenge. Age-related sarcopenia not only markedly increases the risk of physical disability but also profoundly affects patients' quality of life, independence, and overall survival. As such, the development of effective prevention and treatment strategies to mitigate its dual burden on both societal and individual health has become an urgent and critical priority. Skeletal muscle regeneration, a vital physiological process for maintaining muscle health, is significantly impaired in age-related sarcopenia and is considered one of its primary underlying causes. Skeletal muscle satellite cells (MSCs), also known as muscle stem cells, play a pivotal role in generating new muscle fibers and maintaining muscle mass and function. A decline in both the number and functionality of MSCs is closely linked to the onset and progression of sarcopenia. This dysfunction is driven by alterations in intrinsic MSC mechanisms—such as Notch, Wnt/β-Catenin, and mTOR signaling pathways—as well as changes in transcription factors and epigenetic modifications. Additionally, the MSC microenvironment, including both the direct niche formed by skeletal muscle fibers and their secreted cytokines, and the indirect niche composed of extracellular matrix proteins and various cell types, undergoes age-related changes. Mitochondrial dysfunction and chronic inflammation further contribute to MSC impairment, ultimately leading to the development of sarcopenia. Currently, there are no approved pharmacological treatments for age-related sarcopenia. Nutritional intervention and exercise remain the cornerstone of therapeutic strategies. Adequate protein intake, coupled with sufficient energy provision, is fundamental to both the prevention and treatment of this condition. Adjuvant therapies, such as dietary supplements and caloric restriction, offer additional therapeutic potential. Exercise promotes muscle regeneration and ameliorates sarcopenia by acting on MSCs through various mechanisms, including mechanical stress, myokine secretion, distant cytokine signaling, immune modulation, and epigenetic regulation. When combined with a structured exercise regimen, adequate protein intake has been shown to be particularly effective in preventing age-related sarcopenia. However, traditional interventions may be inadequate for patients with limited mobility, poor overall health, or advanced sarcopenia. Emerging therapeutic strategies—such as miRNA mimics or inhibitors, gut microbiota transplantation, and stem cell therapy—present promising new directions for MSC-based interventions. This review comprehensively examines recent advances in MSC-mediated muscle regeneration in age-related sarcopenia and systematically discusses therapeutic strategies targeting MSC regulation to enhance muscle mass and strength. The goal is to provide a theoretical foundation and identify future research directions for the prevention and treatment of this increasingly prevalent condition.

Key words age-related sarcopenia, muscle satellite cells, aging, exercise, nutrition
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