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慢性低度炎症与肌少症

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摘　要

肌少症目前被普遍认为是老年综合症的一种，其主要表现为出现与增龄相关的肌肉质量减少、肌肉功能和肌肉力量下降。可以导致衰弱、跌倒、骨折、代谢性疾病等发病率和死亡的风险增高。其发病机制复杂，目前仍未完全阐明。在其多种可能机制中，慢性低度炎症被认为是肌少症的关键发病机制。炎性因子直接或间接地通过不同的病理生理过程导致肌少症的发生。反应机体炎症情况的肿瘤坏死因子α、IL-6、CRP、IL-15、IL-10、鸢尾素等多种炎症指标以及血常规中白细胞、血小板、中性粒细胞、淋巴细胞、单核细胞及其衍生物与老年人躯体功能、肌肉力量、肌肉质量等密切相关。这些都可能通过调节氧化应激、蛋白质合成与代谢平衡、细胞周期阻滞、骨骼肌再生、细胞凋亡等途径导致骨骼肌损伤，从而导致肌少症。本文将综述目前肌少症与慢性低度炎症之间的关系研究进展。

关键词

肌少症，慢性低度炎症，炎症指标

Chronic Low-Grade Inflammation and Sarcopenia

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Abstract

Sarcopenia is currently widely considered as a type of geriatric syndrome, characterized by age-related decrease in muscle mass, muscle function, and muscle strength. It can lead to increased

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risks of weakness, falls, fractures, metabolic diseases, and mortality. The pathogenesis of sarcopenia is complex and not yet fully understood. Among its various possible mechanisms, chronic low-grade inflammation is considered as a key pathogenic mechanism. Inflammatory factors directly or indirectly contribute to the development of sarcopenia through various pathophysiological processes. Inflammatory markers such as tumor necrosis factor-α, IL-6, CRP, IL-15, IL-10, and irisin, as well as white blood cells, platelets, neutrophils, lymphocytes, monocytes, and their derivatives in routine blood tests, are closely related to physical function, muscle strength, and muscle mass in older adults. These factors may lead to skeletal muscle damage and subsequently sarcopenia by regulating oxidative stress, protein synthesis and metabolic balance, cell cycle arrest, skeletal muscle regeneration, and cell apoptosis pathways. This review summarizes the current research progress on the relationship between sarcopenia and chronic low-grade inflammation.

Keywords

Sarcopenia, Chronic Low-Grade Inflammation, Inflammation Markers

1. 肌少症

肌少症目前被普遍认为是一种老年综合症，其主要表现为出现与年龄增长相关的肌肉质量减少、肌肉功能和肌肉力量下降。可以导致衰弱、跌倒、骨折、代谢性疾病等发病率和死亡的风险增高[1]。分为原发及继发性肌少症，其影响因素主要包括体力活动水平低(可能导致肌肉质量下降) [2]、肌肉代谢改变、慢性低度炎症状态、氧化应激和神经肌肉接头障碍等。从 1970 年 shock 等人的大型队列研究开始[3]，肌少症随之进入人们的视线。1989 年肌少症(Sarcopenia)被首次被 Rosenberg 等人正式提出[4]。2010 年，欧洲老年人肌少症工作组(European Working Group on Sarcopenia in Older People, EWGSOP)发表了第一个肌少症共识[1]。国际肌少症工作组以及亚洲肌少症工作组也分别于 2011、2014 随之发布相关共识[5] [6]。亚洲肌少症工作组共识现已于 2019 年再次更新。研究表明，在 30 岁之后，肌肉的质量每 10 年会下降 3%~8%；在 50 岁后，肌肉力量和躯体功能会每年减少 1%~2% [7]。这些肌肉质量、肌肉力量以及躯体功能的改变都将导致跌倒、骨折、代谢性疾病等发病率和死亡的风险增高。在中国，老年人肌少症的发病率(男性为 8%~14%，女性为 9%~12%)，而住院的老年人肌少症的患病率(男性为 29%，女性为 23%)，远高于社区老年人(男性为 13%，女性为 11%) [8]。在人均期望寿命不断增加的现今社会，因肌少症导致的生活质量下降以及医疗费用的增加是我们必将面临的巨大难题。肌少症的具体病理生理机制尚不清楚。可能有多种原因和相互作用，如神经肌肉连接功能障碍、肌肉蛋白质周转变化、激素水平和敏感性变化、慢性低度炎症、氧化应激、不良生活习惯和生活方式等[9]。在其多种可能机制中，老年人中普遍存在的慢性低度炎症在肌少症的发生和发展中起主导作用[10]。

2. 慢性低度炎症

炎症是对组织功能障碍或体内平衡失衡的适应性反应，被认为是各种生理和病理过程的基础。它通常由有害的刺激和条件引发；例如，当病原体侵入人体并引起感染或损伤时，从而引发炎症反应。控制炎症反应被认为是有益的，提供保护，防止感染，修复受损组织和维持身体平衡，通过消除有害的刺激

和启动愈合/再生过程[11]。炎症反应在机体对抗内外致病因素的过程中发挥着巨大的、积极的作用，但长期持续的炎症反应往往会导致多种慢性疾病，如 2 型糖尿病、冠状动脉粥样硬化性心脏病、骨质疏松、肌少症、衰弱等，慢性低度炎症，目前被认为是各种年龄相关疾病的关键原因，例如动脉粥样硬化性疾病[12]，2 型糖尿病[13]和肌少症[14]。有大量证据表明，在肌少症众多的病理生理机制中，老年人中普遍存在的慢性低度炎症在肌少症的发生和发展中起主导作用[10]。

3. 慢性低度炎症的诱导因素

炎症的增加在一定程度上由促炎基因启动子区域的多态性决定。如 Olivieri 等 2002 年的研究表明 IL-6 基因启动子中的 C/G-174 单核苷酸多态性(Single Nucleotide Polymorphism, SNP)可以显著改变血清中 IL-6 浓度。而在 Giacconi 等人 2004 年的研究中表明，具有与 IL-6 水平升高相关的 GG 基因型的老年男性寿命较 CC 基因型更短[15]。也有许多研究表明，长寿与编码促炎表型的基因型呈负相关，而与编码抗炎表型的基因型呈正相关[15] [16] [17] [18]。

巨细胞病毒等病毒对免疫系统细胞进行慢性刺激，而由这些慢性刺激的免疫细胞引起的免疫反应将诱导先天性或获得性免疫系统分泌促炎细胞因子的释放，并产生恶性循环[19]。

氧化、酰化以及糖基化的 DNA 或者蛋白质等非感染因素也可以慢性刺激免疫系统的细胞分泌促炎介质并启动炎症反应[20]。

细胞衰老也可能是维持炎症的因素之一，Campisi 等 2011 年的研究表明在细胞衰老的过程中，促炎介质(如细胞因子、趋化因子、生长因子和蛋白酶)的分泌增加[21]。

许多研究表明肥胖也可引起炎症。肌内浸润的脂肪细胞容易产生促炎环境。随着年龄的增加，脂肪组织会增加分泌促炎细胞因子(如 TNF 和 IL-6) [22] [23]，并促进肥胖相关胰岛素抵抗[24]。同时脂肪细胞也可以充当内分泌细胞，分泌脂肪因子(如瘦素和脂联素)，研究表明较高的血清瘦素水平以及较低水平的血清脂联素水平与老年人肌肉质量和功能差之间相关[25]。

参与基因调控的小非编码 RNA (Micro-RNA)，在衰老过程中可以增加促炎细胞因子的分泌，也可以作为单链 RNA 与 TLRs 结合的催化剂，诱导 NF-kB 的活化[26]。

线粒体 DNA (Mitochondrial DNA, mtDNA)在循环中随着年龄的增长而增加，并与促炎介质(TNF-α、IL-6、IL-1 受体拮抗剂)的血浆水平呈正相关[27]。mtDNA 可以在细胞外空间释放，并可以作为损伤相关分子模式(Damage-Associated Molecular Patterns, DAMP)的介质引起炎症[28]。

研究表明，老年人肠道的微生物组成和多样性与年轻对照组不同[29]，其中促进健康的细菌(双歧杆菌)会减少[30]，而兼性厌氧菌，包括链球菌、葡萄球菌、肠球菌和肠杆菌，随着年龄的增长在肠道中增加[31]。而这种改变的微生物群组成与促炎介质(如 IL-6 和 IL-8)的血清水平升高有关[32]。

4. 慢性低度炎症与肌少症相关机制

4.1. 慢性低度炎症与骨骼肌蛋白质代谢相关

肌少症为各种因素导致的肌肉蛋白质分解代谢(Muscle Protein Breakdown, MPB)和肌肉蛋白质合成代谢(Muscle Protein Synthesis, MPS)的平衡紊乱[33]。蛋白质降解与蛋白酶体途径及自噬途径相关[34]，在参与这些降解途径的蛋白质中，蛋白酶体系统的两种泛素 E3 连接酶 Atrogin-1 和 MURF1 被广泛认为是肌肉萎缩的主要调节因子[35]。炎症可以诱导胰岛素抵抗，并通过抑制 IGF1-PI3K-Akt-mTOR 途径的蛋白质合成以及通过 FoxO 家族的蛋白质及其下游 E3 泛素连接酶来促进蛋白质分解，促进肌肉萎缩；炎症也可能通过 NF-κB 和 STAT3 等途径直接促进萎缩信号传导[36]。最近的一项综述表明，在慢性低度炎症过

程中，促炎介质水平升高，如 TNFα 和 IL-6，可能通过激活调节泛素-蛋白酶体系统的 FOXO3a 上调这种蛋白水解途径[37]。

4.2. 慢性低度炎症与骨骼肌再生相关

骨骼肌再生需要同时激活多种细胞以及分子途径，是一个高度协调的过程。哺乳动物骨骼肌的再生是由肌肉干细胞(Muscle Stem Cells, MuSCs)介导的，MuSCs 也称为卫星细胞，是成人骨骼肌的主要干细胞。骨骼肌的再生能力受到 MuSC 与其微环境(也称为 MuSC 生态位)之间的相互作用的严格控制[38]。首先，收到来自坏死或受损肌肉纤维(或来自其他周围损伤源)的信号。其次，募集免疫细胞到局部损伤部位。第三，MuSCs 的活化、分化和融合。第四，新形成的肌纤维的成熟和重塑[39]。与肌病、肥胖和衰老相关的慢性低度炎症为 MuSC 的更新创造了一个不利的生态位[40]。骨骼肌再生过程中 M1 巨噬细胞向 M2 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[41]。在衰老的骨骼肌中观察到 M1-M2 巨噬细胞模式的不平衡[42]。在杜氏肌营养不良症(Duchenne Muscular Dystrophy, DMD)中也研究了巨噬细胞和 MuSCs 之间的相互作用，DMD 是一种由功能性抗肌萎缩蛋白缺失引起的原发性肌病，通过 IL-10 给药诱导 M1-M2，通过减少 M1 表型的激活，可以缓解 MuSCs 的持续肌源性激活[43]。

5. 慢性低度炎症标志物与肌少症

5.1. 炎症细胞因子与肌少症

细胞因子由不同的细胞类型分泌，骨骼肌产生的细胞因子称为肌因子。通常来说分为促炎因子和抗炎因子，但随着细胞因子作用持续时间不同，就会表现出多效性和剂量依赖性作用，并具有不同的结果[44]。TNF-α、白细胞介素-6 (IL-6)和成纤维细胞生长因子-21 (Fibroblast Growth Factor21, FGF21)具有双重效应。TNF-α 在肌肉损伤早期可以促进肌肉修复，TNF-α 水平的持续升高又会导致肌肉损伤，但老年人长期低水平 TNF-α 又与肌肉萎缩相关[45] [46] [47] [48]；IL-6 是一种促炎细胞因子，多项研究表明长期暴露于高水平 IL-6 可能会导致肌肉萎缩[10] [49]。但也可由肌纤维和卫星细胞分泌，从而促进肌肉干细胞的增殖[50]；FGF21 的作用与剂量和年龄相关，可以表现为改善胰岛素抵抗、降低肌肉力量等不同作用[51]。研究表明高水平的 CRP 与握力低、肌肉质量减少等有关[10] [52] [53]。IL-15 已被证明在体外和动物实验中对肌肉有许多积极影响。有助于缓解炎症介导的骨骼肌损失的蛋白质积累增加和降解减少、成肌细胞分化、骨骼肌纤维肥大和骨骼肌代谢改变(葡萄糖摄取增加和脂质氧化)等[49]，甚至可以减轻 TNF-α 引起的炎症有害作用，低水平的血浆 IL-15 与老年人的肌少症有关[49] [54]。IL-10 可以抑制 IL-6 的产生，也可以抑制人单核细胞和巨噬细胞的功能，通常被认为是一种抗炎细胞因子。但其在不同组织、器官、疾病状态可能存在多效性，可能有益，也可能无明显效果[55] [56]。鸢尾素已被确定为一种肌因子，可加速脂肪组织的褐变，改善肥胖和葡萄糖稳态[57]。研究表明，在肝硬化患者中，鸢尾素水平较低与肌无力和萎缩以及肌肉减少有关[58] [59] [60]。

5.2. 炎症指标及其衍生物与肌少症

血常规作为临床最常用检测指标，其中 WBC、N、PLT、L、M 以及其衍生物(PLR、NLR、MLR、SII 等)常用来反应机体炎症状态，较于 TNF-α、IL-6、IL-10 等肌少症预测指标临床易得性更强。且已用作预测冠心病、各种肿瘤等疾病的生物标志物。多项研究表明 NLR 的增加与肌少症明显相关[61] [62] [63] [64]。也有研究发现，PLT、WBC、血小板/白细胞比值、PLR、SII 的升高与肌少症显著相关[62] [65] [66]。但也有研究否认 PLR、LMR、NLR 与肌少症存在相关性[67]。目前这些常见炎症指标及其衍生物对肌少症预测的机制及规范化的界定范围尚未完全明确，临床应尚存在局限性。

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