

脂肪细胞因子在骨骼肌萎缩中的作用与机制

方文君^{1,2}, 王欢^{1,2}, 李梦欠^{1,2}, 王浩^{1,2}, 王浩哲^{1,2}, 朱琳^{1,3*}, 刘晓光^{1,2*}

(1 广州体育学院运动与健康学院, 广州 510500; 2 广州体育学院体卫融合创新发展研究中心, 广州 510500; 3 广州体育学院粤港澳大湾区体育科学创新研究中心, 广州 510500)

摘要: 骨骼肌萎缩是蛋白质合成与分解失衡所引发的状态, 表现为骨骼肌质量降低、力量减弱以及机体功能障碍, 与衰老、神经损伤、慢性炎症、癌症恶病质和肥胖等多种因素密切相关。脂肪细胞因子(adipokines)是一类主要由脂肪组织分泌的生物活性物质, 在骨骼肌萎缩的发生、发展及治疗中起着重要作用。在骨骼肌萎缩状态下, 脂肪细胞因子通过与自身受体结合激活多种信号转导途径, 引起细胞增殖与凋亡失调和促炎及抗炎因子分泌紊乱, 影响骨骼肌的能量代谢、炎症反应和胰岛素敏感性, 进一步导致骨骼肌质量和力量的下降。由于骨骼肌萎缩病理机制极为复杂且尚未完全阐明, 探索其潜在治疗靶点对防治该疾病尤为重要。本文综述了肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-6(interleukin-6, IL-6)、抵抗素、瘦素和脂联素(adiponectin, ADN)等脂肪细胞因子的生物学特性以及在骨骼肌萎缩中的作用与机制, 有助于探究脂肪细胞因子作为该类疾病潜在干预靶点的应用前景, 以为骨骼肌萎缩等疾病的防治提供理论参考。

关键词: 骨骼肌萎缩; 脂肪细胞因子; 脂肪组织

中图分类号: Q445 **文献标识码:** A

The role and mechanisms of adipokines in skeletal muscle atrophy

FANG Wen-Jun^{1, 2}, WANG Huan^{1, 2}, LI Meng-Qian^{1, 2}, WANG Hao^{1, 2}, WANG Hao-Zhe^{1, 2}, ZHU Lin^{1, 3*}, LIU Xiao-Guang^{1, 2*}

(1 School of Sport and Health, Guangzhou Sport University, Guangzhou 510500, China; 2 Research Center for Innovative Development of Sports and Healthcare Integration, Guangzhou Sport University, Guangzhou 510500, China; 3 Innovative Research Center for Sports Science in the Guangdong-Hong Kong-Macao Greater Bay Area, Guangzhou Sport University, Guangzhou 510500, China)

Abstract: Skeletal muscle atrophy is a pathological condition triggered by an imbalance between protein synthesis and degradation. It is characterized by reduced skeletal muscle mass, impaired muscle strength, and compromised bodily function, and is closely associated with multiple factors such as aging, nerve injury, chronic inflammation, cancer cachexia, and obesity. With the global aging population and the increasing incidence of chronic diseases, skeletal muscle atrophy has become a major public health concern that severely impairs patients' quality of life and imposes a heavy burden on healthcare systems worldwide. Adipokines are bioactive substances mainly secreted by adipose tissue, which also serve as important endocrine organs involved in regulating various physiological and pathological processes of the body. These molecules play a crucial role in the occurrence, progression, and treatment of skeletal muscle atrophy, acting as key mediators in the crosstalk between adipose tissue and skeletal muscle. Under the state of skeletal muscle atrophy, adipokines bind to their respective receptors to activate a variety of signal transduction pathways. This activation leads to dysregulation of cell proliferation and apoptosis, as well as disordered secretion of pro-inflammatory and anti-inflammatory factors. Such abnormalities further affect the energy metabolism of skeletal muscle, alter the inflammatory response in muscle tissue, and reduce insulin sensitivity of muscle cells, all of which ultimately contribute to the progressive decrease in skeletal muscle mass and strength. Despite extensive research efforts in recent years, the pathological mechanisms of skeletal muscle atrophy remain extremely complex and have not been fully elucidated. The lack of

收稿日期: 2025-09-08; 修回日期: 2025-11-02

基金项目: 国家自然科学基金青年基金项目(32300964); 广东省基础与应用基础研究基金省市联合基金青年项目(2022A1515111105); 广东省普通高校特色创新项目(2023KTSCX064)

*通信作者: 刘晓光, E-mail: liuxg@gzsport.edu.cn; 朱琳, E-mail: 11251@gzsport.edu.cn

in-depth understanding of these mechanisms has resulted in a scarcity of effective clinical interventions and therapeutic strategies for this condition. Therefore, exploring potential therapeutic targets is particularly important for the prevention and treatment of skeletal muscle atrophy. This article reviews the biological characteristics of several key adipokines, including tumor necrosis factor- α , interleukin-6, resistin, leptin, and adiponectin. It also elaborates on their specific roles and underlying mechanisms in skeletal muscle atrophy, focusing on how each adipokine modulates muscle protein metabolism, inflammatory responses, and energy homeostasis through distinct signaling cascades. The comprehensive analysis provided in this review helps to explore the application prospects of adipokines as potential intervention targets for skeletal muscle atrophy. It is expected to lay a solid theoretical foundation for the development of novel therapeutic approaches and provide valuable theoretical references for the prevention and treatment of skeletal muscle atrophy and related diseases.

Key words: skeletal muscle atrophy; adipokines; adipose tissue

1 引言

骨骼肌作为人体最大的代谢器官之一,约占人体重量的40%^[1]。它不仅负责运动和姿势的维持,其质量和功能的完整性对维持骨骼肌系统的正常功能和代谢稳态至关重要^[2]。骨骼肌质量取决于蛋白质合成与分解之间的平衡。当蛋白质合成总速率低于蛋白质降解速率时,就可能导致骨骼肌萎缩,表现为肌纤维体积减小、力量减弱以及机体功能障碍,与衰老、神经损伤和慢性炎症等多因素相关^[3]。骨骼肌萎缩增加了老年患者跌倒和骨折的风险,严重影响生活质量,增加医疗负担^[4]。鉴于骨骼肌萎缩发病机制复杂,目前仍未完全阐明,探寻其潜在作用靶点,对该病的防控与临床干预至关重要。

脂肪细胞因子(adipokines)是一类主要由脂肪组织分泌的生物活性物质。在正常生理状态下,脂肪细胞因子参与骨骼肌稳态的调节,在病理状态下则加剧骨骼肌的分解与萎缩,其复杂的调控网络可

能为骨骼肌萎缩提供新的治疗靶点^[5,6]。骨骼肌萎缩时,脂肪组织功能障碍导致脂肪细胞因子分泌失调,表现为促炎脂肪细胞因子增多和抗炎脂肪细胞因子减少。这种失调通过跨器官调控和局部作用方式影响骨骼肌的能量代谢、炎症反应和胰岛素敏感性,从而改变骨骼肌的质量和功能(图1)^[7,8]。在探讨脂肪细胞因子对骨骼肌萎缩的影响时,通常聚焦于肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-6(interleukin-6, IL-6)、抵抗素(resistin)、瘦素(leptin)与脂联素(adiponectin, ADN)等脂肪细胞因子,因为它们脂肪组织与骨骼肌之间的代谢调控和炎症反应中具有明确且关键的作用,其失调与骨骼肌萎缩的发生发展密切相关,因此被广泛研究并有望作为主要的干预靶点。然而,目前缺乏脂肪细胞因子作为治疗骨骼肌萎缩潜在靶点的系统性总结。

基于此,本文通过对TNF- α 、IL-6、抵抗素、瘦素

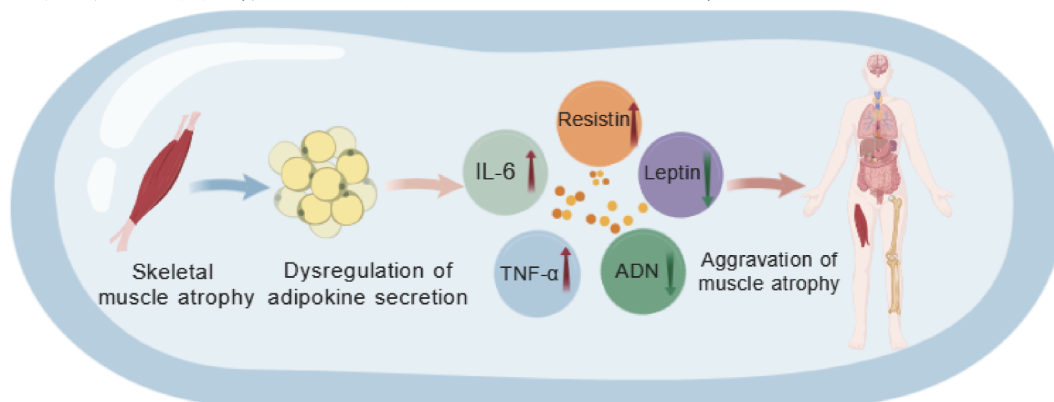


图1 脂肪细胞因子在骨骼肌萎缩中的作用

Skeletal muscle atrophy: 骨骼肌萎缩; Dysregulation of adipokine secretion: 脂肪细胞因子分泌失调; IL-6: interleukin-6, 白细胞介素-6; TNF- α : tumor necrosis factor- α , 肿瘤坏死因子- α ; ADN: adiponectin, 脂联素; resistin: 抵抗素; leptin: 瘦素; Aggravation of muscle atrophy: 骨骼肌萎缩加重。骨骼肌萎缩时,脂肪组织功能障碍导致脂肪细胞因子分泌失调,即促炎脂肪细胞因子增多和抗炎脂肪细胞因子减少,骨骼肌萎缩加重。

Figure 1 Roles of adipokines in skeletal muscle atrophy

During skeletal muscle atrophy, adipose tissue dysfunction leads to dysregulation of adipokine secretion, namely an increase in pro-inflammatory adipokines and a decrease in anti-inflammatory adipokines, which further aggravates skeletal muscle atrophy.

与脂联素的生物学特性以及在骨骼肌萎缩中的表达与作用机制进行梳理,旨在整合现有研究进展,分析其在病理过程中的共性与差异性,并探讨其作为潜在干预靶点的应用前景,为骨骼肌萎缩等疾病的防治提供理论支持。

2 骨骼肌萎缩的定义与分类

骨骼肌萎缩是蛋白质合成与分解失衡所引发的一种状态,病理特征包括肌纤维萎缩、蛋白质丢失和肌球蛋白亚型改变,临床表现为肌力减退、易疲劳和运动障碍,与多种因素相关^[9]。依据发病机制,骨骼肌萎缩可分为原发性和继发性两类。原发性骨骼肌萎缩通常由多种遗传性骨骼肌疾病直接引起,如肌营养不良症、线粒体肌病和代谢性肌病等,常伴有进行性肌萎缩、肌纤维代谢障碍、肌肉痉挛或僵硬等症状^[9,10]。先天性肌病包括杆状体肌病,而肌营养不良症包括杜氏肌营养不良症、贝克氏肌营养不良症以及强直性肌营养不良症^[11]。继发性骨骼肌萎缩则多由后天因素引发,与衰老及多种疾病密切相关,如骨质疏松症、癌症恶病质、肥胖以及慢性肾脏疾病等^[12]。此外,在日常生活中,禁食或营养不良等情况也容易导致骨骼肌萎缩^[13]。它不仅严重影响患者的生活质量,还对其健康构成威胁。然而,目前针对骨骼肌萎缩的有效疗法相对匮乏,未来研究需进一步明确骨骼肌萎缩的分子机制,以开发新的临床治疗方法。

3 脂肪组织与脂肪细胞因子

脂肪组织按功能和细胞特性可分为以下类型:白色脂肪组织(white adipose tissue, WAT)、棕色脂肪组织(brown adipose tissue, BAT)、米色脂肪组织(beige adipose tissue, BeAT)和粉红色脂肪组织(pink adipose tissue, PAT)^[14,15]。其中, WAT负责能量储存,以甘油三酯的形式储存多余能量。BAT则

通过线粒体中的解偶联蛋白1(uncoupling protein 1, UCP1)介导产热,消耗能量以维持体温。BeAT则兼具WAT和BAT的特性,在特定条件下可从WAT转化而来,表现出类似BAT的产热功能^[16]。PAT是一类分泌乳汁的脂肪细胞,在妊娠期和哺乳期间为“粉红色”,断乳后,这类细胞可逆地重新恢复为白色脂肪细胞^[17]。脂肪组织不仅是能量存储的场所,还作为内分泌组织分泌脂肪细胞因子^[18]。

脂肪细胞因子是一类由脂肪组织分泌的生物活性分子,广泛参与能量代谢、炎症反应、免疫调节等多种生理和病理过程^[6]。根据生物学功能,脂肪细胞因子可分为促炎型和抗炎型两大类。促炎脂肪细胞因子,如TNF- α 、IL-6、抵抗素和瘦素等,主要通过激活炎症信号通路,促进炎症反应和蛋白质分解^[19,20]。相反,抗炎脂肪细胞因子,如脂联素等,则通过抑制炎症反应和改善胰岛素敏感性,对机体代谢和炎症反应起到保护和预防作用^[21]。作为重要的炎症调节因子,脂肪细胞因子通过调控炎症反应、介导胰岛素抵抗等途径在骨骼肌萎缩中发挥关键作用。因此,脂肪细胞因子很可能成为骨骼肌萎缩的潜在治疗靶点。表1对不同类型脂肪组织的作用及其分泌的主要脂肪细胞因子进行了总结。

3.1 TNF- α

TNF- α 是一种促炎细胞因子,由单核细胞和巨噬细胞产生,其单体相对分子质量约为17 kD,属于肿瘤坏死因子超家族(TNFSF),该家族还包括TNF- β 、Fas配体和CD40配体等,它们共同参与免疫调节和炎症反应^[27,28]。TNF- α 通过与其受体肿瘤坏死因子受体超家族成员1A(TNFRSF1A)结合,触发炎症级联反应和免疫细胞的激活,从而在肿瘤免疫中发挥重要作用^[29]。在代谢性疾病研究中, TNF- α 因在胰岛素抵抗中的作用而受到广泛关注。Hotamisligil等^[30]通过肥胖小鼠模型经典实验发现,脂肪组织TNF- α 水平升高直接抑制胰岛素受体/胰

表1 不同类型脂肪组织的作用及其分泌的主要脂肪细胞因子
Table 1 Roles of different types of adipose tissue and the main adipokines they secreted

脂肪类型	作用	主要分泌的细胞因子	参考文献
白色脂肪组织	储存能量、缓冲保护、调节代谢	Leptin、脂联素、网膜素、TNF- α 、IL-6、抵抗素、单核细胞趋化蛋白-1、纤溶酶原激活物抑制剂-1、视黄醇结合蛋白4	[22,23]
棕色脂肪组织	产热、维持体温、调节全身代谢	成纤维细胞生长因子21、IL-6、白细胞介素-8、白细胞介素-10、神经调节蛋白4、血管内皮生长因子A、趋化因子 CXCL14、分形趋化因子、视黄醇结合蛋白4	[24,25]
米色脂肪组织	产热、改善代谢状态	TNF- α 、IL-6、血管生成素样蛋白4、成纤维细胞生长因子21	[26]
粉红色脂肪组织	产热、分泌乳汁	Leptin、脂联素、IL-6、胰岛素样生长因子1、成纤维细胞生长因子2	[19]

胰岛素受体底物1(insulin receptor substrate 1, IRS-1)酪氨酸磷酸化,诱发胰岛素抵抗。使用TNF- α 抗体或可溶性肿瘤坏死因子受体2(tumor necrosis factor receptor 2, TNFR2)阻断TNF- α 信号通路能显著减弱骨骼肌和脂肪组织中其对胰岛素受体和IRS-1酪氨酸磷酸化的抑制作用,进而改善胰岛素敏感性。这些研究结果有力地证实了TNF- α 作为促炎细胞因子在肥胖相关胰岛素抵抗中的关键作用,提示阻断TNF- α 可能是治疗骨骼肌萎缩的一种新方法,未来有待更多的临床和基础研究来证实。

3.2 IL-6

白细胞介素6,简称白介素6,是趋化因子家族中的一种多效性细胞因子^[31]。目前,经典的IL-6家族有12个细胞因子成员,包括IL-6、IL-11、IL-27、IL-31、IL-35、IL-39、白血病抑制因子(LIF)、心脏促肾素样细胞因子(CLC)、抑瘤素M(OSM)、睫状神经营养因子(CNTF)、心脏促肾素-1(CT-1)和神经生成素(NPN)^[32]。IL-6由B淋巴细胞、T淋巴细胞和巨噬细胞等免疫细胞合成并分泌。在应激条件下,BAT也可通过 β -肾上腺素信号诱导IL-6的分泌^[33]。现已知,IL-6对免疫调节、急性期反应、再生和骨稳态等具有广泛影响,其功能多样性主要源于IL-6与细胞表面不同类型的IL-6受体(interleukin-6 receptor, IL-6R)的相互作用,经下游信号转导将不同生物信号传给各类细胞和组织^[34]。具体而言,IL-6主要通过经典信号通路(膜结合性受体mIL-6R)、反式信号通路(可溶性受体sIL-6R)和IL-6簇信号转导三种模式传输信号^[35]。例如,IL-6与肝细胞表面的mIL-6R结合会直接诱导急性期反应蛋白的合成,参与机体感染或创伤后的系统性炎症反应^[36]。IL-6在骨骼肌中也发挥重要作用,它可以通过调节肌肉蛋白的合成与分解,影响骨骼肌的代谢和功能,进而参与骨骼肌萎缩和再生等过程^[37]。

3.3 抵抗素

抵抗素是2001年首次被发现的脂肪细胞因子,因其介导胰岛素抵抗而被命名^[38]。抵抗素主要在WAT中表达,BAT中表达较低,在其他组织中几乎不表达。在小鼠和人类中,抵抗素分别由94和108个氨基酸组成,其结构包含N端信号肽、中央 α 螺旋结构域及C端富含半胱氨酸的结构域,属于抵抗素样分子(resistin-like molecule, RELM)激素家族,该家族还包括RELM α 、RELM β 和RELM γ 等成员^[39,40]。在

小鼠体内,血清抵抗素水平与机体胰岛素抵抗以及炎症状态呈正相关,参与2型糖尿病、类风湿性关节炎、慢性肾炎、败血症等疾病的发病过程^[41,42]。在骨骼肌中,抵抗素通过与肌细胞表面的受体结合,激活下游信号通路,进而影响细胞内的胰岛素信号转导。这一过程导致骨骼肌对胰岛素的敏感性降低,表现为葡萄糖摄取能力下降和能量代谢受损^[43]。此外,研究发现24月龄老年小鼠胫骨前肌持续暴露于抵抗素24 h后,NOD样受体热蛋白结构域相关蛋白3炎性小体(NOD-like receptor pyrin domain-containing 3 inflammasome, NLRP3炎性小体)被激活,促进半胱天冬酶-1(caspase-1)、TNF- α 和IL-6等炎症因子的表达,加剧胰岛素抵抗^[44]。抵抗素在全身代谢和炎症过程中的广泛作用,使其成为胰岛素抵抗和相关代谢疾病的潜在治疗靶点。

3.4 瘦素

瘦素是由肥胖(ob)基因编码的信号分子,其分子本质为16 kD亲水性蛋白激素,由167个氨基酸组成,其中96位与146位的半胱氨酸通过二硫键形成稳定的球形结构^[45,46]。1995年,Halaas等^[47]在ob基因突变小鼠中发现瘦素并将其命名为Leptin(又译为“祛脂素”)。瘦素主要由WAT中的脂肪细胞分泌,其分泌水平与脂肪储存量成正比^[22]。瘦素通过作用于下丘脑的瘦素受体(leptin receptor, LEPR),调节食欲和能量消耗,从而维持能量平衡^[48]。饥饿时,瘦素含量降低以增强食欲;饱腹时瘦素可起到减少食欲的作用。瘦素还在肝脏和骨骼肌等外周组织发挥代谢作用。例如,在人原代肌管细胞实验中发现用外源性瘦素处理48 h后,葡萄糖摄取量增加35%($P<0.01$);同时肌细胞内脂质沉积显著降低,这证实了瘦素可能通过自身方式改善肌细胞糖脂代谢稳态^[49]。因此,瘦素通过改善肌细胞代谢可能在骨骼肌萎缩中发挥关键作用。此外,瘦素参与生殖、骨量和慢性炎症性疾病的调节^[50]。

3.5 脂联素

脂联素是一种由WAT产生的具有224个氨基酸的蛋白质,其单体相对分子质量约为30 kD^[51]。脂联素于1995年首次被发现,编码基因位于染色体3q27上,它的结构包含N端信号序列、高变非同源区、22个胶原重复序列(8个Gly-X-Pro和14个Gly-X-Y)的胶原结构域及C端C1q样球状结构域^[52]。脂联素通过与其受体T-钙黏蛋白、脂联素受体1

(AdipoR1)和脂联素受体2(AdipoR2)相互作用,调控脂肪和葡萄糖的代谢^[53]。此外,脂联素已被证实可以改善人类及小鼠的骨骼肌功能。相关研究发现,高脂饮食肥胖小鼠连续注射两周高分子量多聚体形式(high-molecular-weight multimer, HMW)脂联素后,趾长伸肌肌纤维横截面积增大25%,同时肌肉萎缩相关标志物肌肉环指蛋白-1(muscle ring-finger protein-1, MuRF-1)和肌肉萎缩F-box蛋白(muscle atrophy F-box protein, Atrogin-1)都显著降低^[54]。另外,在人原代肌管细胞的实验中发现,用HMW脂联素干预24 h后,相比于对照组,干预组细胞葡萄糖摄取和脂肪酸氧化能力显著上升^[55]。以上结果表明脂联素具有促进骨骼肌肥大、改善肌萎缩以及提高葡萄糖摄取和脂肪酸氧化的作用。

4 脂肪细胞因子在骨骼肌萎缩中的作用及机制

脂肪细胞因子作为重要的炎症调节因子,在骨骼肌萎缩的发生和发展中发挥关键作用。虽然脂肪细胞因子主要由脂肪组织产生,但在骨骼肌萎缩状态下,骨骼肌中的脂肪细胞、免疫细胞(如中性粒细胞、巨噬细胞和淋巴细胞)、成纤维脂肪祖细胞、间充质干细胞以及骨骼肌细胞分泌的脂肪细胞因子等也参与骨骼肌萎缩的调控。这些脂肪细胞因子通过跨器官调控和局部作用方式影响骨骼肌的能量代谢、炎症反应和胰岛素敏感性,进而改变骨骼肌的质量和功能^[56-58]。因此,深入了解脂肪细胞因子在骨骼肌萎缩中的作用机制,不仅有助于全面理解骨骼肌萎缩的复杂过程,还能为治疗骨骼肌萎缩等疾病提供新的思路和策略(图2)。

4.1 TNF- α 在骨骼肌萎缩中的作用与机制

骨骼肌萎缩主要是由于泛素-蛋白酶体途径和自噬-溶酶体途径(线粒体自噬)加速蛋白质降解^[59]。关于TNF- α 在骨骼肌中的作用存在一定的争议:TNF- α 通路在骨骼肌萎缩条件下诱导骨骼肌退化;而在骨骼肌损伤条件下则可能参与骨骼肌再生过程^[60]。骨骼肌萎缩期间,血清中TNF- α 表达上调,促进E3泛素连接酶MAFbx(muscle atrophy F-box, MAFbx)/Atrogin-1基因的表达,加剧骨骼肌萎缩的病理过程^[61,62]。这种变化与泛素偶联有关,并且似乎是由P38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38MAPK)信号介导的^[63]。具体来说,MAFbx/Atrogin-1表达首先激活p38MAPK,这与

Childs等^[64]的研究一致,即实验性固定大鼠后肢10 d导致p38磷酸化增加128%,这与同期比目鱼肌质量减少38%有关。与之相反, Li等^[65]研究发现MAFbx/Atrogin-1基因是p38MAPK信号转导的下游靶标,与p38活性病理性升高促进蛋白质降解和骨骼肌萎缩有关。TNF- α 与肿瘤坏死因子受体1(tumor necrosis factor receptor 1, TNFR1)结合后,激活下游的肿瘤坏死因子受体相关因子2(TNF receptor-associated factor 2, TRAF2)和肿瘤坏死因子受体相关死亡域蛋白(TNF receptor-associated death domain protein, TRADD)。TRAF2和TRADD进一步激活核因子 κ B抑制蛋白(nuclear factor κ B inhibitor, I κ B)激酶复合体(由IKK α 、IKK β 和NEMO组成),导致I κ B的磷酸化和降解。I κ B降解释放出核因子 κ B(nuclear factor κ B, NF- κ B)(p50/p65复合体),使其能够转移到细胞核内。NF- κ B进入细胞核后,结合到DNA上的 κ B位点,激活多种炎症相关基因的转录,包括白细胞介素-1(interleukin-1, IL-1)、IL-6等促炎细胞因子,加剧骨骼肌的炎症反应^[66,67]。NF- κ B信号通路激活通过抑制骨骼肌分化相关基因的表达,主要是成肌细胞决定蛋白1(myoblast determination protein 1, MyoD)和肌生成蛋白(myogenin, MyoG),促进蛋白酶体和自噬-溶酶体对骨骼肌蛋白质的降解,从而阻止骨骼肌再生^[68]。另有研究发现,高脂喂养的C57BL/6J小鼠骨骼肌中I κ B和NF- κ B磷酸化水平上升,可能是由于骨骼肌中饱和脂肪酸激活炎症小体NLRP3后加剧了上述磷酸化过程,促进骨骼肌萎缩发生,这有待更多实验去验证^[69]。以上研究表明, TNF- α 通过激活p38MAPK和NF- κ B信号通路,在骨骼肌萎缩中促进蛋白质降解和炎症反应。TNF- α 抑制剂能够破坏TNF- α 与其受体结合,有效抑制细胞因子驱动的炎症反应。在自身免疫性疾病和炎症性疾病的临床试验中, TNF- α 抑制剂已取得显著进展,并表现出强大的安全性和有效性^[70]。在1型糖尿病中, TNF- α 抑制剂显著降低糖化血红蛋白A1c(glycated hemoglobin A1c, HbA1c)水平并增加C肽水平,减少外源胰岛素的使用,从而在糖尿病治疗中发挥重要作用^[71]。这些结果进一步支持了TNF- α 抑制剂作为骨骼肌萎缩治疗靶点的潜力。然而, TNF- α 在骨骼肌损伤后的再生过程中也发挥重要作用,这提示临床制定治疗策略时需要考虑其双重作用。未来的研究应聚焦于开发特异性更高、副作用更小的TNF- α 抑制剂,并探索

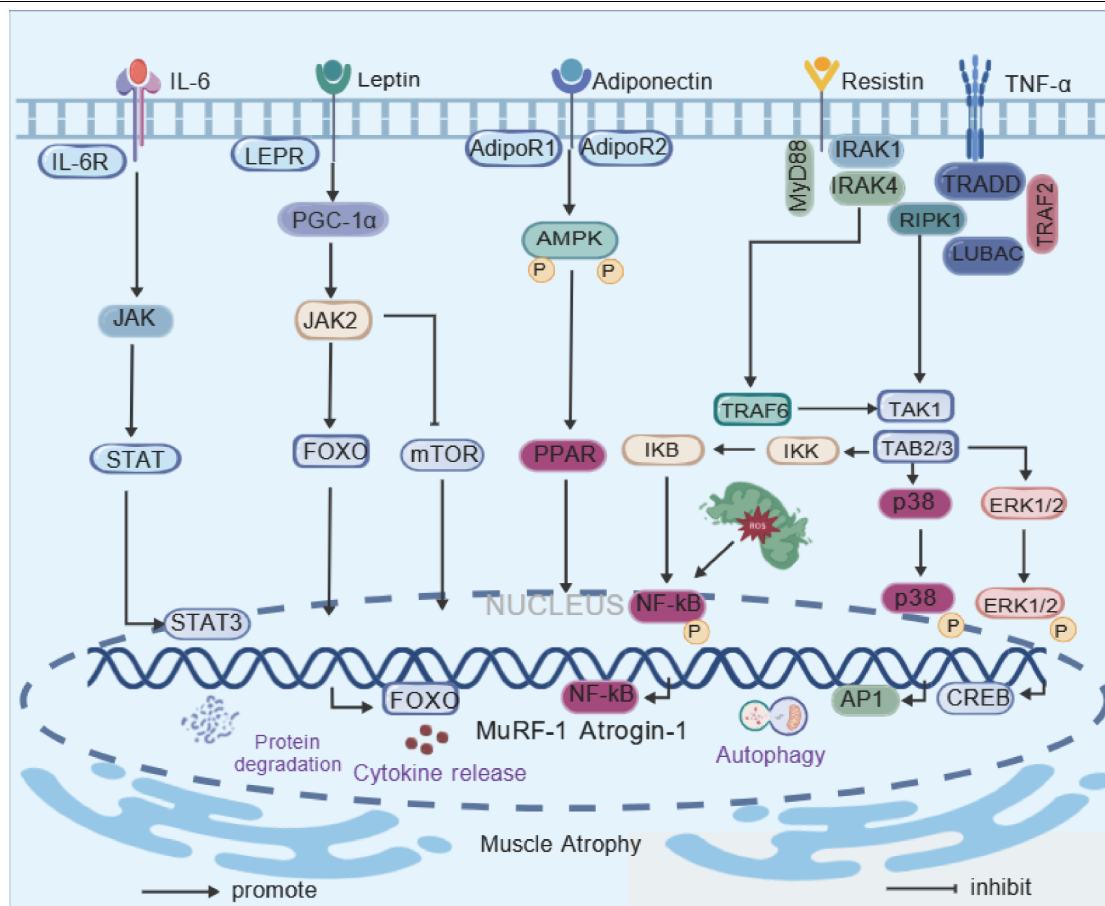


图2 脂肪细胞因子在骨骼肌萎缩中的机制图

IL-6:interleukin-6,白细胞介素-6;IL-6R:interleukin-6 receptor,白细胞介素-6受体;JAK:Janus kinase,Janus激酶;STAT:signal transducer and activator of transcription,信号转导及转录激活蛋白;STAT3:signal transducer and activator of transcription 3,信号转导及转录激活蛋白3;Leptin:瘦素;LEPR:leptin receptor,瘦素受体;PGC-1 α :peroxisome proliferator-activated receptor gamma coactivator 1 α ,过氧化物酶体增殖物激活受体 γ 共激活因子-1 α ;JAK2:Janus kinase 2,Janus激酶2;FOXO:forkhead box protein O,叉头框蛋白O;mTOR:mammalian target of rapamycin,哺乳动物雷帕霉素靶蛋白;Adiponectin:脂联素;AdipoR1:adiponectin receptor 1,脂联素受体1;AdipoR2:adiponectin receptor 2,脂联素受体2;AMPK:AMP-activated protein kinase,AMP激活蛋白激酶;PPAR:peroxisome proliferator-activated receptor,过氧化物酶体增殖物激活受体;Resistin:抵抗素;MyD88:myeloid differentiation primary response protein 88,髓样分化主要反应蛋白88;IRAK1:interleukin-1 receptor-associated kinase 1,白细胞介素-1受体相关激酶1;IRAK4:interleukin-1 receptor-associated kinase 4,白细胞介素-1受体相关激酶4;TRAF6:TNF receptor-associated factor 6,肿瘤坏死因子受体相关因子6;TAK1:transforming growth factor β -activated kinase 1,转化生长因子 β 激活激酶1;TAB2/3:transforming growth factor β -activated kinase 1-binding protein 2/3,转化生长因子 β 激活激酶1结合蛋白2/3;IKK:ikB kinase,IkB激酶;IkB:nuclear factor κ B inhibitor,核因子 κ B抑制蛋白;NF- κ B:nuclear factor κ B,核因子 κ B;TRADD:TNF receptor-associated death domain protein,肿瘤坏死因子受体相关死亡域蛋白;RIPK1:receptor-interacting protein kinase 1,受体相互作用蛋白激酶1;LUBAC:linear ubiquitin chain assembly complex,线性泛素链组装复合体;TRAF2:TNF receptor-associated factor 2,肿瘤坏死因子受体相关因子2;p38 MAPK:p38 mitogen-activated protein kinase,p38丝裂原活化蛋白激酶;TNF- α :tumor necrosis factor- α ,肿瘤坏死因子- α ;ERK1/2:extracellular signal-regulated kinase 1/2,细胞外信号调节激酶1/2;CREB:cAMP response element-binding protein,cAMP反应元件结合蛋白;AP1:activator protein 1,激活蛋白1;MuRF-1:muscle ring finger protein-1,肌肉环指蛋白-1;Atrogin-1:muscle atrophy F-box protein 1,肌肉萎缩F-box蛋白-1;Protein degradation:蛋白质降解;Cytokine release:炎症因子释放;Autophagy:自噬;Muscle atrophy:骨骼肌萎缩。在骨骼肌萎缩中,不同脂肪细胞因子通过与其受体结合,激活或抑制特定的信号转导途径,促进蛋白质降解、炎症因子释放和自噬等,进一步加剧骨骼肌萎缩。

Figure 2 Mechanism diagram of adipokines in skeletal muscle atrophy

In skeletal muscle atrophy, various adipokines bind to their corresponding receptors to either activate or inhibit specific signaling pathways, which promotes events including protein degradation, cytokine release, and autophagy that subsequently aggravate skeletal muscle atrophy.

联合治疗策略,如结合营养补充、运动干预和药物治疗,以提高治疗效果。

4.2 IL-6在骨骼肌萎缩中的作用与机制

IL-6是一种具有多种生物学效应的细胞因子,在慢性炎症或病理状态下,其持续过量会加速炎症反应,而炎症正是骨骼肌萎缩的发病机制之一^[72]。Huang等^[73]发现,骨骼肌萎缩小鼠血清中IL-6的表达显著高于健康对照组,且与骨骼肌质量呈负相关。在另一种以结肠26(C26)癌诱导的小鼠骨骼肌萎缩模型中,同样观察到IL-6水平升高,骨骼肌中Atrogin-1和MuRF-1的表达水平也显著增加,而抑制IL-6被证明可以改善由癌症引起的骨骼肌质量下降^[74]。先前发现,IL-6过表达通过下调核糖体S6激酶(ribosomal S6 kinase, S6K)磷酸化以及上调叉头框蛋白O3a(forkhead box protein O3a, FOXO3a)和Atrogin-1诱导骨骼肌退化^[75]。近年来,研究提出IL-6也可能通过Janus激酶/信号转导与转录激活子3信号通路(Janus kinase/signal transducer and activator of transcriptions 3, JAK/STAT3)发挥作用,即IL-6与IL-6R结合形成IL-6/IL-6R/糖蛋白130(glycoprotein 130, gp130)复合物,激活JAK蛋白,磷酸化转录因子STAT3, STAT3易位到细胞核中,影响骨骼肌萎缩相关基因的转录^[76]。此外,IL-6在骨骼肌表面与IL-6R结合,还通过细胞外信号调节激酶1/2(extracellular signal-regulated kinase 1/2, ERK1/2)-过氧化物酶体增殖物激活受体 γ 辅激活因子-1 α (peroxisome proliferator-activated receptor gamma coactivator 1 α , pGC-1 α)/肌细胞增强因子2C(myocyte enhancer factor 2C, MEF2C)信号通路抑制乙酰胆碱受体 β 亚基(AChR- β)表达,导致神经肌肉接头(NMJ)功能障碍和肌肉收缩功能下降^[77]。Yang等^[72]在脓毒症相关的骨骼肌萎缩小鼠模型中发现,IL-6通过下调PGC-1 α 导致线粒体功能障碍,促进线粒体活性氧(reactive oxygen species, ROS)的产生和氧化应激增强,加速骨骼肌蛋白的降解,最终导致骨骼肌萎缩。在该模型中,持续给予小鼠IGF-1可改善脓毒症诱导的骨骼肌萎缩。IGF-1通过其受体胰岛素样生长因子1受体(insulin-like growth factor 1 receptor, IGF-1R)激活磷脂酰肌醇3激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, AKT)信号通路。PI3K将磷脂酰肌醇-4,5-二磷酸(phosphatidylinositol 4,5-bisphosphate, PIP2)磷酸化后生成磷脂酰肌醇-3,4,

5-三磷酸(phosphatidylinositol 3,4,5-trisphosphate, PIP3),进而激活AKT/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR),促进骨骼肌细胞的增殖和分化,抑制骨骼肌IL-6 mRNA上调,减轻炎症反应,进一步保护骨骼肌免受损伤^[78]。相反,IL-6基因敲除可以通过Akt/mTOR抑制IGF-1 mRNA表达和信号转导,从而减轻骨骼肌萎缩,表现为蛋白降解减少、肌纤维横截面积增加以及骨骼肌收缩功能改善^[79]。榄香烯是中药莪术的有效活性成分,在肿瘤恶病质小鼠模型中表现出减轻骨骼肌萎缩的效果,其机制与抑制血清IL-6的表达有关^[80]。以上研究结果表明,IL-6通过激活JAK/STAT3和ERK1/2信号通路在骨骼肌萎缩中发挥重要作用,提示阻断IL-6及其信号通路的抑制剂可能是治疗骨骼肌萎缩的一种新方法。目前,IL-6抑制剂包括沙利尤单抗(SAR)、托珠单抗(TCZ)等,在癌症、心血管疾病以及类风湿关节炎等领域均开展了广泛的临床试验,在多种疾病治疗中体现其潜在价值^[81]。在类风湿性关节炎治疗方面,IL-6抑制剂不仅减轻了关节炎症,还改善了贫血、心血管疾病、抑郁症和骨质疏松症等并发症^[82]。这些研究显示,IL-6抑制剂已在多个领域展现出良好的临床应用前景,有望为骨骼肌萎缩的治疗提供新的策略和方法。

4.3 抵抗素在骨骼肌萎缩中的作用与机制

目前研究表明,抵抗素促进骨骼肌萎缩的发生,该作用在老年人群中尤为明显^[83]。Kwak等^[84]研究发现,与健康对照组相比,老年骨骼肌萎缩患者肌肉组织中抵抗素水平最高,且与骨骼肌质量呈负相关。抵抗素具有明显的促炎特性,其通过调节炎症反应和代谢过程在骨骼肌萎缩中发挥重要作用^[85]。Toll样受体4(Toll-like receptor 4, TLR4)是一种模式识别受体,能够识别多种病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(damage-associated molecular patterns, DAMPs),在炎症反应中起关键作用^[86]。具体来说,TLR4激活后,通过髓样分化初级反应蛋白88(myeloid differentiation primary response protein 88, MyD88)依赖性通路激活一系列下游信号分子,包括白细胞介素-1受体相关激酶(interleukin-1 receptor-associated kinase, IRAK)和肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6, TRAF6)。TRAF6通过泛素化修

饰激活转化生长因子- β 激活激酶1(transforming growth factor β -activated kinase 1, TAK1), TAK1通过磷酸化激活p38MAPK, p38MAPK是一种应激激活的蛋白激酶, 激活的p38MAPK进一步磷酸化下游的转录因子, 如激活转录因子-2(activating transcription factor-2, ATF-2)和环磷酸腺苷应答元件结合蛋白(cyclic AMP response element-binding protein, CREB), 这些转录因子进入细胞核, 调控炎症相关基因的表达^[87]。Zhao等^[88]研究发现, 抵抗素与TLR4结合后, 同样通过MyD88依赖性通路, 激活I κ B激酶(I κ B kinase, IKK)复合体。IKK复合体磷酸化I κ B, 导致I κ B降解, 释放NF- κ B, NF- κ B随后转移到细胞核内, 结合到DNA上的特定启动子区域, 激活多种炎症相关基因的表达, 包括细胞因子(如TNF- α 、IL-6)、趋化因子和黏附分子等。这些炎症因子通过自分泌和旁分泌作用, 进一步抑制骨骼肌卫星细胞的分化, 减少骨骼肌细胞的生成。骨骼肌异位脂肪沉积也是促进骨骼肌萎缩的重要原因之一。Wen等^[89]用抵抗素通过miR-696诱导脂质在小鼠C2C12骨骼肌细胞中异位沉积, 引发线粒体功能障碍和氧化应激增加。氧化应激产生的ROS会损伤线粒体, 减少ATP生成, 从而影响骨骼肌的能量代谢。综上, 抵抗素通过激活TLR4-MyD88通路引发炎症反应, 抑制骨骼肌卫星细胞分化, 并诱导异位脂肪沉积, 导致线粒体功能障碍和氧化应激, 进而促进骨骼肌萎缩。这些机制表明抵抗素是骨骼肌萎缩的一个潜在治疗靶点。在临床应用方面, 抵抗素在多种疾病中展现出良好的应用前景。高剂量叶酸在肥胖糖尿病小鼠模型中表现出降低抵抗素水平的效果, 为肥胖和2型糖尿病的治疗提供了新的思路^[90]。此外, 有研究发现, 血清抵抗素水平与慢性阻塞性肺病患者的肌肉力量呈负相关, 可以作为预测慢性阻塞性肺病患者肌肉减少症的重要生物标志物^[85]。尽管如此, 目前抵抗素在骨骼肌萎缩中的临床应用还较少。未来的研究方向应包括鉴定抵抗素受体、开发多靶点药物、制定个性化治疗方案以及推进抵抗素在更多疾病中的临床试验, 以进一步评估其作为治疗靶点的潜力。

4.4 瘦素在骨骼肌萎缩中的作用与机制

瘦素具有促进骨骼肌细胞脂肪酸氧化和三酰甘油分解的作用^[91]。然而, 在骨骼肌萎缩状态下, 瘦素的表达情况并不一致, 与年龄、肥胖程度以及是否

存在其他病理状态等多因素相关^[92]。Fuentes等^[93]在肥胖型骨骼肌萎缩患者中发现, 骨骼肌中的瘦素受体(OB-R170)蛋白表达显著降低, 瘦素信号转导的关键蛋白STAT3、腺苷酸激活蛋白激酶 α 亚基(AMP-activated protein kinase α subunit, AMPK α)和乙酰辅酶A羧化酶 β 亚基(acetyl-CoA carboxylase β subunit, ACC β)的磷酸化水平显著降低。与之相反, Chen等^[94]通过基因组分析发现, 人萎缩骨骼肌内LEPR的表达显著上调。瘦素水平升高与骨骼肌萎缩相关转录因子FOXO3a的作用及萎缩特异性基因转录失活有关, 表现为MAFbx/Atrogin-1和MuRF-1表达水平降低, 而肌纤维类型调节因子PGC-1 α 蛋白表达水平升高^[95]。瘦素与受体结合激活Akt/mTOR, 增加核糖体蛋白S6激酶(70 kDa ribosomal protein S6 kinase, p70S6K)和真核起始因子4E结合蛋白1(eukaryotic initiation factor 4E binding protein 1, 4E-BP1)磷酸化, 促进蛋白质合成^[96]。在脊髓性肌肉萎缩症(spinal muscular atrophy, SMA)研究中, 瘦素水平与疾病严重程度的关系尚不明确。研究发现SMA患者的血清瘦素浓度与体质指数(body mass index, BMI)和四肢软组织指数(appendicular lean soft tissue index, ALSTI)(一种肌肉功能指标)无明显关联, 而高瘦素血症与SMA类型和运动功能降低相关, 这提示瘦素可能在SMA的发病中起一定作用, 但其具体机制仍需进一步研究^[97]。Hamrick等^[98]在骨骼肌萎缩的老年小鼠模型中发现, 瘦素可以显著改变骨骼肌微小RNA(microRNA, miRNA)表达谱, 尤其影响与肌肉修复和再生相关的miRNA。虽然瘦素治疗增加了老年小鼠的骨骼肌质量, 但仅能逆转老年小鼠中三种失调的miRNA。以上研究表明, 瘦素在骨骼肌萎缩治疗中具有潜在价值, 通过激活Akt/mTOR信号通路促进蛋白质合成, 激活AMPK α 和ACC β 促进脂肪酸氧化。尽管其在类风湿性关节炎等疾病中的作用及应用潜力已被揭示, 但在肥胖治疗中, 单瘦素给药治疗受限于瘦素抵抗问题, 且缺乏检测瘦素抵抗的可靠方法^[99]。目前, 关于瘦素在骨骼肌疾病中的临床试验较少, 但动物实验表明其可增加骨骼肌质量, 改变肌纤维大小, 并调节肌肉修复相关的miRNA表达。未来可以深入研究瘦素抵抗机制、开发多靶点药物或联合用药策略以进一步探索瘦素在骨骼肌疾病中的作用机制并开展更多临床试验。

4.5 脂联素在骨骼肌萎缩中的作用与机制

脂联素在骨骼肌萎缩中发挥强大的抗炎、抗氧化应激和抗凋亡的作用,并且与促炎细胞因子(如IL-6和TNF- α)呈负相关。然而,在肌腱断裂或神经损伤诱导的脂肪浸润到萎缩的骨骼肌时,脂肪细胞因子稳态可能被破坏,导致慢性疼痛,在这种情况下,萎缩骨骼肌中脂联素表达下调,TNF- α 诱导的分解代谢增强;同时,NADPH氧化酶2(NADPH oxidase 2, NOX2)介导的活性氧激活会引起氧化应激,从而通过叉头框转录因子O1(forkhead box O1, FOXO1)/MuRF-1/Atrogin-1信号通路诱导细胞死亡,加剧骨骼肌萎缩,最终导致人类活动能力和生活质量下降以及预期寿命缩短^[100]。另有研究发现,脂联素的循环水平与肌肉质量以及老年人的身体机能之间存在负相关,即所谓的“脂联素悖论”^[101]。在肥胖且患有代谢综合征的老年患者中,脂联素水平与骨骼肌质量指数(skeletal muscle mass index, SMMI)呈负相关^[102]。同样,在健康老年人中,较高的脂联素水平与较低的SMMI相关^[101]。这些结果表明,脂联素在不同病理状态下的作用机制较为复杂,其在老年人群中水平的升高可能与肌肉质量的减少有关。目前已经提出了许多预防骨骼肌萎缩的尝试(包括营养、激素和药理学方法),旨在逆转肌纤维损失或促进肌纤维肥大。伞形杆菌酮是一种广泛存在于食品中的天然化合物,可有效减轻糖尿病患者的骨骼肌萎缩并改善肌肉功能,显著上调关键的肌源性标志物,包括MyoD、肌生成素、肌球蛋白重链2(myosin heavy chain 2, Myh2)和肌球蛋白,从而促进成肌细胞分化为肌管^[103]。脂联素也能降低骨骼肌萎缩发生的风险。Singh等^[104]评估了球状脂联素(globular adiponectin, gAd)或小分子脂联素模拟物6-C- β -D-葡萄糖苷-(2S,3S)-(+)-5,7,3',4'-四羟基二氢黄酮醇(GTDF)在骨骼肌萎缩中的作用。深入研究发现,GTDF和gAd的保护作用是通过激活AMPK和AKT,进而刺激PGC-1 α ,并抑制叉头框O转录因子(forkhead box O transcription factor, FOXO)的活性,降低与Atrogin-1和MuRF-1蛋白水解途径相关基因的表达,从而改善地塞米松诱导的骨骼肌萎缩。此外,有研究发现SAMP10小鼠(一种加速衰老模型)的血浆脂联素浓度在运动后显著增加,这一过程通过增强脂联素及其受体依赖性信号转导通路AMPK/Akt-mTOR中的蛋白质合成与分解平衡来改善骨骼

肌功能,提示运动通过增强脂联素水平可以预防和治疗骨骼肌萎缩^[105]。以上研究表明,脂联素通过激活AMPK和AKT信号通路,抑制肌肉蛋白分解,在调节骨骼肌代谢和抗炎方面具有显著潜力,作为骨骼肌萎缩的治疗靶点表现出一定的可行性。但在不同病理状态下的作用机制较为复杂,且存在“脂联素悖论”等现象,这提示未来需要进一步研究以明确其作为临床治疗靶点的可行性和安全性。与此同时,脂联素受体激动剂(如AdipoRon)在杜氏肌营养不良症、心血管疾病及脓毒症等领域的临床试验仍处于早期阶段,目前主要聚焦于机制探索与小规模观察,未来还需开展更多大规模研究^[80]。尽管脂联素在动物模型中表现出良好的抗炎效果,但其在人体中的临床试验数据仍然有限,且脂联素水平在不同人群中存在显著差异,这增加了个体化治疗的复杂性。

5 总结与展望

骨骼肌萎缩是一种以骨骼肌质量减少和力量下降为主要特征的疾病,其病理机制复杂,且与多种因素相关。当前针对骨骼肌萎缩的治疗策略,包括体育锻炼、营养补充以及药物治疗等,存在诸多局限性,并不适用所有的骨骼肌萎缩患者,且成本较高,难以长期维持。脂肪细胞因子作为重要的炎症调节因子,通过调控炎症反应和介导胰岛素抵抗等多种机制参与骨骼肌萎缩的发病过程,使其成为防治骨骼肌萎缩的潜在靶点,具有广泛的应用前景。近年来,脂肪细胞因子在乳腺癌、类风湿性关节炎、心血管疾病和糖尿病等疾病的临床试验中取得了显著进展。然而,关于脂肪细胞因子在骨骼肌萎缩中的临床研究相对有限,且多停留在动物实验层面,尚未在人类临床试验中得到充分验证。脂肪细胞因子转化为骨骼肌萎缩临床干预靶点,仍面临诸多亟待解决的问题,如骨骼肌萎缩的病理机制尚未完全阐明、患者存在较大的个体差异等。因此,未来还需要进一步充分了解骨骼肌萎缩的发病机制,并针对老年人群、慢性病患者等特殊群体制定个性化治疗方案,以提高脂肪细胞因子作为治疗靶点的安全性和有效性。

参考文献

- [1] Csapo R, Gumpenberger M, Wessner B. Skeletal muscle extracellular matrix—what do we know about its composition, regulation, and physiological roles? A

- narrative review. *Front Physiol*, 2020, 11: 253
- [2] Jia J, Wang L, Zhou Y, et al. Muscle-derived extracellular vesicles mediate crosstalk between skeletal muscle and other organs. *Front Physiol*, 2024, 15: 1501957.
- [3] Van Hall G. Cytokines: Muscle protein and amino acid metabolism. *Curr Opin Clin Nutr Metab Care*, 2012, 15: 85–91.
- [4] Wiedmer P, Jung T, Castro JP, et al. Sarcopenia-molecular mechanisms and open questions. *Ageing Res Rev*, 2021, 65: 101200.
- [5] Hue I, Capilla E, Rosell-Moll E, et al. Recent advances in the crosstalk between adipose, muscle and bone tissues in fish. *Front Endocrinol (Lausanne)*, 2023, 14: 1155202.
- [6] Sierawska O, Sawczuk M. Interaction between selected adipokines and musculoskeletal and cardiovascular systems: A review of current knowledge. *Int J Mol Sci*, 2023, 24: 17287.
- [7] Pellegrinelli V, Rouault C, Rodriguez-Cuenca S, et al. Human adipocytes induce inflammation and atrophy in muscle cells during obesity. *Diabetes*, 2015, 64: 3121–34.
- [8] Sharma B, Dabur R. Role of pro-inflammatory cytokines in regulation of skeletal muscle metabolism: A systematic review. *Curr Med Chem*, 2020, 27: 2161–88.
- [9] Yin L, Li N, Jia W, et al. Skeletal muscle atrophy: From mechanisms to treatments. *Pharmacol Res*, 2021, 172: 105807.
- [10] Cohen H, Angulski ABB, Quick JD, et al. Synthetic bottlebrush block copolymer prevents disease onset in Duchenne muscular dystrophy. *Proc Natl Acad Sci U S A*, 2025, 122: e2513599122.
- [11] Urtizberea JA, Severa G, Malfatti E. Metabolic myopathies in the era of next-generation sequencing. *Genes (Basel)*, 2023, 14: 954.
- [12] Howard EE, Pasiakos SM, Fussell MA, et al. Skeletal muscle disuse atrophy and the rehabilitative role of protein in recovery from musculoskeletal injury. *Adv Nutr*, 2020, 11: 989–1001.
- [13] Schmid S, Heim-Kupr B, Pérez-Schindler J, et al. PGC-1 β modulates catabolism and fiber atrophy in the fasting-response of specific skeletal muscle beds. *Mol Metab*, 2022, 66: 101643.
- [14] Fève B, Cinti S, Beaupère C, et al. Pink adipose tissue: A paradigm of adipose tissue plasticity. *Ann Endocrinol (Paris)*, 2024, 85: 248–51.
- [15] Giordano A, Smorlesi A, Frontini A, et al. White, brown and pink adipocytes: The extraordinary plasticity of the adipose organ. *Eur J Endocrinol*, 2014, 170: R159–71.
- [16] Pilkington AC, Paz HA, Wankhade UD. Beige adipose tissue identification and marker specificity-overview. *Front Endocrinol (Lausanne)*, 2021, 12: 599134.
- [17] Pallio G, Mannino F. New insights into adipose tissue metabolic function and dysfunction, 2nd edition. *Int J Mol Sci*, 2024, 25: 9258.
- [18] Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am J Physiol Cell Physiol*, 2021, 320: C375–91.
- [19] Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, et al. The role of adipokines in health and disease. *Biomedicines*, 2023, 11: 1290.
- [20] Kirichenko TV, Markina YV, Bogatyreva AI, et al. The role of adipokines in inflammatory mechanisms of obesity. *Int J Mol Sci*, 2022, 23: 14982.
- [21] Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm*, 2010, 2010: 802078.
- [22] Sahu B, Bal NC. Adipokines from white adipose tissue in regulation of whole body energy homeostasis. *Biochimie*, 2023, 204: 92–107.
- [23] Alzaid F, Fagherazzi G, Riveline JP, et al. Immune cell-adipose tissue crosstalk in metabolic diseases with a focus on type 1 diabetes. *Diabetologia*, 2025, 68: 1616–31.
- [24] 陈宏锦, 潘晓茜, 高平进, 等. 棕色脂肪组织与心血管疾病的关系. *中华细胞与干细胞杂志(电子版)*, 2020, 10: 182–86.
- Chen HJ, Pan XQ, Gao PJ, et al. Relationship between brown adipose tissue and cardiovascular diseases. *Chinese J Cell Stem Cells(Electronic Edition)*, 2020, 10: 182–86.
- [25] 张雅晴, 王红蕊, 张宇, 等. 棕色和米色脂肪在肥胖中的研究进展. *生命科学*, 2021, 33: 355–62.
- Zhang YQ, Wang HR, Zhang Y, et al. Research progress of brown and beige adipose tissue in obesity. *Chin Bull Life Sci*, 2021, 33: 355–62.
- [26] Ghesmati Z, Rashid M, Fayezi S, et al. An update on the secretory functions of brown, white, and beige adipose tissue: Towards therapeutic applications. *Rev Endocr Metab Disord*, 2024, 25: 279–308.
- [27] Xu J. The role of tumor necrosis factor receptor superfamily in cancer: Insights into oncogenesis, progression, and therapeutic strategies. *NPJ Precis Oncol*, 2025, 9: 275.
- [28] Pocino K, Carnazzo V, Stefanile A, et al. Tumor

- necrosis factor- α : Ally and enemy in protean cutaneous sceneries. *Int J Mol Sci*, 2024, 25: 7762.
- [29] Osgood JA, Brown AC, Burnham KL, et al. Evidence for enhancer activity in intron 1 of TNFRSF1A using CRISPR/Cas9 in human induced pluripotent stem cell-derived macrophages. *Sci Rep*, 2025, 15: 34885.
- [30] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : Direct role in obesity-linked insulin resistance. *Science*, 1993, 259: 87–91.
- [31] Ji T, Huang G, Cao Y, et al. Advances in interleukin-6 family cytokines and the role in respiratory diseases. *J Inflamm Res*, 2025, 18: 3125–41.
- [32] Zhang Z, Wang P, Xiong Q, et al. Advancements in the study of IL-6 and its receptors in the pathogenesis of gout. *Cytokine*, 2024, 182: 156705.
- [33] Katkenov N, Mukhatayev Z, Kozhakhmetov S, et al. Systematic review on the role of IL-6 and IL-1 β in cardiovascular diseases. *J Cardiovasc Dev Dis*, 2024, 11: 206.
- [34] Zhu C, Ding X, Chen M, et al. Exercise-mediated skeletal muscle-derived IL-6 regulates bone metabolism: A new perspective on muscle–bone crosstalk. *Biomolecules*, 2025, 15: 893.
- [35] Kaur S, Bansal Y, Kumar R, et al. A panoramic review of IL-6: Structure, pathophysiological roles and inhibitors. *Bioorg Med Chem*, 2020, 28: 115327.
- [36] Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*, 2014, 6: a016295.
- [37] Lin W, Song H, Shen J, et al. Functional role of skeletal muscle-derived interleukin-6 and its effects on lipid metabolism. *Front Physiol*, 2023, 14: 1110926.
- [38] Stepan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. *Nature*, 2001, 409: 307–12.
- [39] Li Y, Yang Q, Cai D, et al. Resistin, a novel host defense peptide of innate immunity. *Front Immunol*, 2021, 12: 699807.
- [40] Shi Y, Zhu N, Qiu Y, et al. Resistin-like molecules: a marker, mediator and therapeutic target for multiple diseases. *Cell Commun Signal*, 2023, 21: 18.
- [41] Romejko K, Rymarz A, Szamotulska K, et al. Resistin contribution to cardiovascular risk in chronic kidney disease male patients. *Cells*, 2023, 12: 999.
- [42] Badoer E. Cardiovascular and metabolic crosstalk in the brain: Leptin and resistin. *Front Physiol*, 2021, 12: 639417.
- [43] Fan HQ, Gu N, Liu F, et al. Prolonged exposure to resistin inhibits glucose uptake in rat skeletal muscles. *Acta Pharmacol Sin*, 2007, 28: 410–6.
- [44] Liu Y, Wang D, Li T, et al. The role of NLRP3 inflammasome in inflammation-related skeletal muscle atrophy. *Front Immunol*, 2022, 13: 1035709.
- [45] Sharma V, Unjum Saqib BZ, Aran KR. Leptin as a potential neuroprotective target in Parkinson's disease: Exploring its role in neuroinflammation, oxidative stress, and dopaminergic neurodegeneration. *Neuroscience*, 2025, 572: 134–44.
- [46] Fan X, Yuan W, Huang W, et al. Recent progress in leptin signaling from a structural perspective and its implications for diseases. *Biochimie*, 2023, 212: 60–75.
- [47] Halaas JL, Gajiwala KS, Maffei M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science*, 1995, 269: 543–6.
- [48] Bodur C, Duensing A, Myers MG. Molecular mechanisms and neural mediators of leptin action. *Genes Dev*, 2025, 39: 792–807.
- [49] Miro C, Cicatiello AG, Nappi A, et al. Leptin enhances the intracellular thyroid hormone activation in skeletal muscle to boost energy balance. *Cell Metab*, 2025, 37: 936–53.e7.
- [50] Liu C, Li X. Role of leptin and adiponectin in immune response and inflammation. *Int Immunopharmacol*, 2025, 161: 115082.
- [51] Khoramipour K, Chamari K, Hekmatikar AA, et al. Adiponectin: structure, physiological functions, role in diseases, and effects of nutrition. *Nutrients*, 2021, 13: 1180.
- [52] 赵佳慧, 赵梓娟, 陈雨, 等. 脂联素与炎症关系的研究进展. *现代畜牧兽医*, 2023, (02): 69–73.
Zhao JH, Zhao ZJ, Chen Y, et al. Research progress on the relationship between adiponectin and inflammation. *Modern Journal of Animal Husbandry and Veterinary Medicine*, 2023, (02): 69–73.
- [53] Zhu Q, Jia X, Li S, et al. Role of adiponectin and its receptors adipoR1/2 in inflammatory bowel disease. *Cell Commun Signaling*, 2025, 23: 356.
- [54] Krause MP, Milne KJ, Hawke TJ. Adiponectin-consideration for its role in skeletal muscle health. *Int J Mol Sci*, 2019, 20: 1528.
- [55] Civitarese AE, Ukropcova B, Carling S, et al. Role of adiponectin in human skeletal muscle bioenergetics. *Cell Metab*, 2006, 4: 75–87.
- [56] Wang L, Valencak TG, Shan T. Fat infiltration in skeletal muscle: Influential triggers and regulatory mechanism. *iScience*, 2024, 27: 109221.

- [57] Trayhurn P, Drevon CA, Eckel J. Secreted proteins from adipose tissue and skeletal muscle-adipokines, myokines and adipose/muscle cross-talk. *Arch Physiol Biochem*, 2011, 117: 47–56.
- [58] Jang SY, Choi KM. Impact of adipose tissue and lipids on skeletal muscle in sarcopenia. *J Cachexia Sarcopenia Muscle*, 2025, 16: e70000.
- [59] 柯义兵, 阿布都克热木·达吾提, 郭浩然, 等. 骨骼肌萎缩相关分子机制及信号通路研究进展. *生理学报*, 2024, 76: 1056–68.
- Ke YB, Abdulkrem Dawut, Guo HR, et al. Research progress on the molecular mechanisms and signaling pathways related to skeletal muscle atrophy. *Acta Physiol Sin*, 2024, 76: 1056–68.
- [60] Stratos I, Behrendt AK, Anselm C, et al. Inhibition of TNF- α restores muscle force, inhibits inflammation, and reduces apoptosis of traumatized skeletal muscles. *Cells*, 2022, 11: 2397.
- [61] Webster JM, Kempen L, Hardy RS, et al. Inflammation and skeletal muscle wasting during cachexia. *Front Physiol*, 2020, 11: 597675.
- [62] Li J, Yi X, Yao Z, et al. TNF receptor - associated factor 6 mediates TNF- α induced skeletal muscle atrophy in mice during aging. *J Bone Mineral Res*, 2020, 35: 1535–48.
- [63] Polge C, Cabantous S, Deval C, et al. A muscle-specific MuRF1-E2 network requires stabilization of MuRF1-E2 complexes by telethonin, a newly identified substrate. *J Cachexia Sarcopenia Muscle*, 2018, 9: 129–45.
- [64] Childs TE, Spangenburg EE, Vyas DR, et al. Temporal alterations in protein signaling cascades during recovery from muscle atrophy. *Am J Physiol Cell Physiol*, 2003, 285: C391–98.
- [65] Li YP, Chen Y, John J, et al. TNF- α acts via p38 MAPK to stimulate expression of the ubiquitin ligase atrogin1/MAFbx in skeletal muscle. *FASEB J*, 2005, 19: 362–70.
- [66] Wu W, Wang J, Xiao C, et al. SMYD2-mediated TRAF2 methylation promotes the NF- κ B signaling pathways in inflammatory diseases. *Clin Transl Med*, 2021, 11: e591.
- [67] Zhang L, Blackwell K, Altaeva A, et al. TRAF2 phosphorylation promotes NF- κ B-dependent gene expression and inhibits oxidative stress-induced cell death. *Mol Biol Cell*, 2011, 22: 128–40.
- [68] Singh A, Phogat J, Yadav A, et al. The dependency of autophagy and ubiquitin proteasome system during skeletal muscle atrophy. *Biophys Rev*, 2021, 13: 203–9.
- [69] Yaspelkis BB, Kvasha IA, Figueroa TY. High-fat feeding increases insulin receptor and IRS-1 coimmunoprecipitation with SOCS-3, IKK α /beta phosphorylation and decreases PI-3 kinase activity in muscle. *Am J Physiol Regul Integr Comp Physiol*, 2009, 296: R1709–15.
- [70] He M, Yang J, Yan S, et al. Conducting a real-world study of tumor necrosis factor- α inhibitors-induced systemic lupus erythematosus based on the FAERS database. *Sci Rep*, 2025, 15: 6838.
- [71] Bazile C, Abdel Malik MM, Ackeifi C, et al. TNF- α inhibitors for type 1 diabetes: Exploring the path to a pivotal clinical trial. *Front Immunol*, 2024, 15: 1470677.
- [72] Yang B, Yang X, Sun X, et al. IL-6 deficiency attenuates skeletal muscle atrophy by inhibiting mitochondrial ROS production through the upregulation of PGC-1 α in septic mice. *Oxid Med Cell Longev*, 2022, 2022: 9148246.
- [73] Huang Z, Zhong L, Zhu J, et al. Inhibition of IL-6/JAK/STAT3 pathway rescues denervation-induced skeletal muscle atrophy. *Ann Transl Med*, 2020, 8: 1681.
- [74] Zimmers TA, Fishel ML, Bonetto A. STAT3 in the systemic inflammation of cancer cachexia. *Semin Cell Dev Biol*, 2016, 54: 28–41.
- [75] Radigan KA, Nicholson TT, Welch LC, et al. Influenza a virus infection induces muscle wasting via IL-6 regulation of the E3 ubiquitin ligase Atrogin-1. *J Immunol*, 2019, 202: 484–93.
- [76] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol*, 2018, 15: 234–48.
- [77] Zhao Y, Yan H, Liu K, et al. Acetylcholine receptor- β inhibition by interleukin-6 in skeletal muscles contributes to modulating neuromuscular junction during aging. *Mol Med*, 2024, 30: 171.
- [78] Nystrom G, Pruznak A, Huber D, et al. Local insulin-like growth factor prevents sepsis-induced muscle atrophy. *Metabolism*, 2009, 58: 787–97.
- [79] Washington TA, White JP, Davis JM, et al. Skeletal muscle mass recovery from atrophy in IL-6 knockout mice. *Acta Physiol (Oxf)*, 2011, 202: 657–69.
- [80] Gianoli S, Tang J, Odegard KC, et al. Harnessing adiponectin for sepsis: Current knowledge, clinical insights and future therapies. *Crit Care*, 2025, 29: 300.
- [81] Onishi A, Tanaka M, Fujii T, et al. Comparative effectiveness of subcutaneous sarilumab 200 mg biweekly, subcutaneous tocilizumab 162 mg biweekly, and intravenous tocilizumab 8 mg/kg every 4 weeks in patients with rheumatoid arthritis: A prospective cohort

- study. *Arthritis Res Ther*, 2025, 27: 52.
- [82] Taylor PC, Feist E, Pope JE, et al. What have we learnt from the inhibition of IL-6 in RA and what are the clinical opportunities for patient outcomes? *Ther Adv Musculoskelet Dis*, 2024, 16: 1759720x241283340
- [83] Wilhelmsen A, Tsintzas K, Jones SW. Recent advances and future avenues in understanding the role of adipose tissue cross talk in mediating skeletal muscle mass and function with ageing. *GeroScience*, 2021, 43: 85–110.
- [84] Kwak MK, Baek JY, Park SJ, et al. Higher circulating resistin levels linked to increased sarcopenia risk in older adults. *J Clin Endocrinol Metab*, 2025, 110: e2994–3001.
- [85] Gao J, Deng M, Li Y, et al. Resistin as a systemic inflammation-related biomarker for sarcopenia in patients with chronic obstructive pulmonary disease. *Front Nutr*, 2022, 9: 921399.
- [86] Kim HJ, Kim H, Lee JH, et al. Toll-like receptor 4 (TLR4): New insight immune and aging. *Immun Ageing*, 2023, 20: 67.
- [87] Benomar Y, Gertler A, De Lacy P, et al. Central resistin overexposure induces insulin resistance through Toll-like receptor 4. *Diabetes*, 2013, 62: 102–14.
- [88] Zhao Y, Wu J, Liu X, et al. Decoding nature: Multi-target anti-inflammatory mechanisms of natural products in the TLR4/NF- κ B pathway. *Front Pharmacol*, 2024, 15: 1467193.
- [89] Wen F, Zhang H, Bao C, et al. Resistin increases ectopic deposition of lipids through miR-696 in C2C12 cells. *Biochem Genet*, 2015, 53: 63–71.
- [90] Kranenburg E, Kubant R, Cho CE, et al. Folic acid reduces insulin resistance in mice with diet-induced obesity by altering one-carbon metabolism and DNA methylation patterns of hypothalamic and hepatic insulin receptor gene. *Mol Nutr Food Res*, 2025, 68: e70181.
- [91] Pereira S, Cline DL, Glavas MM, et al. Tissue-specific effects of leptin on glucose and lipid metabolism. *Endocr Rev*, 2021, 42: 1–28.
- [92] Lee DG, Lee JH. Association of leptin in sarcopenia and bone density in elderly women: An observational analysis. *Diagnostics (Basel)*, 2025, 15: 1620.
- [93] Fuentes T, Ara I, Guadalupe-Grau A, et al. Leptin receptor 170 kDa (OB-R170) protein expression is reduced in obese human skeletal muscle: A potential mechanism of leptin resistance. *Exp Physiol*, 2010, 95: 160–71.
- [94] Chen YW, Gregory CM, Scarborough MT, et al. Transcriptional pathways associated with skeletal muscle disuse atrophy in humans. *Physiol Genomics*, 2007, 31: 510–20.
- [95] Tero-Vescan A, Degens H, Matsakas A, et al. Exercise-induced muscle–fat crosstalk: Molecular mediators and their pharmacological modulation for the maintenance of metabolic flexibility in aging. *Pharmaceuticals*, 2025, 18: 1222.
- [96] Miron M, Lasko P, Sonenberg N. Signaling from Akt to FRAP/TOR targets both 4E-BP and S6K in *Drosophila melanogaster*. *Mol Cell Biol*, 2003, 23: 9117–26.
- [97] Miletic M, Stevic Z, Peric S, et al. Adiponectin and leptin-considerations in adult patients with spinal muscular atrophy type 3. *Diagnostics (Basel)*, 2025, 15: 529.
- [98] Hamrick MW, Herberg S, Arounleut P, et al. The adipokine leptin increases skeletal muscle mass and significantly alters skeletal muscle miRNA expression profile in aged mice. *Biochem Biophys Res Commun*, 2010, 400: 379–83.
- [99] Obradovic M, Sudar-Milovanovic E, Soskic S, et al. Leptin and obesity: Role and clinical implication. *Front Endocrinol (Lausanne)*, 2021, 12: 585887.
- [100] Shinohara I, Kataoka T, Mifune Y, et al. Influence of adiponectin and inflammatory cytokines in fatty degenerative atrophic muscle. *Sci Rep*, 2022, 12: 1557.
- [101] Walowski CO, Herpich C, Enderle J, et al. Analysis of the adiponectin paradox in healthy older people. *J Cachexia Sarcopenia Muscle*, 2023, 14: 270–8.
- [102] De Luis D, Primo D, Izaola O, et al. Relationship between adiponectin and muscle mass in patients with metabolic syndrome and obesity. *J Diabetes Complications*, 2024, 38: 108706.
- [103] Kim DY, Kang YH, Kang MK. Umbelliferone attenuates diabetic sarcopenia by modulating mitochondrial quality and the ubiquitin-proteasome system. *Phytomedicine*, 2025, 144: 156930.
- [104] Singh AK, Shree S, Chattopadhyay S, et al. Small molecule adiponectin receptor agonist GTDF protects against skeletal muscle atrophy. *Mol Cell Endocrinol*, 2017, 439: 273–85.
- [105] Tanaka Y, Kita S, Nishizawa H, et al. Adiponectin promotes muscle regeneration through binding to T-cadherin. *Sci Rep*, 2019, 9: 16.