MSTN对肥胖、糖尿病发生发展的影响和机制以及运动对MSTN的调控

何永[1] 付绍婷[2] 王晓慧[1]*

([1]上海体育学院, 运动健康学院, 上海 200438; [2]上海师范大学, 体育学院, 上海 200234)

摘要 肌肉生长抑制素(myostatin, MSTN)除负性调控骨骼肌质量外, 还在肥胖、糖尿病的发生发展中起重要作用。肥胖和糖尿病患者的血清MSTN含量、骨骼肌MSTN水平显著增加, 而降低MSTN表达水平或者抑制其活性可减少脂肪在体内的累积, 延缓肥胖和糖尿病的发生发展。降低MSTN表达水平或活性延缓肥胖和糖尿病发生发展, 除通过增加骨骼肌质量实现外, 还可通过增加葡萄糖摄取, 促进脂肪细胞发育、代谢和白色脂肪棕色化, 提高瘦素敏感性, 减轻炎症反应, 以及提高线粒体功能等途径实现。运动也可显著降低肥胖和糖尿病患者的MSTN水平, 这可能是运动减脂、改善胰岛素敏感性、预防糖尿病发生发展的重要机制之一。该文就MSTN对肥胖、糖尿病发生发展的影响和机制以及运动对其调控作一综述, 这不仅为肥胖、糖尿病的预防和治疗提供了新靶点, 也为运动改善肥胖和糖尿病发生发展的机制提供了新视角。

关键词 肌肉生长抑制素; 肥胖; 糖尿病; 骨骼肌质量; 运动

The Roles and Mechanisms of MSTN in the Developments of Obesity and Diabetes Mellitus and the Regulation of Exercise on MSTN

HE Yong[1], FU Shaoting[2], WANG Xiaohui[1]*

([1]*Shanghai University of Sports, School of Sports Health, Shanghai 200438, China*;
[2]*Shanghai Normal University, Institute of Physical Education, Shanghai 200234, China*)

Abstract In addition to negatively regulate skeletal muscle mass, MSTN (myostatin) also plays an important role in the occurrence and development of obesity and diabetes. In obese and diabetic patients, serum MSTN content and the expression level of MSTN in skeletal muscle are significantly increased, and reducing MSTN expression or inhibiting its activity reduces fat accumulation in body and delay the occurrence and development of obesity and diabetes. The inhibition of MSTN expression or activity delays the development of obesity and diabetes, which is achieved not only by increasing skeletal muscle mass, but also by increasing glucose uptake, promoting adipocyte development, metabolism and browning of white adipose tissue, improving leptin sensitivity, reducing inflammatory response, and improving mitochondrial function and so on. Exercise can also reduce the level of MSTN in obese and diabetic patients, which may be one of the mechanisms about exercise reducing fat, improving insulin sensitivity, reducing blood glucose and lipid, and thus preventing the occurrence and development of obese and diabetes. This review focuses on the effects and mechanisms of MSTN in obesity and diabetes, as well as its regulation by exercise, which provides a new target for prevention and treatment of obesity and diabetes, and a new

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*通讯作者。Tel: 021-65507509, E-mail: wangpan96@126.com
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*Corresponding author. Tel: +86-21-65507509, E-mail: wangpan96@126.com

perspective about the mechanisms of the improvement of obesity and diabetes by exercise.

Keywords myostatin; obesity; diabetes; skeletal muscle mass; exercise

肌肉生长抑制素(myostatin, MSTN)是转化生长因子β(transforming growth factor-β, TGF-β)超家族的一员, 因负性调控骨骼肌质量而得名。近年来的研究发现, MTSN除负性调控骨骼肌质量外, 还与糖脂代谢紊乱以及肥胖和糖尿病的发生发展密切相关。大量研究表明, 肥胖和糖尿病患者[1-2]、高脂饮食诱导肥胖大鼠[3]的血清MSTN含量、骨骼肌MSTN表达水平均明显增加, 而降低MSTN表达水平或者抑制MSTN活性可显著增加小鼠的骨骼肌质量、降低血糖水平、增强葡萄糖耐受能力, 并降低高脂饮食诱导的肥胖[3]和糖尿病[4]发生率。

骨骼肌是人体代谢最为活跃的组织, 目前研究已证实骨骼肌质量的多少与机体的代谢水平密切相关。MSTN在肥胖和糖尿病发生发展中的作用部分通过改变骨骼肌质量实现。动物实验表明, MSTN前肽(MSTN前体蛋白由N末端的前肽和C末端的成熟结构域组成, MSTN前肽可与成熟MSTN结合并抑制其活性)过表达的C57BL/6[4]和db/db[5]小鼠, 其骨骼肌质量增加, 且血清葡萄糖和脂肪酸水平降低。近年来研究发现, 抑制MSTN活性还可通过促进骨骼肌细胞的葡萄糖摄取和利用[6]、抑制脂肪细胞的增殖与分化[7]以及促进白色脂肪棕色化[8]等参与肥胖和糖尿病的发生与发展进程。

运动是目前公认的减轻肥胖、改善糖尿病的最安全有效的干预手段。抗阻运动[17]和有氧运动[18]对肥胖和糖尿病小鼠, 在减轻体重、改善血糖血脂和提高胰岛素敏感性的同时, 也显著降低肥胖和糖尿病小鼠血清MSTN含量、骨骼肌MSTN的表达水平, 提示运动可能通过降低MSTN水平来减轻肥胖和糖尿病。本文就MSTN在肥胖和糖尿病发生与发展中的作用和机制以及运动对其调控作一综述, 为肥胖和糖尿病的潜在治疗靶点提供依据, 也为运动改善肥胖和糖尿病发生发展的机制提供新视角。

1 MSTN在肥胖、糖尿病发生发展中的作用

MSTN是分泌型蛋白质, 除高表达于骨骼肌外, 在脂肪和心肌组织中也有表达, 它在内质网被水解切割为羧基末端的活性结构域和氨基末端的抑制性前肽, 然后释放入血。分泌入血的MSTN以多蛋白复合物的形式存在, 羧基末端的活性结构域以非共价键的形式与抑制性前肽或其他抑制性蛋白如卵泡抑素(follistatin, FST)和FST样蛋白3(follistatin-like-3, FSTL3)结合, 处于失活状态。当具有活性的羧基末端从多蛋白复合物解离后, 与细胞表面的II型或IIb型activin受体(ActRII或ActRIIb)结合, 通过经典的TGF-β-Smad信号通路以及Smad信号非依赖的途径调控肌肉质量[8]。

*MSTN*基因缺失或者突变动物出现肌肉肥大、“双肌”表型[9]。但近年来大量的研究表明, MSTN还参与糖脂代谢的调控, 与肥胖和糖尿病的发生发展密切相关。肥胖和糖尿病个体的血清MSTN含量和骨骼肌MSTN表达水平显著升高[2,10], 且血清MSTN与肥胖个体BMI、腰围和臀围呈正相关, 与胰岛素敏感性呈负相关[2](表1)。尾静脉注射腺相关病毒(adeno-associated virus, AAV)介导的过表达MSTN前肽(myostatin propeptide, MPRO)抑制MSTN活性, 可使糖尿病模型小鼠-db/db小鼠的血糖和胰岛素水平显著降低、葡萄糖耐受能力和胰岛素敏感性显著增强[5], 也可有效降低高脂膳食小鼠的高血糖和高血脂, 降低其2型糖尿病的发病率[4], 证实了MSTN在肥胖和糖尿病发生发展中的重要作用。此外, 运动对高脂饮食大鼠的体成分(减少腹部脂肪含量、增加后肢骨骼肌质量)和胰岛素抵抗的改善作用, 也与其降低血清MSTN含量、肌肉MSTN蛋白和*ActRIIb* mRNA表达水平有关[3]。

2 抑制MSTN表达或活性延缓肥胖、糖尿病发生发展的机制

2.1 依赖于骨骼肌质量的调控

MSTN是骨骼肌质量的重要调控因子。利用小檗碱降低胰岛素抵抗小鼠的MSTN表达水平可抑制高脂饮食所致的体重和脂肪重量的增加、改善糖脂代谢紊乱, 以及增加骨骼肌质量[12]。上文提到的AAV-MPRO(抑制MSTN活性)降低db/db小鼠血糖、提高胰岛素敏感性以及降低高脂饮食小鼠2型糖尿病发病率的作用, 都与骨骼肌质量增加有关[4-5]。另外, 链脲佐菌素(*Streptozotocin*, *STZ*)诱导的1型糖尿

表1 肥胖和糖尿病个体血清MSTN含量、骨骼肌MSTN表达水平变化

Table 1 Changes in serum MSTN levels and skeletal muscle MSTN expression levels in obese and diabetic individuals

研究对象 Subjects	MSTN表达水平和活性改变 The change of MSTN expression and activity	其他因子变化 Other indicators	参考文献 References
Obese patients (148 cases, 45.9±14.3 years, 37.2±8.0 kg/m^2)	Serum MSTN levels ↑	Serum MSTN levels are negatively correlated with lean body mass/weight and serum adiponectin levels	2021[1]
Diabetic patients (10 adult males, 32±4.9 years, 26.6±1.04 kg/m^2; 21 females, 32±2.4 years, 26.04±1.17 kg/m^2)	Serum MSTN levels ↑	MSTN levels are negatively correlated with lean body mass and muscle strength	2020[2]
Obese patients (74 outpatients, 30 males and 44 females, BMI≥25 kg/m^2)	Serum MSTN levels ↑	MSTN levels are positively correlated with insulin resistance	2018[10]
MSTN propeptide overexpression high-fat feeding rats	MSTN activity ↓	Glucose tolerance ↑, skeletal muscle content ↑, serum insulin levels ↓	2019[4]
MSTN propeptide overexpression high fat feeding mice	MSTN activity ↓	Body weight and body fat ↓, blood glucose ↓, lipid metabolism ↑, skeletal muscle content ↑, insulin sensitivity ↑, mitochondrial function ↑	2020[6]
Obese mice treated with Berberine	Skeletal muscle MSTN protein and mRNA levels ↓	Body weight and body fat ↓, inflammatory status ↓, skeletal muscle mass ↑, insulin sensitivity ↑,	2020[12]
MSTN propeptide overexpression db/db mice	MSTN activity↓	Blood glucose ↓, lipid metabolism ↑, insulin levels ↓, mitochondrial function ↑, skeletal muscle content ↑, insulin sensitivity ↑	2017[5]
MSTN knockout type I diabetic mice	Without MSTN expression	Body weight and body fat ↓, skeletal muscle content ↑, glucose uptake capacity ↑, insulin sensitivity ↑	2016[13]

↑: 指标的水平上调; ↓: 指标的水平下调。

↑: the levels of indicators upregulate; ↓: the levels of indicators downregulate.

病小鼠的MSTN表达较高, 且肌肉质量和肌纤维横截面积明显减少[13]。此外, 无论是普通还是高脂饮食状态下, 特异性抑制骨骼肌MSTN信号可增加瘦体重、减少脂肪含量、改善葡萄糖代谢, 并减轻肥胖, 而特异性阻断脂肪组织MSTN信号则无此作用[11], 表明骨骼肌MSTN在肥胖和糖尿病发生发展中发挥重要作用, 且该作用至少部分是通过调控骨骼肌质量实现的。

2.2 非依赖于骨骼肌质量的调控

2.2.1 通过PI3K/Akt和AMPK促进葡萄糖摄取 骨骼肌是机体主要的运动器官, 也是糖代谢的主要场所。葡萄糖转运蛋白4(glucose transporter 4, GLUT4)介导的葡萄糖转运是影响骨骼肌代谢的主要步骤。肌内注射AAV-MPRO局部抑制MSTN活性后, 可通过增加GLUT4蛋白表达水平促进高脂饮食诱导的肥胖小鼠趾长伸肌和胫骨前肌对葡萄糖的摄取[6]。体外实验也表明, AAV-MPRO预处理可通过促进GLUT4的细胞膜转位提高胰岛素抵抗C2C12细胞的糖摄取能力和糖原合成[4]。

磷脂酰肌醇3激酶(phosphatidylinositol-3-kinase, PI3K)/蛋白激酶B(protein kinase B, PKB, 又称Akt)和腺苷酸激活的蛋白激酶(5′-AMP-activated kinase,

AMPK)可促进GLUT4由胞质转位于细胞膜上, 是调控葡萄糖稳态的两条信号通路。多种小分子化合物通过激活PI3K/Akt和AMPK信号通路, 增加GLUT4蛋白表达水平或者促进GLUT4向细胞膜的转位, 最终促进骨骼肌细胞摄取葡萄糖; 而加入PI3K抑制剂(LY294002)或AMPK抑制剂(CC)能逆转上述促进作用[14-15]。研究发现, 使用MSTN多克隆抗体或者AAV-MPRO预处理抑制MSTN活性可改善骨骼肌细胞胰岛素抵抗、促进胰岛素刺激的葡萄糖摄取, 与其激活PI3K/Akt信号通路、刺激GLUT4由胞质向细胞膜的转位有关[4]。而*MSTN*基因敲除或者MSTN拮抗剂减轻高脂饮食诱导小鼠胰岛素抵抗、提高胰岛素敏感性、促进葡萄糖摄取的作用, 也与其激活PI3K/Akt和AMPK信号通路, 增加GLUT4蛋白表达水平有关[16]。运动改善饮食诱导肥胖小鼠的胰岛素抵抗、提高其胰岛素敏感性的作用, 还与MSTN蛋白表达降低, 激活PI3K/Akt信号通路有关[3]。

2.2.2 通过ADSSL1-AMPK-ACC通路促进脂肪细胞发育及脂代谢 研究表明, *MSTN*基因敲除或活性抑制可减轻高脂饮食诱导或基因缺陷导致的肥胖小鼠体内脂肪的累积[7]。在细胞水平上, 脂肪组织沉积是脂肪细胞数量增加和单个脂肪细胞体积增大的结果。其中, 脂肪细胞数目由多潜能干细胞定向分化为脂肪前体细胞的程度决定, 而单个脂肪细胞的体积与甘油三酯积累有关。利用MSTN干扰RNA和MSTN重组蛋白证实了MSTN对脂肪前体细胞分化的促进作用[7]。

除了调控脂肪细胞发育外, MSTN还可影响甘油三酯在细胞内的累积。甘油三酯在细胞内的累积主要取决于脂肪分解与合成之间的动态平衡。脂肪分解包含三个主要步骤: 甘油三酯分解并由脂肪组织释放入血、脂肪酸被转入线粒体内以及脂肪酸在线粒体内的β-氧化。利用基因芯片和qRCR方法证实, *MSTN*基因敲除小鼠白色脂肪组织内与脂肪分解相关的甘油三脂脂肪酶(adipose triacylglycerol lipase, *ATGL*)、激素敏感性脂肪酶(hormone sensitive lipase, *HSL*)、单酰基甘油脂肪酶(monoacylglycerol lipase, *MGL*)基因表达水平上调、甘油三酯含量明显减少, 以及白色脂肪细胞的体积更小[4]。基于6-plex标记的定量蛋白组学和RT-PCR技术揭示, *MSTN*敲除小鼠脂肪酸β-氧化相关酶的基因, 包括肉碱棕榈酰基转移酶2(carnitine *O*-palmitoyltransferase 2, *CPT2*)、羟酰基辅酶A脱氢酶(hydroxyacyl-coenzyme A dehydrogenase, *HADH*)、短链特异性酰基辅酶A脱氢酶(acyl-CoA dehydrogenase, *ACAD*)、烯酰辅酶A水合酶(Enoyl-CoA hydratase, *ECHS1*)等基因表达水平显著升高, 表明*MSTN*基因敲除可促进脂肪酸β-氧化[19]; 同时紫外吸收光谱分析结果显示*MSTN*基因敲除小鼠的骨骼肌内甘油三酯含量明显减少[19]。体外实验也表明, 外源加入MSTN可降低*ATGL*和*HSL*基因表达水平、抑制肌内脂肪细胞的脂解作用以及减少甘油的释放[20]。

AMPK是细胞内的能量感受器, 受AMP/ATP值的影响。AMPK活性是影响脂肪酸β-氧化的关键蛋白, 增强AMPK活性可提高脂肪酸β氧化[21]。腺苷琥珀酸合成酶同工酶1(adenylosuccinate synthetase isozyme 1, ADSSL1)是催化AMP合成的关键蛋白, *MSTN*敲除小鼠的ADSSL1活性显著增强、AMP/ATP比例提高, AMPK信号通路被激活, 进而促进脂肪酸β氧化[21]。乙酰辅酶A羧化酶(acetyl-CoA carboxylase, ACC)是脂肪酸合成的限速酶, 在脂肪酸合成代谢中发挥着重要作用。研究证实, AMPK可通过调控下游因子ACC来发挥作用[16]。*MSTN*基因敲除小鼠的ACC磷酸化水平增加, 可以抑制脂肪酸合成并促进脂质氧化[16]。

2.2.3 通过FNDC5/Irisin促进白色脂肪棕色化 哺乳动物主要含有两种脂肪组织, 即白色脂肪组织(white adipose tissue, WAT)和棕色脂肪组织(brown adipose tissue, BAT)。前者包含单个较大脂滴, 含有大量甘油三酯, 将机体多余的能量以脂肪的形式储存起来; 后者包含多房小脂滴, 胞内含有大量线粒体, 以氧化磷酸化非偶联的方式消耗甘油三酯, 产生热量。在寒冷、激素或者运动的刺激下, 白色脂肪组织会出现褐色脂肪样细胞, 被称作“白色脂肪棕色化”, 它是防治肥胖及肥胖相关疾病的新方法[22]。

除了调控脂肪细胞发育和脂代谢外, MSTN还在白色脂肪棕色化中起重要调控作用。*MSTN*基因敲除小鼠的皮下白色脂肪组织包含众多体积较小的棕色脂肪细胞样细胞, 胞内充满多房小脂滴[23]。PR结构域蛋白16(PRD1-BF1-RIZ1 homologous domain containing protein 16, PRDM16)是决定BAT分化的关键转录调控因子, *PRDM16*基因敲除小鼠棕色脂肪细胞几乎完全丧失棕色脂肪细胞特性[24]。PPARγ共激活因子1α(PPAR coactivator 1α, PGC-1α)是高表

达于棕色脂肪组织的诱导型转录共激活因子, 可通过与过氧化物酶增殖激活受体γ(peroxisome proliferator-activated receptor γ, PPARγ)相互作用促进线粒体生物发生、棕色脂肪组织的产热[25]。解偶联蛋白1(uncoupling protein 1, *UCP1*)特异性表达于BAT, 也被称作是决定棕色脂肪产热水平的关键基因。此外, *CD137*和跨膜蛋白26(transmembrane protein 26, *TMEM26*)是白色脂肪组织转变为棕色脂肪细胞的表面标志物。上述基因均被认为是白色脂肪棕色化的标志物, 可反映白色脂肪棕色化的程度。研究发现, *MSTN*敲除小鼠能量利用增加, 同时采用qPCR和Western blot方法揭示其皮下白色脂肪组织*PGC-1α*、*UCP1*、*PRDM16*、*CD137*及*TMEM26*基因表达水平上调[23,26], 这表明*MSTN*基因敲除可促进白色脂肪的棕色化。

此外, III型纤连蛋白结构域5(fibronectin type III domain containing 5, FNDC5)是鸢尾素(Irisin)的前体, 在促进在白色脂肪棕色化、减少脂肪沉积中起重要作用[27]。MSTN很可能通过调控FNDC5/Irisin实现对白色脂肪组织棕色化的促进作用, 这是因为*MSTN*基因敲除小鼠肌管细胞的上清可显著增加原代脂肪细胞*UCP1*、*PRDM16*、*PGC-1α*、*TMEM26*和*CD137*等基因表达水平, 而加入FNDC5中和抗体可逆转上述这一作用[23,28]。

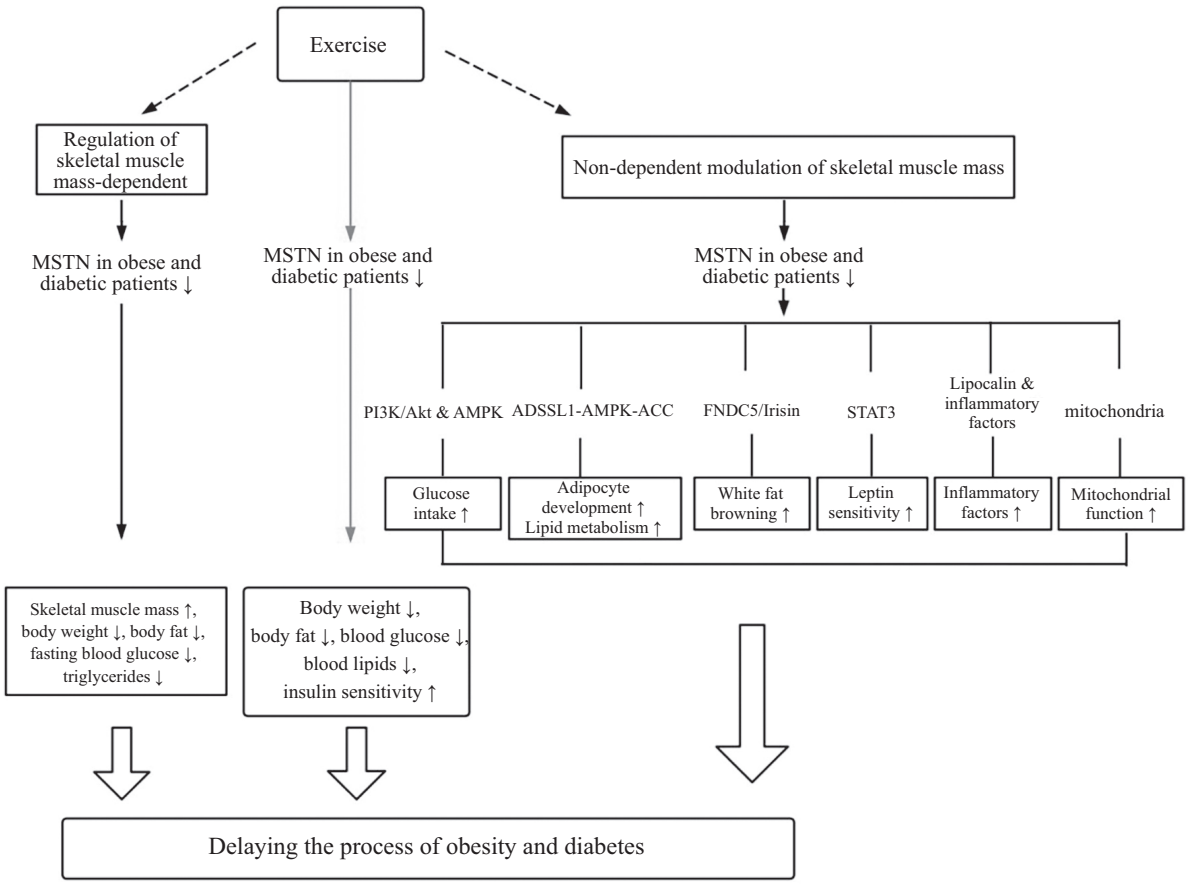
2.2.4 通过STAT3提高瘦素敏感性 瘦素主要由白色脂肪细胞分泌, 在降低食欲、减少能量摄入以及降低血糖方面发挥重要作用。然而, 据报道, 肥胖和糖尿病个体的血清瘦素水平不是降低, 而是异常升高, 且出现了瘦素抵抗(对瘦素不敏感或无反应); 减轻瘦素抵抗对于治疗肥胖和糖尿病具有重要意义[29]。

研究表明, MSTN可调控瘦素敏感性。与野生型小鼠相比, *MSTN*基因敲除小鼠对瘦素的敏感性更高, 表现为*MSTN*基因敲除小鼠连续两天静脉注射瘦素后, 体重减轻得更多, 且这2天内累计进食量也更少[30]。不仅如此, 基础状态下*MSTN*基因敲除小鼠的血浆瘦素水平也显著下降。介导了瘦素大部分功能的下游因子–信号转导和转录激活因子3(signal transducer and activator of transcription 3, STAT3)是反映瘦素敏感性的重要指标, 其磷酸化和表达水平的增加有利于提高瘦素敏感性[31]。但下丘脑内pSTAT3含量与野生型小鼠无明显差异。以上结果提示, *MSTN*基因敲除小鼠的瘦素敏感性更高[30]。

2.2.5 通过脂联素和炎症因子减轻炎症反应 肥胖及肥胖相关疾病是一种系统性的慢性低度炎症, 与肥胖及肥胖相关疾病发生及糖脂代谢紊乱密切相关。肥胖导致脂肪和炎症因子增加, 而增加的脂肪和炎症因子又会加重糖脂代谢紊乱、促进肥胖及其相关疾病的发生与发展, 因此抗炎成为肥胖、糖尿病等疾病的有效治疗方法。其中, 最经典的脂肪因子脂联素是人体含量最丰富的分泌型脂肪细胞因子, 在降低血糖、促进脂质氧化、改善胰岛素抵抗中起重要作用。肥胖和糖尿病患者血清中脂联素水平显著降低, 并且较低的脂联素水平与胰岛素抵抗、脂代谢异常以及糖尿病发生风险等密切相关[32,33]; 反之, 增加脂联素表达水平则可改善血脂、减少脂肪堆积[43]。经典炎症因子如白介素6(interleukin 6, IL-6)、IL-Iβ、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)可直接抑制骨骼肌的脂肪降解, 并增加脂肪底物沉积, 提示上述炎症因子的阻断剂可成为治疗肥胖糖尿病的新策略[34]。

肥胖患者降低体重后, MSTN水平降低、脂联素水平增加, 且MSTN水平的变化与脂联素水平相关, 这表明MSTN和脂联素可能会相互影响, 并调节骨骼肌和脂肪含量[37]。但MSTN与脂联素的具体机制尚未清晰。*MSTN*基因敲除提高高脂喂养小鼠的胰岛素敏感性, 减少肝脏脂肪堆积的作用, 也与其降低血清TNF-α水平有关; 而外源补充MSTN重组蛋白则增加血清TNF-α含量, 并产生胰岛素抵抗[35]。此外, 利用多克隆单体阻断MSTN活性减轻高脂饮食诱导肥胖小鼠的骨质流失和对骨超微结构的破坏作用, 也是通过增加血清脂联素浓度、降低血清TNF-α和IL-6的水平实现的[36]。

2.2.6 通过促进线粒体生物发生提高线粒体功能 线粒体是葡萄糖和脂肪进行氧化磷酸化的主要场所, 线粒体功能障碍是导致肥胖和糖尿病的重要原因之一[38]。新型肥胖和糖尿病动物模型TALLYHO/Jng小鼠的肝脏和肾脏组织揭示了其线粒体呼吸链复合物I、IV的表达水平和活性降低, 提示线粒体功能缺陷[39]。利用CRISPR/Cas9技术敲除*MSTN*表达可显著增加C2C12细胞线粒体生物合成相关基因*PGC-1α*、*COX1*、*COX2*的表达水平, 促进线粒体生物发生[40]; *MSTN*基因敲除小鼠PGC-1α表达水平增加, 线粒体数量增加、线粒体功能得到改善[41], 证实了MSTN对线粒体生物合成和功能的影响。而



↑: 指标的水平上调; ↓: 指标的水平下调。

↑: the levels of indicators upregulate; ↓: the levels of indicators downregulate.

图1 肌肉生长抑制素对肥胖、糖尿病发生发展的影响和机制及运动对肌肉生长抑制素的调控

Fig.1 Effects and mechanisms of myostatin in the development of obesity and diabetes and the regulation of exercise on myostatin

MSTN表达水平升高所致的线粒体功能受到抑制, 与肥胖老年人葡萄糖摄取能力下降、脂质氧化减少有关[42]。

以上结果提示在抑制MSTN表达和活性后, 一方面可通过调控骨骼肌质量, 另一方面还可通过非依赖于骨骼肌质量途径介导葡萄糖摄取、脂肪发育及脂代谢、白色脂肪棕色化、瘦素敏感性、炎症反应以及线粒体生物发生来调控代谢进程, 减轻肥胖和糖尿病的发生发展(图1)。

3 运动对肥胖及糖尿病患者MSTN水平的调控作用

研究表明, 作为减轻肥胖、改善糖尿病的有效干预手段, 运动也可以调控血清和骨骼肌MSTN的水平(表2)。例如, 为期8周、每周3次的上半身抗阻训练、下半身抗阻训练以及全身抗阻训练均可降低中年男性血清MSTN水平, 并伴随着骨骼肌质量和力量的增加[45]。为期8周、每周3次的高强度间歇运动在降低大鼠的骨骼肌MSTN水平的同时, 能显著增加大鼠腓肠肌质量及肌纤维横截面积[44]。动物和人体实验表明, 对于肥胖和糖尿病个体而言, 不同方式的运动也可调控其血清和骨骼肌MSTN水平, 这可能是运动改善肥胖和糖尿病发生与发展的重要机制之一。例如, 持续12周、每周3次的中等强度滑雪式竞走可显著降低肥胖中老年人的血清MSTN浓度, 并改善其血糖血脂水平, 提高胰岛素敏感性[48]。再如, 对于患有T2DM的老年男性, 为期12周的70%的1次最大负荷强度(repetition maximum, RM)的抗阻训练也可降低血浆MSTN含量, 并改善胰岛素抵抗[18]。最近一项对51名2型糖尿病患者分别进行为期12周的有氧–抗阻训练、抗阻–有氧训练的实验研究, 也证实两种不同组合训练方式均能降低患者的体重、BMI和血清MSTN水平, 并提高患者血清Irisin和卵泡抑素(follistatin, FST)水平[46]。而FST可直接抑制MSTN的表达, 并促

表2 不同运动方案对肥胖及糖尿病患者或大鼠MSTN的调控

Table 2 Modulation of MSTN in obese and diabetic patients or rats by various exercise regimens

研究对象 Subjects	运动方案 Exercise programs	MSTN表达水平的变化 Changes of MSTN expression	其他指标变化 Other indicators	参考文献 References
Obese middle-aged and elderly people (9 men and 23 women; 61±12 years)	Twelve weeks ski racing, 60%-70% HR max, 3 times/week	Serum MSTN levels ↓	Blood glucose level ↓, insulin resistance index ↓, total cholesterol ↓	2021[48]
Type II diabetes males	Twelve weeks of combined aerobic-resistance or resistance-aerobic training, 3 times/week	Serum MSTN levels ↓	Serum irisin level ↑, follicle inhibitory hormone level ↑	2020[46]
Elderly men, postmenopausal obese women	Six months aerobic exercise + diet intervention, 3 times/week; incremental intensity exercise	Skeletal muscle MSTN levels ↓ in women; serum MSTN levels ↓ in men	Body weight ↓, total fat mass ↓, fasting plasma insulin ↓, fasting plasma glucose ↓	2014[50]
Type I diabetic rats	Six-weeks incremental intensity running exercise, 5 times/week	Serum MSTN levels ↓, skeletal muscle *MSTN* mRNA levels ↓	Blood glucose ↓, plasma insulin ↑, TNF-α, IL-6, IL-1β ↓	2019[47]
Obese rats	Eight weeks climbing training, 2 times a day, every 3 days training; weight bearing is 20% of body weight increased to 50%	Skeletal muscle MSTN levels ↓	Body weight and abdominal fat content ↓, muscle mass and grip strength ↑, TNF-α and IL-6 ↓, serum leptin, adiponectin ↑	2016[17]
Type I diabetic rats	Four weeks swimming training, 90 min/day (45 min in the morning and 45 min in the afternoon)	Skeletal muscle MSTN levels ↓	Blood glucose ↓, gastrocnemius muscle mass ↑	2015[49]

↑: 指标的水平上调; ↓: 指标的水平下调。

↑: the levels of indicators upregulate; ↓: the levels of indicators downregulate.

进脂肪褐变, 与能量代谢有着密切联系[8]。

对于肥胖和糖尿病大鼠, 研究发现持续8周的负重爬梯训练(抗阻训练的一种形式)可降低高脂饮食诱导的肥胖大鼠的血浆MSTN含量, 这与运动减轻肥胖大鼠的体重和脂肪含量以及减少骨量流失、骨微结构破坏的作用有关[17]。每周5次、持续6周的有氧运动也可有效降低1型糖尿病大鼠的血浆和骨骼肌中MSTN水平以及TNF-α、IL-6、IL-1β等炎症因子的表达水平, 并且有效降低该大鼠体重和减轻胰岛素抵抗[47]。此外, 对雄性小鼠进行持续4周的低强度有氧运动或者给与C2C12成肌细胞施加持续24 h、频率为1 Hz的电脉冲刺激, 发现有氧运动或电刺激均能提高雄激素受体(androgen receptor, AR)水平, 而AR水平的提高可抑制MSTN转录, 进而抑制其下游IL-6及pSTAT3的表达; 而IL-6及pSTAT3水平均与肥胖及糖尿病的发生发展密切相关[51], 提示运动等可通过调控AR-MSTN-炎症和瘦素等通路来实现其对代谢等的调控作用。以上结果表明, 有氧运动、抗阻运动和有氧–抗阻的组合运动都可调控肥胖和糖尿病患者MSTN水平, 并发挥改善血糖血脂和胰岛素敏感性的作用(图1)。

4 总结与展望

综上所述, MSTN除了负性调控骨骼肌质量外, 还与肥胖和糖尿病发生密切相关; 降低MSTN表达水平或抑制其活性是肥胖和糖尿病治疗的潜在治疗靶点。MSTN表达水平降低或活性受抑后, 一方面通过增加骨骼肌质量, 另一方面通过促进葡萄糖摄取, 调控脂肪细胞发育、脂代谢和白色脂肪棕色化, 改变瘦素敏感性以及降低炎症等来实现其对代谢的调控作用。此外, 有氧运动、抗阻运动和有氧–抗阻的合并运动防治肥胖和糖尿病的作用, 与其降低血清和组织MSTN水平密切相关, 但作用机制尚不清楚, 未来值得进一步研究。

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