

自噬在衰老相关肌少症的研究进展

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[摘要] 随着全球人口老龄化加剧,与年龄相关的肌肉减少症发病率越来越高。肌肉减少症表现肌肉力量质量降低以及身体机能降低,与跌倒和残疾风险增加密切相关,给个人、社会和经济带来沉重负担。在众多肌少症病理生理机制中,自噬占有一席之地。自噬是一种重要的细胞自我保护机制,通过溶酶体降解错误折叠的蛋白质和受损的细胞器,维持细胞稳定。自噬可以通过调节卫星细胞的再生能力、缓解氧化应激、抑制炎症反应和抗凋亡来缓解肌少症。本文综述了肌肉减少症与自噬之间的特定相互作用,并探索其可能的治疗方法,希望能寻找到更多有用的具体研究,为改善肌少症带来更多有前途的治疗方法。

[关键词] 骨骼肌; 衰老; 肌少症; 自噬; 治疗

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Progress in autophagy in aging-related sarcopenia

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[Abstract] With the aging of the global population, the incidence rate of age-related sarcopenia is increasing. Sarcopenia is characterized by a decrease in muscle strength and physical function, which is closely related to an increased risk of falls and disabilities, and imposes a heavy burden on individuals, society, and the economy. Autophagy plays a significant role in the pathological and physiological mechanisms of sarcopenia. Autophagy is an important cellular self-protection mechanism that maintains cell stability by degrading misfolded proteins and damaged organelles through lysosomes. Autophagy can alleviate sarcopenia by regulating the regenerative capacity of satellite cells, alleviating oxidative stress, inhibiting inflammatory responses, and resisting apoptosis. This article reviews the specific interactions between sarcopenia and autophagy, and explores possible treatment methods, hoping to find more useful and specific research to bring more promising treatment methods for improving sarcopenia.

[Key words] skeletal muscle; aging; sarcopenia; autophagy; treatment

引言

1989年, Rosenberg首次提出了与年龄相关的肌肉质量减少的现象,并创造了“少肌症”这一术语^[1]。2018年EWGSOP将其定义为一种进行性和全身性骨骼肌肌量减少的疾病,会增加福尔斯、骨折、身体残疾和死亡等不良结局^[2]。肌少症的流行病学与年龄、性别、种族、地理和生长发育相关^[3]。随着人类预期寿命的增加,肌少症的发病越来越高,据统计,2000年全世界年龄≥60岁的人口估计为6亿,预计到2025年将增至12亿,到2050年将增至20亿^[4]。60-70岁人群的患病率为5-13%,80岁以上人群的患病率为11-50%^[5]。肌少症的发生会给个人、社会和经济带来沉重负担。自噬主要是通过去除错误折叠或聚集的蛋白质、清除受损的细胞器等方面发挥管理作用,防止受损物质过度堆积造成细胞死亡^[6]。基础水平的自噬对维持骨骼肌完整性起到不可或缺的作用。随着年龄的增加,自噬及线粒体自噬功能失调,

会导致骨骼肌萎缩,肌肉力量质量降低和身体功能障碍。因此,针对自噬和线粒体自噬可能会成为治疗肌少症的潜在靶点。

1 自噬的概述

1.1 自噬及调控途径。自噬是细胞内的主要分解代谢系统,细胞内基质、长寿蛋白、蛋白质聚集体和受损死亡的细胞器被转运至溶酶体并最终被降解的过程^[7]。自噬可根据底物转运到溶酶体的方式,分为巨自噬、微自噬和分子伴侣介导自噬三种类型(本文的自噬均为巨自噬)^[8]。自噬由一系列高度复杂调控的步骤组成,包括起始、衍生、融合、成熟、降解、再循环等过程^[9]。自噬体的起始和扩张依赖于ULK1和PI3-K复合物的激活以及磷脂酰肌醇3-磷酸(PI3P)的合成^[10]。自噬小体的延伸和成熟需要ATG5-ATG12-ATG16L泛素系统和LC3处理过程的泛素样系统^[9]。招募和整合LC3-II和ATG5-ATG12分布于自噬体内部和外部表面,随后迅速与溶酶体融合时降解。其中选择性自噬是通

过多功能衔接分子P62/SQSTM1, 选择性促进多聚化泛素蛋白聚集体的周转^[11]。

自噬的调控有多种途径, 其上游信号通路主要涉及mTOR依赖性通路和mTOR非依赖性通路^[9]。mTORC1的下游是ULK1复合体, 可以启动自噬。饥饿期间, mTOR受到抑制, 促进ULK1和ATG13去磷酸化, 激活复合物以促进自噬。mTOR是自噬调控的中枢, 上游的许多分子都可以通过调控它来调节自噬。PI3K和AKT的磷酸化、胰岛素(IGF-1)和胰岛素受体(IGF-1R)介导可以激活mTOR来抑制自噬^[12,13]。除此之外, 在能量应激下, 代谢调节因子AMPK可以间接磷酸化TSC2来抑制mTOR信号来促进自噬^[14]。AMPK在自噬调控中起着重要作用, 它还可以直接磷酸化ULK1激活自噬^[15]。AMPK可以通过多种上游调节因子介导, 如Ca²⁺/CaMKK β (钙调素依赖性蛋白激酶 β)、p53的下调均可以通过AMPK/mTOR信号通路促进自噬^[16,17]。FOXO3a也是调控自噬的关键因子之一, FOXO3a可以增强LC3、Beclin-1和p62的表达促进自噬^[18]。SIRT3是一种富含线粒体的NAD⁺依赖性HDAC, 它可以激活AMPK/mTOR途径促进自噬^[19]。由此可知, 自噬调控的机制复杂多样, 在维护细胞功能稳定起到至关重要的作用。

1.2 自噬在肌肉健康中的作用。骨骼肌占身体总质量的40%以上, 具有很强的适应性, 自噬对于维持骨骼肌完整性起到不可或缺的作用。因为该途径存在缺陷的小鼠会表现出肌肉退化和线粒体功能障碍, 这些表型会随着衰老而加剧^[20,21]。在小鼠肌肉中的ATG7特异性缺失被证明会导致严重的肌肉萎缩、神经肌肉连接恶化和寿命缩短。重要的是, 质粒介导的ATG7在老年骨骼肌中过表达14天, 恢复了自噬, 改善了神经肌肉连接的完整性, 增加了肌纤维的大小^[22]。在人类中, ATG7突变可引起神经、肌肉和内分泌功能低下等神经发育障碍^[23]。因此, 骨骼肌自噬是维持肌肉功能和全身能量代谢所需的重要过程^[24]。

2 自噬与肌少症的分析

2.1 肌少症中的自噬通量

在一项关于年龄对雄性Fisher344大鼠足底肌自噬影响的研究中, 发现上游自噬调节蛋白Beclin-1随着年龄的增长而上调, ATG7和ATG9保持不变, 而下游自噬调节蛋白LC3基因和蛋白表达下降, 表明年龄相关的自噬降解下降^[25]。还有部分研究也与这一结果一致, 多种机制可能导致啮齿动物和人类自噬溶酶体系统与年龄相关的进行性衰退, 包括自噬基因表达降低^[26,27]。此外, 抑制自噬会加剧神经肌肉接头与年龄相关的退化, 并加剧由去神经支配而导致的肌肉质量损失^[22]。有趣的是, 一项研究发现小鼠肌肉中的Atg7敲除会诱导泛素-蛋白酶体系统成分萎缩相关泛素酶atrogen-1和MuRF-1上调, 导致肌纤维尺寸减少40%^[20]。在衰老的马骨骼肌中, 也发现自噬标志物的表达下降^[28]。而最近的研究使用年轻和老年人类志愿者的活检样本清楚地显示了年龄依赖性的自噬缺陷, 如Atg7蛋白的数量减少和LC3-II/LC3-I蛋白的比例下降^[22]。另一项在人类测量了自噬蛋白Atg7和Beclin1的升高, 而LC3-II/I没有变化, 这一结果也表明自噬体分解随着年龄的增长而受到干扰^[29]。总之, 这些研究

表明年龄相关的小鼠、马和人类的肌纤维功能和肌肉力量下降, 与自噬受损有明显关系, 这明确了增强选择性自噬对于预防肌肉减少症的重要性。

2.2 自噬调节肌卫星细胞的静止和再生。肌卫星细胞位于肌纤维的质膜和肌底层之间, 当肌肉受损或细胞外其它信号介导时, 肌肉干细胞会大量增殖并分化成多种肌纤维^[30]。自噬调节肌肉再生机制包括维持干细胞的静止状态、激活和分化。当肌肉处于稳定状态时, 基础自噬可以通过更新细胞器和蛋白质来维持肌肉干细胞的静止状态和干性。当肌肉损伤后, 自噬增加能够为肌肉干细胞激活和增殖过程提供生物能量。分化过程中通过线粒体自噬促进线粒体形成, 促进成肌细胞的代谢转化, 平衡线粒体介导的凋亡^[31]。先前有研究表明, 干细胞的稳定状态可能由AMPK/p27Kip1通路调节肌肉干细胞中自噬和凋亡之间的平衡所维护的^[32]。衰老的肌肉中, 干细胞自噬能力下降, 导致ROS水平的升高, 静止的MuSCs改变状态成为不可逆的预衰老状态。让Atg7基因过表达或自噬激活剂来重新激活自噬, 都可以起到逆转衰老MuSCs的再生能力^[33,34]。有研究表明, 肌肉组织受损后, SIRT1能够介导ATG7去乙酰化和AMPK磷酸化, 从而激活自噬和干细胞增殖, 当SIRT1缺陷会导致MSC激活延迟, 说明SIRT1调节的自噬可能在MSC激活过程中发挥重要作用^[35]。在肌分化过程中, 研究发现成肌细胞分化过程中LC3-II和Atg7水平增加, SQSTM1降低, Atg7敲低降低自噬, 同时在分化成肌细胞中增加Caspase3活性, 最终导致肌生成显著受损, 证明了自噬在成肌细胞分化过程中缓解线粒体氧化应激和凋亡信号的不良作用^[36]。以上研究表明自噬不仅能够维持肌肉卫星细胞的静止状态, 还能激活卫星细胞增殖, 并且在成肌细胞分化过程中也起着至关重要的作用。

2.3 自噬抑制炎症反应。之前的研究证明年龄相关的肌少症长期处于低水平炎症状态^[37]。一项关于肌肉减少症老年人的研究中发现血清IL-6、IL-18、TNF- α 显著高于非肌肉减少组, 提示高水平TNF- α 与肌肉减少症的风险增加有关^[38]。自噬对炎症反应的诱导和调节具有重要影响。自噬失调导致ROS产生, 通过核转位和信号激活促进炎症产生, 特别是通过NF- κ B核转位^[39]。自噬可以通过清除受损线粒体、降低ROS浓度来减少炎症, 可能通过抑制炎性小体激活来抑制IL-1 β 的分泌^[38]。自噬功能障碍可能导致过度炎症和NLRP3炎症小体过度激活, 自噬能去除NLRP3炎症小体激活物, 抑制炎症反应^[40]。当敲除小鼠中的关键自噬基因Atg7时会诱发炎症、减少肌纤维的大小和数量、损害肌肉功能, 并缩短存活时间^[41]。最近的研究也表明, 自噬参与了骨骼肌肌微环境单核细胞分化和巨噬细胞极化, 巨噬细胞的分化和吞噬功能需要依赖Ulk1和Atg7激活的自噬, 自噬还能影响巨噬细胞的极化^[42]。巨噬细胞ATG7敲除的小鼠中促炎M1巨噬细胞的比例发生了变化, 可能影响骨骼肌再生过程中的免疫微环境^[43]。年龄相关的低度炎症可能与自噬缺陷有关, 通过调控自噬可能会出现良好的治疗效果。

2.4 自噬缓解氧化应激和抗凋亡。自噬负责清除过量的ROS生成缓解氧化应激^[44]。大量研究证明, 氧化应激可能与肌肉减

少症的病理有关^[45,46]。功能失调的自噬伴随抗氧化反应的功能减少,导致氧化应激,使肌肉的收缩性和可塑性能力减弱^[47]。黄芩素预处理能够增加线粒体自噬受体FUN14结构域的表达来促进自噬,并清除ROS,从而减弱心脏肥大^[48]。另一项在D-半乳糖诱导的C2C12成肌细胞衰老模型中,通过改善自噬功能,清除ROS,改善了骨骼肌萎缩。辣椒素介导自噬并恢复溶酶体功能,以缓解氧化应激和肌肉萎缩^[49]。最近的研究发现,成肌细胞分化过程中的自噬缺陷会增加细胞凋亡信号传导,下调Atg7增加了Caspase3的瞬时激活、DNA片段和成肌细胞的凋亡率。同样,3-MA处理也增加了成肌细胞的凋亡^[50]。上述结果表明,自噬在成肌细胞分化过程中调节凋亡信号,保护分化的成肌细胞。因此,自噬通过对氧化应激,凋亡及相关损伤的调节来延缓肌肉减少的发生,未来有必要对自噬和氧化应激及凋亡对肌肉减少症的影响及其具体机制进行更多的研究。

3 基于自噬靶点对肌少症的治疗作用

3.1运动。人类和啮齿类动物中,运动已被证明可以促进自噬活动,并导致许多组织中基础自噬水平的上调。大量研究表明运动可以改善骨骼肌状态,还可以刺激骨骼肌中的蛋白质合成代谢,因此运动是治疗肌少症的重要方法之一。有研究表明15个月中年时期长期自愿抗拒运动的小鼠与同龄久坐的对照组相比,运动小鼠比目鱼肌肥大,是由于该运动可以增强自噬途径,抑制小鼠后肢的肌肉减少^[51]。在另外的报道中发现,老年耐力运动训练可以增加老年大鼠骨骼肌中的LC3II/LC3I比值,激活自噬^[22]。12周的运动干预抑制了骨骼肌质量损失的下降,并伴有Atrogin-1和MuRF1的下调,Beclin1水平升高,LC3-II/LC3-I比值改善,p62水平下降,Bax水平降低,Bcl-2水平升高,以及PGC-1 α , Mfn2, Drp1, 和PINK1水平升高。进一步验证了,运动上调磷酸化的AMPK水平,从而调节自噬的功能状态和线粒体质量控制^[52]。耐力运动也被证实对肌少症有治疗作用,有氧运动时可以通过p38MAPK介导来激活线粒体自噬可以消除氧化应激,保证足够数量的健康线粒体来维持高效的能量转换^[53]。另一项报告证明耐力运动可以促进老年人骨骼肌BNIP3、parkin表达,促进线粒体自噬来消除氧化损伤和功能失调的线粒体^[54]。此外,还有研究表明耐力运动可以激活卫星细胞增殖分化,可以防止衰老相关的肌肉再生功能下降^[55]。以上证据表明适度运动可以延缓骨骼肌衰老,部分研究证明运动可以通过调节自噬来保护骨骼肌,但自噬和线粒体自噬对肌少症的具体作用机制还尚未完全阐明,需要进一步研究。

3.2热量限制。热量限制是一种饮食干预方法,通过将热量摄入降低20-50%,而不导致营养不良,一种经典的抗衰老干预措施。研究表明,热量限制可以通过多种途径保护肌肉^[56]。早前的一项报道称热量限制能够减弱衰老相关的代谢损伤,保持肌肉质量和力量^[57]。进一步的研究发现,热量限制可以诱导自噬并随后上调AMPK、SIRT1,下调mTOR来减少氧化损伤延缓衰老^[58]。另一项报道,CR可以通过增加啮齿动物骨骼肌中ATG蛋白以及LC3和LAMP2基因的表达来减轻与衰老相关的自噬损伤^[29]。CR

能够上调ULK1自噬蛋白,抑制mTOR蛋白上调自噬,小鼠表现出活动能力更强,延缓肌肉减少症发病^[59]。然而,也有研究报道在其他线粒体疾病甚至与自噬基因功能失调相关的临床病症的情况下,CR可能会缩短寿命^[60]。

3.3其它。鸢尾素是一种运动诱导的肌因子,是FNDC5蛋白的裂解产物^[61],在骨骼肌中以生物活性肽的形式表达,运动和寒冷可诱导其分泌。骨骼肌分泌的鸢尾素约占所有组织中鸢尾素总量的72%^[62]。它可以随着年龄的增长呈现下降趋势,与多种衰老相关疾病密切相关^[63]。根据目前的研究,鸢尾素参与骨骼肌的发育和健康。在C2C12细胞中,鸢尾素可以有效增加骨骼肌细胞与肌管融合,提高骨骼肌质量,并激活骨骼肌中的卫星细胞,促进蛋白质合成和肌肉肥大^[64]。在C2C12细胞中沉默FNDC5还会导致MyHCIIa mRNA显著减少,而FNDC5的过表达可以增加PGC-1 α 和MyHCIIa的mRNA水平表达^[65]。这些均能说明骨骼肌分泌的鸢尾素可促进骨骼肌的生长发育、改善功能、抑制肌肉萎缩。但鸢尾素通过调控自噬起到的治疗作用只在其它疾病中得到证实。如在一项心肌缺血的研究中,鸢尾素治疗能够介导OPA1诱导的线粒体自噬,并保护心肌细胞免受心肌梗死后的进一步损伤^[66]。由此可知,鸢尾素具有保护骨骼肌的作用,但其具体机制及能否通过调节自噬和线粒体自噬起作用还需要更多的研究来探索。

尿磷脂A(UA)是一类天然化合物,UA能够阻止功能失调的线粒体的积累,在体内和体外诱导线粒体自噬,延缓秀丽隐杆线虫衰老,并在年龄相关的肌肉功能衰退的小鼠模型中,改善了改善线粒体和运动能力^[67]。在人类临床试验中,用UA治疗4周,UA具有良好的安全性,并能刺激线粒体自噬改善临床前衰老模型的肌肉健康^[68]。亚精胺是一种膳食化合物,也是一种自噬诱导剂。口服补充亚精胺增强了心脏自噬,线粒体自噬和线粒体呼吸,改善心肌细胞弹性和抑制炎症反应^[69]。亚精胺能够调控自噬延长寿命和保护心肌,但很少有研究调查亚精胺对肌肉减少症的积极影响。

人参皂苷化合物K(CK)对身体具有保护作用,包括抗癌、抗炎、抗糖尿病、抗血管生成、抗衰老、缓解肌少症等^[70]。最近的一项研究发现,在体外和体内,CK可以增加AMPK磷酸化、自噬水平,在体外,当用自噬抑制剂3-MA预处理棕榈酸酯诱导的C2C12肌管时,CK对内质网应激缓解、细胞凋亡减少和肌管形成促进作用减弱,表明AMPK介导的自噬信号通路可能参与CK对ER应激、细胞凋亡和抗肌肉萎缩的影响^[71]。另一项研究发现,人脐带间充质间质细胞及其外泌体能够通过增强AMPK/ULK1介导自噬来减轻糖尿病和肥胖诱导的肌肉萎缩。此研究证实了干细胞对肌少症治疗的又一机制,未来还需要更多的研究来证实。

4 结论

随着全球人口的老齡化,年龄相关性肌少症发病率和死亡率增加,降低生活质量,加剧社会压力,给个人和社会带来沉重负担。自噬是一种重要的细胞自我保护机制,可降解错误折叠的蛋白质和受损的细胞器以维持细胞稳态。基于自噬在自我修复和自我更新中的作用,自噬与人类疾病的关系尤其是老年性相关疾病引起了人们的广泛关注。研究表明,自噬能够通过抑制炎

症、缓解氧化应激、调节卫星细胞的再生能力、维持线粒体功能等作用,起到治疗肌少症的作用。尽管自噬也存在相互矛盾的数据,但越来越多的证据表明,它们在老年骨骼肌中受损。所以,增强骨骼肌中的自噬似乎是预防甚至治疗老年人骨骼肌功能障碍的一个有希望的治疗靶点。尽管有一些建设性的发现,但更多旨在寻找针对自噬功能的新的治疗方法的研究面临着更多的挑战。

[参考文献]

[1]ROSENBERG I H.Sarcopenia:origins and clinical relevance[J/OL].Clinics in Geriatric Medicine,2011,27(3):337-339.

[2]CRUZ-JENTOFT A J,BAHAT G, BAUER J, et al. Sarcopenia: revised European consensus on definition and diagnosis[J/OL]. Age and Ageing,2019,48(4):601.

[3]DENNISON E M, SAYER A A, COOPER C. Epidemiology of sarcopenia and insight into possible therapeutic targets[J/OL]. Nature Reviews. Rheumatology,2017,13(6):340-347.

[4]BEARD J R, OFFICER A, DE CARVALHO I A, et al. The World report on ageing and health: a policy framework for healthy ageing[J/OL].Lancet (London, England),2016,387(10033):2145-2154.

[5]Sarcopenia: diagnosis and treatment - PubMed[EB/OL]. [2025-01-16].<https://pubmed.ncbi.nlm.nih.gov/18615226/>.

[6]GLICK D, BARTH S, MACLEOD K F. Autophagy: cellular and molecular mechanisms[J/OL]. The Journal of Pathology, 2010, 221(1):3-12.

[7]MIZUSHIMA N,YOSHIMORI T,LEVINE B.Methods in mammalian autophagy research[J/OL].Cell,2010,140(3):313-326.

[8]H Y,T M.Molecular Mechanisms of Macroautophagy, Microautophagy, and Chaperone-Mediated Autophagy[J/OL]. Journal of Nippon Medical School = Nippon Ika Daigaku zasshi, 2024, 91(1)[2024-11-30].<https://pubmed.ncbi.nlm.nih.gov/37271546/>.

[9]PARZYCH K R, KLIONSKY D J. An overview of autophagy: morphology, mechanism, and regulation[J/OL]. Antioxidants & Redox Signaling,2014,20(3):460-473.

[10]NAKATOGAWA H. Mechanisms governing autophagosome biogenesis[J/OL]. Nature Reviews. Molecular Cell Biology, 2020, 21(8):439-458.

[11]LAMARK T,SVENNING S,JOHANSEN T.Regulation of selective autophagy: the p62/SQSTM1 paradigm[J/OL]. Essays in Biochemistry,2017,61(6):609-624.

[12]Insulin and IGF-1 elicit robust transcriptional regulation to modulate autophagy in astrocytes - PubMed[EB/OL]. [2025-01-16].<https://pubmed.ncbi.nlm.nih.gov/36503893/>.

[13]Gomisin N attenuated cerebral ischemia-reperfusion injury through inhibition of autophagy by activating the PI3K/AKT/mTOR pathway-PubMed[EB/OL].[2025-01-16].<https://pubmed.ncbi.nlm.nih.gov/36634381/>.

pubmed.ncbi.nlm.nih.gov/36634381/.

[14]MX L,J Y,Y Q,et al.ESMOLOL PROTECTS AGAINST LPS-INDUCED CARDIAC INJURY VIA THE AMPK/mTOR/ULK1 PATHWAY IN RAT[J/OL].Shock(Augusta,Ga.),2023,59(3)[2025-01-16].<https://pubmed.ncbi.nlm.nih.gov/36579896/>.

[15]XIAO H, HAN B, GUO J, et al. [HTD4010 attenuates myocardial injury in mice with septic cardiomyopathy by promoting autophagy via the AMPK/mTOR signaling pathway] [J/OL]. Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University,2024,44(3):507-514.

[16]SUN B,OU H, REN F, et al. Propofol inhibited autophagy through Ca²⁺/CaMKK β /AMPK/mTOR pathway in OGD/R-induced neuron injury[J/OL]. Molecular Medicine (Cambridge, Mass.), 2018,24(1):58.

[17]PENG M,YE F, FAN C, et al. Endogenous S100P-mediated autophagy regulates the chemosensitivity of leukemia cells through the p53/AMPK/mTOR pathway[J/OL]. American Journal of Cancer Research,2024,14(3):1121-1138.

[18]ALI T, RAHMAN S U, HAO Q, et al. Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation[J/OL]. Journal of Pineal Research,2020,69(2):e12667.

[19]ZHENG Y, SHI B, MA M, et al. The novel relationship between Sirt3 and autophagy in myocardial ischemia-reperfusion[J/OL].Journal of Cellular Physiology,2019,234(5):5488-5495.

[20]MASIERO E, AGATEA L, MAMMUCARI C, et al. Autophagy is required to maintain muscle mass[J/OL]. Cell Metabolism, 2009,10(6):507-515.

[21]NEMAZANY I, BLAAUW B, PAOLINI C, et al. Defects of Vps15 in skeletal muscles lead to autophagic vacuolar myopathy and lysosomal disease[J/OL].EMBO molecular medicine, 2013,5(6):870-890.

[22]CARNIO S, LOVERSO F, BARAIBAR M A, et al. Autophagy impairment in muscle induces neuromuscular junction degeneration and precocious aging[J/OL]. Cell Reports, 2014, 8(5): 1509-1521.

[23]COLLIER J J,GUISSART C,OLÁHOVÁ M,et al. Developmental Consequences of Defective ATG7-Mediated Autophagy in Humans[J/OL]. The New England Journal of Medicine, 2021, 384(25):2406-2417.

[24]SANDRI M. Autophagy in skeletal muscle[J/OL]. FEBS letters,2010, 584(7):1411-1416.

[25]WOHLGEMUTH S E, SEO A Y, MARZETTI E, et al. Skeletal muscle autophagy and apoptosis during aging: effects of calorie restriction and life-long exercise[J/OL]. Experimental

Gerontology,2010,45(2):138–148.

[26]DRUMMOND M J,ADDISON O,BRUNKER L,et al. Downregulation of E3 ubiquitin ligases and mitophagy-related genes in skeletal muscle of physically inactive, frail older women: a cross-sectional comparison[J/OL]. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 2014, 69(8):1040–1048.

[27]RUSS D W,BOYD I M, MCCOY K M, et al. Muscle-specificity of age-related changes in markers of autophagy and sphingolipid metabolism[J/OL].Biogerontology,2015,16(6):747–759.

[28]LI C, WHITE S H, WARREN L K, et al. Skeletal muscle from aged American Quarter Horses shows impairments in mitochondrial biogenesis and expression of autophagy markers[J/OL]. Experimental Gerontology, 2018,102:19–27.

[29]FRY C S, DRUMMOND M J, GLYNN E L, et al. Skeletal muscle autophagy and protein breakdown following resistance exercise are similar in younger and older adults[J/OL]. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,2013,68(5):599–607.

[30]The satellite cell in skeletal muscle: A story of heterogeneity-PubMed[EB/OL].[2025-01-16].<https://pubmed.ncbi.nlm.nih.gov/38670703/>.

[31]CHEN W, CHEN Y, LIU Y, et al. Autophagy in muscle regeneration:potential therapies for myopathies[J/OL]. Journal of Cachexia, Sarcopenia and Muscle,2022,13(3):1673–1685.

[32]WHITE J P,BILLIN A N,CAMPBELL M E,et al.The AMPK/p27 Kip1 Axis Regulates Autophagy/Apoptosis Decisions in Aged Skeletal Muscle Stem Cells[J/OL]. Stem Cell Reports, 2018, 11(2):425–439.

[33]GARCÍA-PRAT L,MARTÍNEZ-VICENTE M,PERDIGUERO E, et al.Autophagy maintains stemness by preventing senescence[J/OL]. Nature, 2016, 529(7584):37–42.

[34]Geriatric muscle stem cells switch reversible quiescence into senescence-PubMed[EB/OL].[2025-01-16].<https://pubmed.ncbi.nlm.nih.gov/24522534/>.

[35]TANG A H, RANDO T A. Induction of autophagy supports the bioenergetic demands of quiescent muscle stem cell activation[J/OL]. The EMBO journal,2014,33(23):2782–2797.

[36]BAECHLER B L,BLOEMBERG D,QUADRILATERO J. Mitophagy regulates mitochondrial network signaling, oxidative stress, and apoptosis during myoblast differentiation[J/OL]. Autophagy,2019,15(9):1606–1619.

[37]REZUS E, BURLUI A, CARDONEANU A, et al. Inactivity and Skeletal Muscle Metabolism: A Vicious Cycle in Old Age[J/OL]. International Journal of Molecular Sciences, 2020, 21(2):592.

[38]LI C W, YU K, SHYH-CHANG N, et al. Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention[J/OL]. Journal of Cachexia, Sarcopenia and Muscle,2019,10(3):586–600.

[39]Reactive oxygen species: impact on skeletal muscle - PubMed[EB/OL].[2025-01-16].<https://pubmed.ncbi.nlm.nih.gov/23737208/>.

[40]BIASIZZO M, KOPITAR-JERALA N. Interplay Between NLRP3 Inflammasome and Autophagy[J/OL].Frontiers in Immunology, 2020,11:591803.

[41]HOU G Z, GUO Q, HAN P P. [Autophagy Activation and Mitochondrial Quality Control in Sarcopenia][J/OL]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. Acta Academiae Medicinae Sinicae, 2022,44(4):709–716.

[42]JACQUEL A, OBBA S, BOYER L, et al. Autophagy is required for CSF-1-induced macrophagic differentiation and acquisition of phagocytic functions[J/OL]. Blood, 2012, 119(19): 4527–4531.

[43]Impaired macrophage autophagy induces systemic insulin resistance in obesity - PubMed[EB/OL]. [2025-01-16]. <https://pubmed.ncbi.nlm.nih.gov/27229537/>.

[44]VAN DER POL A, VAN GILST W H, VOORS A A, et al. Treating oxidative stress in heart failure: past, present and future[J/OL].European Journal of Heart Failure,2019,21(4):425–435.

[45]ZHANG H, QI G, WANG K, et al. Oxidative stress: Roles in skeletal muscle atrophy[J/OL]. Biochemical Pharmacology, 2023,214:115664.

[46]KINOSHITA H, ORITA S, INAGE K, et al. Skeletal Muscle Cell Oxidative Stress as a Possible Therapeutic Target in a Denervation-Induced Experimental Sarcopenic Model[J/OL]. Spine,2019,44(8):E446–E455.

[47]ABRIGO J, SIMON F, CABRERA D, et al. Mitochondrial Dysfunction in Skeletal Muscle Pathologies[J/OL]. Current Protein & Peptide Science,2019,20(6):536–546.

[48]LIU B Y, LI L, LIU G L, et al. Baicalin attenuates cardiac hypertrophy in mice via suppressing oxidative stress and activating autophagy in cardiomyocytes[J/OL]. Acta Pharmacologica Sinica,2021,42(5):701–714.

[49]WANG H H, SUN Y N, QU T Q, et al. Nobiletin Prevents D-Galactose-Induced C2C12 Cell Aging by Improving Mitochondrial Function[J/OL]. International Journal of Molecular Sciences,2022,23(19):11963.

[50]SARRAF S A, SIDERIS D P, GIAGTZOGLU N, et al. PINK1/Parkin Influences Cell Cycle by Sequestering TBK1 at Damaged Mitochondria, Inhibiting Mitosis[J/OL]. Cell Reports, 2019,29(1):225–235.e5.

- [51] WHITE Z, TERRILL J, WHITE R B, et al. Erratum to: Voluntary resistance wheel exercise from mid-life prevents sarcopenia and increases markers of mitochondrial function and autophagy in muscles of old male and female C57BL/6J mice[J/OL]. *Skeletal Muscle*, 2017, 7(1):4.
- [52] ZENG Z, LIANG J, WU L, et al. Exercise-Induced Autophagy Suppresses Sarcopenia Through Akt/mTOR and Akt/FoxO3a Signal Pathways and AMPK-Mediated Mitochondrial Quality Control[J/OL]. *Frontiers in Physiology*, 2020, 11:583478.
- [53] VAINSHTEIN A, GRUMATI P, SANDRI M, et al. Skeletal muscle, autophagy, and physical activity: the ménage à trois of metabolic regulation in health and disease[J/OL]. *Journal of Molecular Medicine (Berlin, Germany)*, 2014, 92(2):127-137.
- [54] PRYDE K R, SMITH H L, CHAU K Y, et al. PINK1 disables the anti-fission machinery to segregate damaged mitochondria for mitophagy[J/OL]. *The Journal of Cell Biology*, 2016, 213(2):163-171.
- [55] ABREU P, MENDES S V D, CECCATTO V M, et al. Satellite cell activation induced by aerobic muscle adaptation in response to endurance exercise in humans and rodents[J/OL]. *Life Sciences*, 2017, 170:33-40.
- [56] XIE W Q, XIAO W F, TANG K, et al. Caloric restriction: implications for sarcopenia and potential mechanisms[J/OL]. *Aging*, 2020, 12(23):24441-24452.
- [57] BAKER D J, BETIK A C, KRAUSE D J, et al. No decline in skeletal muscle oxidative capacity with aging in long-term calorically restricted rats: effects are independent of mitochondrial DNA integrity[J/OL]. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 2006, 61(7):675-684.
- [58] NING Y C, CAI G Y, ZHUO L, et al. Short-term calorie restriction protects against renal senescence of aged rats by increasing autophagic activity and reducing oxidative damage[J/OL]. *Mechanisms of Ageing and Development*, 2013, 134(11-12):570-579.
- [59] VAN NORREN K, RUSLI F, VAN DIJK M, et al. Behavioural changes are a major contributing factor in the reduction of sarcopenia in caloric-restricted ageing mice[J/OL]. *Journal of Cachexia, Sarcopenia and Muscle*, 2015, 6(3):253-268.
- [60] SZAFRANSKI K, MEKHAIL K. The fine line between lifespan extension and shortening in response to caloric restriction[J/OL]. *Nucleus (Austin, Tex.)*, 2014, 5(1):56-65.
- [61] BOSTRÖM P, WU J, JEDRYCHOWSKI M P, et al. A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis[J/OL]. *Nature*, 2012, 481(7382):463-468.
- [62] ROCA-RIVADA A, CASTELAO C, SENIN L L, et al. FNDC5/irisin is not only a myokine but also an adipokine[J/OL]. *PLoS One*, 2013, 8(4):e60563.
- [63] ZHANG H, WU X, LIANG J, et al. Irisin, an exercise-induced bioactive peptide beneficial for health promotion during aging process[J/OL]. *Ageing Research Reviews*, 2022, 80: 101680.
- [64] REZA M M, SUBRAMANIAM N, SIM C M, et al. Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy[J/OL]. *Nature Communications*, 2017, 8(1):1104.
- [65] MEN X M, XU Z W, TAO X, et al. FNDC5 expression closely correlates with muscle fiber types in porcine longissimus dorsi muscle and regulates myosin heavy chains (MyHCs) mRNA expression in C2C12 cells[J/OL]. *PeerJ*, 2021, 9:e11065.
- [66] XIN T, LU C. Irisin activates Opa1-induced mitophagy to protect cardiomyocytes against apoptosis following myocardial infarction[J/OL]. *Aging*, 2020, 12(5):4474-4488.
- [67] RYU D, MOUCHIROUD L, ANDREUX P A, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents[J/OL]. *Nature Medicine*, 2016, 22(8):879-888.
- [68] ANDREUX P A, BLANCO-BOSE W, RYU D, et al. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans[J/OL]. *Nature Metabolism*, 2019, 1(6):595-603.
- [69] EISENBERG T, ABDELLATIF M, SCHROEDER S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine[J/OL]. *Nature Medicine*, 2016, 22(12):1428-1438.
- [70] ZHA W, SUN Y, GONG W, et al. Ginseng and ginsenosides: Therapeutic potential for sarcopenia[J/OL]. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, 2022, 156: 113876.
- [71] KIM T J, PYUN D H, KIM M J, et al. Ginsenoside compound K ameliorates palmitate-induced atrophy in C2C12 myotubes via promyogenic effects and AMPK/autophagy-mediated suppression of endoplasmic reticulum stress[J/OL]. *Journal of Ginseng Research*, 2022, 46(3):444-453.

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