综　述

肿瘤相关性肌少症研究进展

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[摘要]　肌少症是一种与恶性肿瘤及其治疗方式密切相关的疾病，是以进行性的全身广泛性骨骼肌质量下降和力量降低为主要特征的综合征，可导致身体残疾、生活质量下降，甚至死亡等不良预后事件的发生。肌少症可能是由年龄、营养不良、炎症、肿瘤、消耗性疾病等多种因素参与的疾病状态，而恶性肿瘤及相关化疗所引起的肌少症多与炎症反应、氧化应激、线粒体损伤等有关。本文对近年来肿瘤相关性肌少症的检测方法、发病机制、临床特征及干预措施等进行综述。

[关键词]　肌少症；肿瘤；研究进展；发病机制

Research progress on tumor-related sarcopenia

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[**Abstract**]　Sarcopenia is considered to be a disease closely related to the existence and treatment of malignant tumors. It is characterized by a syndrome of progressive and generalized loss of skeletal muscle mass and strength, which can lead to adverse prognostic events such as physical disability, decreased quality of life and even death. Sarcopenia may be a condition in which age, malnutrition, inflammation, tumors, wasting diseases and many other factors are involved. Sarcopenia caused by malignant tumor and related chemotherapy is mostly related to inflammatory reaction, oxidative stress, mitochondrial damage and so on. In this paper, the research progress on tumor-associated sarcopenia in recent years is reviewed from its test methods, pathogenesis, clinical features, and intervention strategies.

[**Key words**]　sarcopenia; tumors; research progress; pathogenesis

肌少症最早由Rosenberg于1989年提出，主要用于描述年龄相关性骨骼肌质量和力量下降及机体活动功能降低的疾病状态[1]。随着对骨骼肌代谢研究的深入，人们对肌少症的认识不再局限于年龄层面，而是延伸到肿瘤、炎症、激素水平、营养状况、慢性消耗性疾病甚至基因水平[2-3]。2010年欧洲肌少症工作组(European Working Group on Sarcopenia in Older People，EWGSOP)将肌少症定义为以进行性的全身广泛性骨骼肌质量下降和力量降低为主要特征的一类综合征，可导致如身体残疾、

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生活质量下降甚至死亡等不良预后[4]。2018年初，EWGSOP2对肌少症的定义和诊断再次修订，将骨骼肌力量下降作为诊断肌少症的关键性指标，当同时出现少肌量和低体能时定义为重症肌少症[5]。肌少症在肿瘤患者中较普遍，发生率为15%~50%[6-7]。有研究发现，肌少症在消化系统肿瘤患者中发生率较高(12%~78%)[8]。近年来研究发现，肌少症是癌症患者术后并发症、化疗毒性、不良反应及预后欠佳的独立危险因素，且对预后具有重要的预测价值[9-10]。由于肌少症对肿瘤患者的生存和生活质量影响较大，采取针对性的干预措施和进行前瞻性随机对照试验迫在眉睫。本文对肌少症与肿瘤的关系进行综述，旨在提高对肿瘤相关性肌少症的认识。

1 肌少症的检测方法

目前临床上用于测定人体骨骼肌含量的方法有多种，如人体测量法、生物电阻分析法(bioelectrical impedance analysis，BIA)、双能X线吸收技术(dual-energy X-ray absorption technology，DXA)、全身钾含量法(total body kalium content method，TBK)、计算机断层扫描(computed tomography，CT)和磁共振成像(magnetic resonance imaging，MRI)等，其中CT和MRI被公认为是测定骨骼肌含量的金标准，临床广泛用于评价骨骼肌的含量及营养状态[4]。

2 肿瘤相关性肌少症的发病机制

2.1 氧化损伤和线粒体功能障碍 癌症恶病质患者肌肉中存在变形的线粒体，与骨骼肌结构完整性的丧失有关。动物实验证实，恶病质大鼠骨骼肌中*UCP2*基因过表达且肌肉的氧化能力降低[11]，荷瘤小鼠线粒体中ATP的合成减少且存在解偶联[12]。线粒体功能改变与肌少症的发生关系密切。实际上，受损的线粒体不仅具有较低的生物能效率，而且会产生大量的活性氧(reactive oxygen species，ROS)，ROS产生增加可破坏骨骼肌纤维中线粒体的稳定性，从而增加其对凋亡刺激的敏感性，同时下调与线粒体生物发生相关的途径，进而促进肌少症的发生[13]。

2.2 细胞因子 大量研究发现，肿瘤或免疫细胞释放的细胞因子可改变骨骼肌的代谢途径，如增加蛋白水解、心肌细胞凋亡或减少氨基酸转运和再生等。在癌症恶病质中，由免疫细胞和肿瘤细胞产生的促炎细胞因子中作用最显著的是肿瘤坏死因子-α(TNF-α)、白细胞介素-6(IL-6)，两者与骨骼肌的炎症反应有关[14-15]。TNF-α可激活核因子-κB途径及诱导肌肉蛋白中泛素介导的蛋白酶体降解(UPR)，对骨骼肌具有直接分解代谢的作用[16]，同时其是恶病质患者糖异生增加、蛋白水解和脂肪组织丢失的主要原因，并与恶病质骨骼肌中解偶联蛋白2和3的上调有关[17]。此外，TNF-α可促进骨骼肌中中性粒细胞和巨噬细胞的聚集，而肿瘤中中性粒细胞和巨噬细胞浸润增加与患者预后不良和恶病质加重有关[18]。有研究发现，γ干扰素是骨骼肌细胞中肌球蛋白基因的抑制剂，能够激活泛素基因的表达，可与TNF-α协同促进肌肉萎缩[14]。IL-6在恶病质患者中水平较高，并与体重减轻相关[19]。研究发现，IL-6低表达时可作为骨骼肌生长因子，高表达时则可引发肌肉萎缩[20]，同时其与啮齿动物模型的恶病质相关，被认为可诱导炎症和分解代谢途径的激活，从而通过JAK信号转导通路抑制肌肉细胞中蛋白质的合成。在线粒体水平，一些细胞因子通过p38激酶的磷酸化激活过氧化物酶体增殖物激活受体γ辅激活剂1-α(PGC-1α)的转录，从而导致PGC-1α的活化，进而导致呼吸作用增强以及与线粒体解偶联和能量消耗相关基因的表达[9]。

2.3 化疗药物 理论上，肿瘤治疗过程中肌肉质量的逐渐侵蚀可能部分归因于不受控制的肌肉蛋白质分解代谢，这种分解代谢随着肿瘤生长而加剧[21]。化疗可能导致线粒体损伤，降低氧化磷酸化和PGC-1α活化所需的细胞色素C的表达，后者是一种调节能量代谢、线粒体生物发生和肌纤维代谢的蛋白质转录辅激活剂[22]。化疗也可能增加肌肉中ROS的含量并诱导氧化应激，促进其他与肌少症相关的过程，如蛋白水解、上调TNF-α的表达和抑制肌肉细胞分化[23]等。化疗后肿瘤生长因子-β(TGF-β)的表达增加，可上调肌生长抑制素，改变肌肉代谢的平衡[24]。化疗也可通过抗血管生成导致肌肉微血管减少[25]。有研究发现，化疗期间的一些不良事件如疲劳、食欲不振、恶心、呕吐和腹泻等，会对食物摄入、体力活动产生负面影响，从而导致肌肉质量急剧下降[26]。

3 肿瘤相关性肌少症的临床特征

3.1 肌少症与并发症 目前有循证医学研究认为，术前肌少症与术后并发症的关系密切[27]。Elliott等[28]对252例局部晚期食管癌患者进行研究发现，肌少症患者肺部并发症较非肌少症患者常见(55% *vs.* 36%，*P*=0.01)。此外，肌少症是食管癌患者术后90 d非计划再入院的独立危险因素[29]。Silva De Paula等[30]对250例卵巢癌和子宫内膜癌患者进行研究发现，肌少症和骨骼肌质量是术后并发症的重要预测指标。一项纳入4262例接受胃切除术的胃癌患者的荟萃分析显示，术前肌少症与不良病理分期

(高pT分期、高TNM分期)明显相关。研究发现，癌症患者术后总并发症发生率(P<0.01)及严重并发症发生率(P=0.02)与其术前是否合并肌少症密切相关；进一步亚组分析显示，术前年龄超过65岁且来自亚洲的肌少症患者，术后发生并发症或严重并发症的风险较高[31]。Otsuji等[32]对256例肝门部胆管癌患者进行术后并发症分析，结果显示，与非肌少症组相比，肌少症组术后肝衰竭(33% *vs.* 16%)和腹腔脓肿(29% *vs.* 18%)发生率增高。同时，肌少症也是膀胱癌根治术后并发症和预后的独立预测因子[33]。但Kuwada等[34]对491例胃癌患者进行研究发现，肌少症与胃癌术后并发症无关，而与年龄、体重指数(BMI)、胃癌TNM分期以及住院时间延长相关，且为预后不良的独立预测因子。Kim等[35]对272例非小细胞肺癌进行研究发现，术后并发症、住院时间及重症监护时间与肌少症无关。尽管肌少症对肿瘤患者并发症的影响尚存在争议，但可能与肿瘤的病理类型、部位、手术方式、疾病进展阶段等密切相关。

3.2 肌少症与肿瘤治疗的相互影响 已知化疗和靶向治疗会导致肌少症，从而造成身体机能和生活质量下降，而治疗前存在肌少症可增强化学药物的毒性，增高残疾发生率，导致抗肿瘤效果和预后欠佳[30]。化疗、激素治疗、免疫疗法和靶向疗法作为全身系统疗法对癌症患者的身体成分和骨骼肌力量具有显著影响，同时外科手术和放疗可削弱局部肌肉的力量[36]。相较其他癌症患者，合并肌少症的癌症患者化疗的疗程和剂量会发生改变，进而导致总生存期(OS)缩短[37]。与非肌少症患者相比，肌少症相关食管癌患者术前行新辅助化疗发生剂量限制毒性(DLT)的风险增加[38-39]。关于乳腺癌的循证研究发现，肌少症患者3—5级化疗毒性反应的发生率较高(5.6% *vs.* 25%)[36]。一项针对姑息性全身治疗的转移性大肠癌患者的大型纵向研究发现，肌少症与DLT风险增加明显相关[40]。

3.3 肌少症与预后 目前关于肿瘤相关性肌少症的研究普遍认为，肌少症与肿瘤患者预后不良密切相关。Kitano等[41]对110例肝外胆管癌患者进行研究发现，肌少症患者根治性术后无复发生存率和总生存率较非肌少症患者低。此外，与非肌少症患者相比，肌少症患者的血小板/淋巴细胞比值增高(159 *vs.* 119，P=0.003)，$CD8^+$ T细胞数量减少。由此可见，肌少症与全身或局部免疫系统相互影响，从而在患者的临床结局中起关键作用。有研究对147例非小细胞肺癌患者进行分析发现，肌少症患者的5年总生存率明显低于非肌少症患者(77.37% *vs.* 87.27%，P=0.0131)，多变量分析显示，术前肌少症状态是非小细胞肺癌的独立预后因素[42]。Kurita等[43]对82例接受FOLFIRINOX方案化疗的胰腺癌患者进行研究发现，肌少症与非肌少症患者的中位OS分别为11.3个月和17.0个月，治疗失败时间分别为3.0个月和6.1个月；多因素分析显示，肌少症是OS的独立预后因素，且与血液学毒性明显相关。另有研究发现，肌少症与头颈部癌症[43]、胃癌[44-45]、肝癌[46]、直肠癌[47-48]及卵巢癌[49]等全身多处多系统肿瘤的预后密切相关，可作为肿瘤预后的独立预测因子。

4 肿瘤相关性肌少症的干预措施

4.1 非药物干预 尽管运动干预似乎并不能持续增加肌肉的质量，但在增加肌肉力量和改善身体机能方面效果显著[50]。常规运动计划(包括抵抗运动和耐力运动)通过改善肌肉质量、力量和机体功能而对肌少症患者产生显著的积极影响[51]。2018年发布的临床实践指南为运动干预作为肌少症的主要治疗方法提供了有力的证据[52]。抵抗运动对改善骨骼肌力量和质量的益处不言而喻，且被证实有助于骨骼肌强度和力量的增加。两项针对老年人肌少症运动干预的系统评价表明，骨骼肌的力量、质量和平衡力量均得到明显改善，其局限性在于专门招募肌少症参与者，样本量较小，且由于训练方式、持续时间等因素导致训练效果不一致[53-54]。另一项系统评价明确了运动对肌少症肥胖患者的影响[55]。目前针对肌少症的特定运动计划在临床实践中存在很大空缺，同时具体的运动项目存在一定差异。

营养干预的证据并不一致[51]。有研究调查了运动与营养联合治疗肌少症的效果，系统性地回顾了针对年老体弱肌少症患者的非药物干预措施，证实了运动干预的有效性[54]。尽管有证据表明营养干预对肌肉质量的影响很小，但补充营养可改善身体机能[54]。目前正在进行运动联合营养干预的大规模试验，如欧洲SPRINTT试验[56-57]。

尽管一些证据表明饮食方式(如摄入足够的蛋白质、维生素D、抗氧化营养素和长链多不饱和脂肪酸等)对健康有益，但与运动疗法相比，营养干预对肌少症的作用尚不清楚[58]。许多研究都是基于临床观察，缺乏高质量的随机对照试验。关于构建系统性营养模式如蛋白质等营养素的摄取时间、吸收及分布情况仍存在争议[59]。最近的共识建议老年人增加蛋白质摄入量[60]。然而，唯一的比较正常摄入量和增加蛋白质摄入量对运动影响的干预试验是在非肌肉减少性运动障碍患者中进行的，结果表明，这些干预措施之间没有差异[61]。

口服高蛋白营养补充剂对营养不良导致的肌少

症有较好效果[62]。各种营养素的价值值得考究，如必需氨基酸亮氨酸及其代谢产物衍生的多不饱和脂肪酸，对改善肌肉质量和功能有一定作用[63-64]，可在一定程度上提升健康老年人的肌肉质量和功能[65]。

4.2 药物干预 目前尚无获得批准用于治疗肌少症的特定药物。系统回顾和荟萃分析侧重于改善老年人肌肉质量、力量和身体机能的药物干预[66]，这些药物包括维生素D、雌激素(孕酮)、脱氢表雄酮、生长激素、生长激素释放激素、胰岛素样生长因子-1(IGF-1)、吡格列酮、雄激素和血管紧张素转换酶抑制剂(ACEI)等。在维生素D基线水平较低(<25 nmol/L)的女性中，维生素D对骨骼肌强度和体能表现出积极的影响。尽管大剂量雄激素试验表明雄激素可增强肌肉的力量和功能，但应注意其对心血管的不良反应，而小剂量的雄激素会增加蛋白质合成，从而导致肌肉质量增加[67]。循环中高或低水平的IGF-1都可导致心血管疾病风险增加，而其是否可促进肌肉力量增加尚缺乏有力证据。关于IGF-1的小型试验表明，IGF-1与老年患者的体位性低血压、男性乳房发育、肌炎和水肿等不良反应有关[68]。

针对肌少症的药物研究重点为开发可用于肌少症的新药。小型Ⅰ期和Ⅱ期临床试验[69]对选择性雄激素受体调节剂(SARMS)的研究未获得满意效果。早期证据表明，抑制肌生成抑制素可能有效，主要与肌生成抑制素具有阻止肌肉分化、肥大和蛋白质合成的作用有关。迄今为止的研究结果并不一致，Ⅱ期验证试验结果表明，肌生长抑制素抗体与肌肉质量增加及某些低肌肉强度患者的身体表现改善相关[70]。肌少症的药物治疗需要更多的试验来验证并致力于新药的开发。

5 总结与展望

目前关于肌少症的研究涉及年龄、性别、营养状态等因素，且与全身多处多系统肿瘤关系密切。肌少症影响肿瘤患者的营养状况和生活质量，且对肿瘤患者的手术、化疗和靶向治疗及预后表现为负面影响。目前纠正肿瘤相关性肌少症的干预措施较多，但尚未标准化和系统化。术前明确有无肌少症可在一定程度上预测术后并发症及预后。因此，了解肌少症与肿瘤的关系，对于指导临床治疗、预测并发症及预后具有重要意义。积极纠正肿瘤患者的肌少症，或可改善其生活质量和预后，甚至增强肿瘤对化疗、靶向治疗及免疫治疗的耐受性。

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