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肌肉减少症发生机制的研究进展

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摘　要

伴随着社会老龄化的来临，人们将更多目光投向了肌肉减少症。肌肉减少症是人口老龄化社会进展所必经的，主要临床表现为一种进行性和全身广泛性的骨骼肌疾病，以骨骼肌质量肌力下降和全身功能减退为主要特征，早期识别肌肉减少症对延缓老年衰弱有积极意义。目前我国对于肌肉减少症的研究处于探索阶段，本文将从肌肉减少症发生机制的部分新进展进行综述。

关键词

肌肉减少症，发生机制，免疫系统，炎症，维生素D

Research Advances in the Pathogenesis of Sarcopenia

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Abstract

With the advent of the aging society, people pay more attention to sarcopenia. Sarcopenia is a progressive and generalized skeletal muscle disease, which is characterized by the decline of skeletal muscle mass and muscle strength and general dysfunction. Early identification of sarcopenia is of positive significance for delaying aging frailty. At present, the research on sarcopenia in China is in the exploration stage. This paper will review some new advances in the pathogenesis of sarcopenia.

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Keywords

Sarcopenia, Pathogenesis, Immune System, Inflammation, Vitamin D

1. 引言

全世界的预期寿命持续增加，尤其是 65 岁以上的人群[1]。人口老龄化对公共卫生构成巨大挑战，给国家和社会带来沉重负担。衰老是导致疾病和残疾易感性增加的重要因素[2]。肌肉减少症(简称为肌少症)是一种与年龄有关的疾病，与跌倒、骨折、身体残疾和死亡等不良结局的发生性呈正相关，一项发生在日本的前瞻性研究通过参加健康检查的 1851 名 65 岁或以上的居民进行了一项为期 5.8 年的观察，与非肌肉减少症患者相比，存在肌肉减少症的个体倾向于增加残疾风险(P = 0.087) [3]；另一项荟萃分析纳入了 33 项研究(45,926 人)，与非肌少症患者相比，少肌症患者跌倒的风险(P < 0.001)和骨折(P = 0.001)显着增加[4]。常见于老年人、营养不良、慢性消耗性疾病、恶性肿瘤等。因此，早期识别肌少症对延缓老年衰弱有积极意义，对促进健康老龄化是医疗保健提供者的优先事项[5]。2018 年欧洲老年人肌少症工作组(EWGSOP)提出将低肌力作为诊断肌少症的首要条件，其建议的诊断标准为肌力低下、肌肉质量减少和体能低下[6]。并将肌肉力量放于最重要的位置，相关研究表示在预测肌少症不良结果方面认为力量比质量更好[7]。同时表明当检测到身体机能低下可确定肌肉减少症的严重程度。

2. 肌肉减少症发生机制的临床进展

当前对于造成肌肉减少症的病因尚未完全得到阐明，就当前所认知的肌肉减少症形成的原因主要包括营养不良(厌食症为甚) [8]、慢性炎症[9]、维生素 D 缺乏和维生素 D 受体[10]、性腺功能减退[11]、激素状态[12]、缺乏运动[13]、神经肌肉接头[14]、肠道菌群[15]、线粒体功能障碍[16]、肌肉蛋白质的合成代谢减弱[17]和免疫系统变化[18]等。因此，本综述旨在讨论上述部分肌肉减少症形成的病因及机制。

2.1. 免疫系统与肌肉减少症

免疫系统和肌肉减少症的关系是密切相关的，众所周知，免疫系统随着年龄老化会发生一系列动态变化，现在统称为免疫衰老[19]，在老年人的大多数慢性疾病中起着关键作用，是影响着自然免疫和获得性免疫的多因素现象[20]。免疫系统是由免疫器官和内脏器官的黏膜构成，免疫器官包括胸腺、骨髓、脾脏、淋巴结，共同协作参与了自然免疫和获得性免疫。在免疫衰老状态下，黏膜的先天性屏障发生改变和破坏，衰老的免疫细胞积累，两者协同改变自然免疫成分的功能，影响获得性免疫细胞，导致亚临床炎症和衰竭状态。相关文献报道，骨骼肌的再生潜力取决于骨骼肌和免疫细胞之间的相互作用[21]。在获得性免疫中，以淋巴细胞为主，淋巴细胞浸润的骨骼肌及其分泌的蛋白质被认为在肌肉修复和再生中发挥重要作用[22]，但同时淋巴结的数量随着年龄的增长而减少，呈现出与年龄相关的退行性特征。即表现为年轻个体淋巴细胞分泌的蛋白质可以促进肌肉细胞的增殖和迁移，维持骨骼肌的再生能力，而衰老淋巴细胞分泌的蛋白质可以抑制肌肉细胞的增殖和迁移，这表明可能与肌肉减少症患者的肌肉质量减少有关[23]。细分淋巴细胞可为 T 淋巴细胞和 B 淋巴细胞，现以 T 淋巴细胞为例进行阐述，从生理学上讲，T 淋巴细胞对于骨骼肌的修复、再生和分化至关重要。$CD8^+$ T 细胞可以穿透受损肌肉，促进单核细胞趋化

蛋白-1 (MCP-1)分泌募集 Gr1 高巨噬细胞，促进成肌细胞增殖[24]。在免疫老化过程中，T 淋巴细胞表型的减少和变化，从 $CD8^+$到 $CD4^+$，可能与肌肉质量减少有关[23]。

2.2. 维生素 D/维生素 D 受体与肌肉减少症

维生素 D 缺乏症在老年人群中很普遍，认知中它会对肌肉骨骼肌健康产生负面影响，因此值得未来深入的研究。维生素 D (血清 25-羟基维生素 D (25(OH)D_3))缺乏症通常表现为骨痛、疲劳、肌肉疼痛(肌痛)、肌肉萎缩和虚弱，以及肌肉减少症的风险增加[25] [26]。尽管这些肌肉症状是维生素 D 缺乏症的一些主要特征之一，但维生素 D 与骨骼肌之间的关系仍不完全清楚。相关研究表明维生素 D/维生素 D 受体(VDR)轴可能与肌生成(骨骼肌的形成)、骨骼肌再生中的作用和钙稳态密切相关，但由于大型随机对照试验(RCT)和体外进行的分子研究产生的相互矛盾的结果，目前维生素 D/维生素 D 受体(VDR)轴与肌肉萎缩的关系仍很复杂[27]。肌肉萎缩中的维生素 D/VDR 拟议机制，主要包含以下机制：第一是关键的分解途径(在骨骼肌中，大部分细胞内蛋白水解通过泛素－蛋白酶体途径(UPP)发生，而自噬溶酶体途径也有影响[28])；第二是线粒体功能受损和氧化损伤(人类骨骼肌体外模型表明，线粒体生物能量学对活性 1,25(OH)$_2$$D_3$ 的响应有所改善[29]，从而提高了耗氧率和裂变/融合动力学。肌肉中 CYP27B1-VDR 内分泌途径可能对肌肉功能具有选择性影响。相反，饮食诱导的小鼠 25(OH)D_3 缺乏会导致线粒体功能降低，同时体内 VDR 敲低，多个线粒体相关基因组被下调，这表明 VDR 可能是线粒体生物能量功能所必需的，但主要是通过调节关键的线粒体基因组[29]。然而，最近的研究已经确定了 VDR 敲低的小鼠可表现出肌肉内 ATP 减少[30])；第三是肥胖和细胞衰老(细胞衰老主要受两种主要的抗凋亡途径-p16/Rb 和 p53-p21 调节，缺乏维生素 D 的小鼠增加了 p16、p21、p53 和 p19 的肌肉水平，诱导细胞衰老和提高衰老相关分泌表型因子(即 TNFα、MMP3 和 IL-6)的表达[31]。p16 和 p21 上调也见于老年人和大鼠的肌肉中，将衰老细胞移植到大鼠肌肉中会导致衰老标志物升高，并伴有肌肉减少症相关的肌肉变薄[32])。但维生素 D/VDR 对线粒体功能的周边作用仍需要继续进一步研究。

2.3. 炎症与肌肉减少症

随着年龄的增长而发生的免疫系统损害称为低度慢性炎症状态[33]，炎症反应是机体发挥免疫反应、抵御机体内外有害因素的重要过程。衰老诱导的炎症反应是一种慢性全身性低度炎症反应，伴随着促炎细胞因子的增加以及抗炎细胞因子水平降低。肿瘤坏死因子-α (TNF-α)、白介素-4 (IL-4)、白介素-6 (IL-6)、白介素-10 (IL-10)、白介素-15 (IL-15)、C-反应蛋白(CRP)、瘦素等炎症介质的过度释放和持续作用会造成组织细胞损伤和肌肉损失，从而导致老年人肌肉质量减少以及肌力下降。相关研究发现，较高水平的白细胞介素-6 (IL-6)与肌肉力量的大幅度下降有关[34]；另一项研究表明，90 岁男性和女性的高水平 IL-6 和 CRP 与较差的握力以及较高水平的 IL-6 和 CRP 与较差的 Barthel 指数之间存在密切关联，表明炎症标志物对老年人的身体机能产生负调节作用[35]。此外，促炎细胞因子的表达和活性可被抗炎细胞因子(如 IL-4 和 IL-10)拮抗，可延缓肌肉减少症和缓解肌肉萎缩[36] [37]。一项横断面研究发现，IL-15 信号传导减少发生与年龄相关，可使老年人的骨骼肌比年轻人更能抵抗 IL-15 的肥大效应，最终导致肌肉减少症[38]。此外，TNF-α 通过 TRAF6 (TNF receptor-associated factor 6, TRAF6)激活 NF-κB (nuclear factor-kappa B, NF-κB)信号通路，诱导肌萎缩相关基因 MuRF-1 和 MAFbx 表达，通过泛素－蛋白酶体途径降解骨骼肌纤维[39]。因此，猜想降低慢性炎症反应是以恢复老年人肌肉功能成为治疗肌肉减少症的潜在策略。

3. 结语与展望

肌肉减少症是一种起病隐匿、缓慢进行性骨骼肌减少性疾病，主要症状包括肌肉质量和肌力的丧失，并伴有跌倒，虚弱和生活自理能力下降等不良后果的风险增加，是威胁老年人生命健康的主要疾病之一。

目前全世界对于肌肉减少症的诊断并无统一标准。肌肉减少症的发生与衰老过程中骨骼肌萎缩、线粒体功能障碍、慢性炎症反应、激素水平下降、肠道菌群失调、运动缺乏及营养不良等多种因素相关。由于目前尚没有确切治疗肌肉减少症的药物，大多数文献指出，运动与饮食干预是主要的预防和治疗方式。虽然运动和饮食干预可改善肌少症，但又不完全适用于老年人，因为老年人常伴随多种基础疾病，本身基础身体素质较差，无法实现高强度运动和充足蛋白质的摄入。为此，还需深入研究以确定老年人最佳的运动和饮食干预方案。况且目前对于肌少症的学习的认识主要来自临床观察和动物实验，因此深入学习肌少症的病因有助于了解肌少症的病理生理机制，为预测肌少症的发生及辅助诊断提供新思路。同时，也有利于预防和开发针对肌肉减少症的特异性治疗方法。

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