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肌少症小鼠模型的研究进展

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【摘要】 通过对肌少症相关文献检索,总结出肌少症小鼠造模方法与模型评价方案。对药物注射、衰老、肌肉萎缩和转基因 4 种造模方式的操作、优缺点、适用范围进行综述,总结肌肉功能、肌肉力量、肌肉耐力 3 种肌少症小鼠模型的评价方式,对比其优缺点,以期为肌少症的后期研究提供参考。

【关键词】 肌少症;动物模型;骨骼肌衰老;造模方法
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Research progress in mouse models of sarcopenia

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【**Abstract**】 We searched the literature related to sarcopenia to retrieve information on modeling method and model-evaluation schemes using sarcopenic mice. Here, we review the operation method, advantages and disadvantages, and application scopes of the four modeling method, including drug injection, aging, muscle atrophy, and transgenic mice, and summarize the method used to evaluate muscle function, muscle strength, and muscle endurance. We then compare their advantages and disadvantages, to provide a reference for subsequent research into sarcopenia.

【**Keywords**】 sarcopenia; animal model; skeletal muscle aging; modeling method
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肌少症(sarcopenia)又称肌肉衰减综合征,最初定义仅考虑肌肉质量的损失,2018 年欧洲老年人肌少症工作组将肌少症定义为老年常发性肌肉疾病,主要表现为肌肉力量降低、肌肉质量下降、肌肉功能减退[1]。研究表明 60 岁以下人群的患病率为 8% ~ 36%,60 岁以上的患病率为 10% ~ 27%,此疾病易导致老年人自理能力下降、跌倒、骨折、残疾甚至于死亡[2]。在老年人中更为普遍,但肌肉质量的下降从 40 岁就开始。国内外学者对于肌少症发病机制进行了一系列研究,认为年龄[3]、氧化应激[4]、泛素-蛋白酶体系统[5]、雷帕霉素信号通路[6]、肌肉生长抑制素含量[7]等均与肌少症的发生存在一定的关系。目前肌少症的发生机制尚无统一的定论,也有可能为多种因素联合,且无确切的治疗方法[8],建模方法作为该研究的基础,需进行深入地研究,因此本文从模型建造的方法与评估方式进行归纳总结,综述其适用条件,以期为肌少症小鼠模型建立及评估提供思路。

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1　肌少症动物模型

肌少症建模常用动物有大鼠[9]、小鼠[10]、线虫[11]、恒河猴[12]、斑马鱼[13]、猪[14]、牛[15]、果蝇[16]等。但均存在一定的局限性，小鼠模型应用最为广泛，其原因在于小鼠衰老过程与人有相似之处，且研究成本低、时间短[17]。根据不同的实验方式，将肌少症造模方法分为以下 4 类。

1.1　药物注射模型

药物注射指将诱导肌肉衰老的物质注射至动物体内，从而诱发肌少症，目前使用地塞米松与 D-半乳糖作为诱导剂的研究较多。

地塞米松（dexamethasone）是一种人工合成的糖皮质激素，具有抗炎、抗毒素、免疫抑制、抗过敏等作用[18]，长期大量注射地塞米松会导致骨骼肌蛋白降解，同时抑制骨骼肌蛋白合成从而造成骨骼肌萎缩、肌肉质量减少、肌力减弱[19]。LEE 等[20]证明使用地塞米松对小鼠腹腔注射将导致其瘦肉组织占比下降、腓肠肌萎缩表明建模的可行性。此建模方法多采用幼龄小鼠，其引发的肌肉力量与功能的变化与人体相近，体重下降的表现与人体老年型肌少症有着些许不同[21]，且分子机制方面与自然衰老存在着不同[22]。目前国内外对此方法的认可度较高，但需对给药剂量与时长进行探究。

D-半乳糖（D-galactose）是一种还原性糖，被用于小鼠衰老模型建立[23]。王婧[24]发现 D-半乳糖干预会导致小鼠肌肉力量下降，运动能力减弱等。除此之外，小鼠还表现出衰老的一系列症状[25]，其原理为 D-半乳糖影响功能性代谢，导致机体出现类似衰老的生理变化[26]。此方法可逐渐增加衰老的程度，但对小鼠机体的恢复能力影响不大，如需研发肌少症治疗药物需对此点进行关注。

1.2　衰老模型

衰老是肌少症的主要影响因素[27]，因此衰老模型被广泛应用于肌少症的模型建立，目前较为常用的衰老模型建立主要通过运用自然衰老小鼠、快速老化小鼠、高脂喂养等方式。

自然衰老模型因其肌肉萎缩形态与老年人的形态最为接近，而且因其操作简单常被用于肌少症的研究。OH 等[28]研究发现老年小鼠的肌肉力量、质量和纤维大小明显低于年轻小鼠，可判定为肌少症。小鼠预期寿命为 24 个月，15 月龄小鼠相当于人体 50 岁，而雌激素的缺乏会导致肌少症的发生[29]。因此 15 月龄以上的雄性小鼠为最优选择。

快速老化小鼠的生存期短，在老年期表现出与老年人一样的衰老特征，建模时长也需 6 ~ 8 个月。NOGUCHI 等[30]将快速老化小鼠饲喂至 35 周龄，通过测定其肌肉质量、肌纤维横截面积及控制骨骼肌分解的蛋白水平证明其处于肌少症的患病状态。此模型被广泛应用于运动对肌少症的干预作用[31]及新药物治疗肌少症的评估[32]。

高脂喂养模型与其他衰老模型建立方法相比，时间相对较短，DOWLING 等[33]对小鼠喂养高脂饲料 8 周，发现其体重升高，耐力下降，肌肉质量比下降。PERRY 等[34]高脂喂养后同样发现其肌肉质量下降，同时其心脏的重量将会增加。除此之外长时间的高脂饲养将会对肝[35]、肾[36]等造成损伤，因此此方法使用较少。

1.3　肌肉萎缩模型

肌肉萎缩模型指通过去神经或固定关节导致的失神经性或废用性肌少症。此方法建模时间短，对设施要求低，但对实验人员的操作要求较高。

手术切除法是指通过切除小鼠腿部运动神经构建小鼠肌少症模型的方法，运动神经是控制骨骼肌生长发育的重要因素，去神经元会导致肌细胞形态和结构异常，从而导致肌无力，诱发肌少症。JEONG 等[37]横断小鼠右后腿坐骨神经发现小鼠肌肉纤维萎缩，形态和结构紊乱。切除坐骨神经会导致血清指标血管生成素样蛋白增加，同时活性氧的含量减少[38]，这两种物质的含量与骨骼肌萎缩相关。由于小鼠体型过小，导致切除小鼠腿部神经的操作对手术者要求高，因此研究者多采用大鼠建模。

后肢卸载模型是航天事业为模拟失重状态开发的一种动物模型。方法为将鼠尾固定至金属转盘上，使小鼠后肢抬起，15 d 就会导致骨骼肌萎缩[39]。但此模型导致的Ⅰ型肌肉萎缩，与衰老导致Ⅱ型肌肉萎缩并不一致，且对小鼠的恢复能力并没有影响[40]。此模型在应对卧床、微重力或不活动状态下的肌少症效果良好。

固定关节模型是指模拟骨折后石膏固定关节而构建的废用性肌少症模型，用石膏绷带固定小鼠腿部导致小鼠腿部无法活动，从而诱发肌少症。BURKS 等[41]用手术钉固定住小鼠腿部关节 21 d，发现固定后的肌肉减少是因为骨骼肌肌肉纤维的损失并不是肌肉纤维发生萎缩。固定关节可以很好的模仿患者患病在床的肌少症，但是其发病特征

与老年性肌少症特征有所区别,在对于老年形态的肌少症的研究中,此模型并不适用。

1.4 转基因模型

肌少症的发生与氧化应激、炎症、线粒体功能障碍密切相关。转基因模型通过控制基因表达,影响小鼠的肌肉含量,其优点在于与快速老化小鼠相比其建模时间更短。此方法包括基因敲除模型与基因过表达模型。

基因敲除模型是指将目的基因敲除或者其他基因替换目的基因从而构建小鼠模型,通过敲除小鼠体内白细胞介素 10,导致小鼠寿命变短老化速度加快,但问题在于小鼠会伴随小肠的炎症反应[42]。AHN 等[43]发现超氧化物歧化酶 1 的缺失会导致小鼠肌肉质量下降,其原因在于氧化应激将导致小鼠体内代谢失衡,从而减少骨骼肌蛋白质合成。视神经萎缩蛋白 1(opticatrophy 1, OPA1)和发动蛋白相关蛋白 1(dynamin-related proteinl 1, DRP1)基因双敲除小鼠的腓肠肌与比目鱼肌都会出现质量减少的症状[44],同时使小鼠发生全身炎症反应、加快衰老导致寿命减少[45]。

基因过表达模型是通过人为增加小鼠体内目的基因的表达,从而诱发肌少症。一些研究发现体内的炎症因子的过多积累会导致肌少症的发生,比如肿瘤坏死因子-α、白细胞介素-6[46]、C-反应蛋白、白细胞介素-1β 等。LI 等[47]研究发现通过对小鼠的 TNF 基因进行替换会导致小鼠腓肠肌中 TNF-α 水平升高,与此同时小鼠的肌力下降,同时发现老年小鼠的胫骨前肌、比目鱼肌和腓肠肌的质量相比年轻小鼠低。YOSHIDA 等[48]发现 Wnt/β-catenin 信号通路激活会导致小鼠的肌肉发生萎缩,(前)肾素受体((pro)renin receptor,(P)RR)表达可以激活 Wnt/β-catenin 信号通路,从而导致小鼠的肌少症。通过抑制(P)RR 的表达可以改善老年性肌肉萎缩。研究人员可根据研究目的挑选不同的转基因小鼠模型。

根据表 1 可知,4 种建模方法各有优缺,研究者

表 1 肌少症建模方法及特点

Table 1 Modeling methods and characteristics of sarcopenia

建模方法 Modeling method		优势 Dominance	不足 Deficiency	适用型 Applicable	参考文献 Reference
药物注射模型 Drug injection model	地塞米松 Dxamethasone	耗时短,操作简便 Short time-consuming, simple operation	存在并发症,易死亡 There are complications, easy to death	老年型 Veteran form	[20-22]
	D-半乳糖 D-galactose	耗时短,操作简单 Short time-consuming, simple operation	新颖,报道较少 Novel, less reported		[24-26]
转基因模型 Transgenic model	基因敲除 Gene knock-out	成功率高,耗时短 High success rate, short time-consuming	技术复杂 Technical sophistication		[43-45]
	基因过表达 Gene overexpression	成功率高,耗时短 High success rate, short time-consuming	技术复杂 Technical sophistication		[47-48]
衰老模型 Aging model	自然衰老 Natural aging	成功率高,与人体相似 High success rate, similar to the human body	时间成本过高 High time cost		[28-29]
	快速衰老 Rapid aging model	耗时短 Short time-consuming	模型建造复杂 Model construction is complex		[30-31]
肌肉萎缩模型 Muscle atrophy model	高脂喂养 High fat diet	花费低,操作简单 Low cost, simple operation	导致并发症 Lead to complications	肥胖型 Obesity	[33-34]
	手术 Operation	造模时间短,成功率高 Modeling time is short, success rate is high	难度高,易感染 Difficult and susceptible to infection	神经缺失型 Nervous absence type	[37-38]
	后肢卸载 Hindlimb unloading	耗时短,费用低 Short time-consuming, low cost	需专业设备 Need professional equipment,	失用型 Lost-use type	[39-40]
	固定关节 Fixed joints	耗时短,费用低 Short time-consuming, low cost	需专业设备 Need professional equipment		[41]

应根据研究内容(病理生理学及其进展或评估治疗效果)、预算、设备和时间要求选用合适的建模方法。

2　肌少症模型评价方案

模型的成功构建是实验研究的第一步,在建造小鼠模型时失误将导致造模失败,影响后续研究;若用造模失败的小鼠进行研究,可能会导致实验与理论结果出现较大差距,甚至对后续的检测、研究、开发产生极大影响,所以对小鼠模型进行评价是实验中极为重要的一步。肌少症的临床表现为肌肉质量下降、握力降低、步速下降等[49],目前对小鼠肌少症的评价主要是从肌肉功能、质量和力量 3 个方向。腓肠肌是下肢活动的重要肌肉,对于其骨骼肌的研究多数用腓肠肌作为代表[50],还可在其基础上测定其比目鱼肌、胫骨前肌等作为小鼠肌少症模型评判标准。常用的模型评价方案,见表 2。

表 2　小鼠肌力评测方法

Table 2　Mice muscle strength evaluation method

测评方法 Evaluation method		测量指标 Indicators of measurement	优势 Dominance	不足 Deficiency	参考文献 References
肌肉力量 Muscular strength	抓力仪 Grab force meter	前肢抓力,四肢抓力 Forelimb grip, limb grip	简单,方便快捷,指标明确 Simple, convenient and quick, clear indicators	需进行训练 Need to be trained	[51-53]
	网格实验 Grid test	四肢抓力,耐力,悬挂能力 Limbs grip, endurance, suspension ability	简单,价格低廉 Simple, low price	测试时间久 Test time is long	[54-55]
	强迫游泳 Forced swimming	肌肉耐力 Muscular endurance	简单,便捷,价格低廉 Simple, convenient and cheap	会造成小鼠死亡,血液获取困难 Ccause death of mice, difficulty in obtaining blood	[56]
肌肉质量 Muscle mass	电子计算机断层扫描 Computed tomography	骨骼肌厚度,面积,指数,CT 值 Skeletal muscle thickness, area, index, CT value	速度快,空间分辨率高 Fast speed and high spatial resolution	辐射剂量高,设备成本高 High radiation dose, high equipment cost	[57-58]
	双能 X 射线 Dual energy X-ray absorptiometry	骨骼肌质量及质量指数 Skeletal muscle mass and mass index	精度高,时间短,辐射低 High precision, short time, low radiation	设备昂贵,技术难度高 Equipment is expensive, technical difficulty is high	[59-60]
	核磁共振 Magnetic resonance imaging	骨骼肌面积,质量,脂肪含量 Skeletal muscle area, mass, fat content	准确度高,无辐射,软组织分辨率高 High accuracy, no radiation, high soft tissue resolution.	耗时长,设备成本高 Takes a long time, the equipment cost is high	[61]
肌肉功能 Muscle function	转棒式疲劳仪 Rotary rod fatigue tester	步速,耐力 Stride speed, endurance	操作简单,方便快捷,指标明确 Operation is simple, convenient and quick, the index is clear	需进行训练 Need to be trained	[62]
	跑步机 Treadmill	耐力,跑步距离,速度 Endurance, running distance, speed	操作简单,使用方便快捷,指标明确 Operation is simple, convenient and quick to use, clear indicators	需进行训练 Need to be trained	[63]

2.1　肌肉力量

肌肉力量欧洲老年人肌少症工作组在 2019 年修订了肌少症的定义,将肌肉力量下降作为肌少症的重要评价标准[1]。目前常用的小鼠肌力的评测方法有测定抓力、耐力等。测定抓力的方法有抓力仪测定实验[50]、网格测试[64]等。肌肉耐力的测定方法有强迫游泳实验、举重实验等。小鼠抓力仪测定肌力的方法为将小鼠放置于小鼠抓力仪上,水平向后拉动鼠尾,测定 3 次后取平均值或最大值记录小鼠抓力[52],此方法分为测定前肢抓力与四肢抓力[53]。网格测试操作步骤为将小鼠放置于网格间距为 12 mm 的铁丝网中间后倒置铁丝网,记录小鼠在铁丝网上停留时间[54],采用此种测试方法可测定小鼠的肌肉耐力与四肢抓力[55]。强迫游泳实验是指将小鼠尾部绑上重物,放置于泳池内,在其 5 s 内无法浮出水面时记录其游泳时间[56]。其中抓力因直观、简便在肌少症的模型检测方面较为常用,强迫游泳虽操作简单,但测试时易导致小鼠死亡。实验过程中需注意小鼠成长期间的体重变化,在实际操作中应排除体重带来的影响。

2.2　肌肉质量

目前双能 X 线吸收(dual energy X-ray

absorptiometry, DXA)、计算机断层扫描(computed tomography, CT)、磁共振(magnetic resonance imaging, MRI),可用于评估肌肉质量 DXA 是临床中最常用的诊断方式,这些影响学测定方法同样也适用于小鼠[65]。VAN DER HEYDEN 等[57]研究表明 CT 配合计算机算法可以准确的测定出小鼠的肌肉含量,PASETTO 等[58]研究出无需造影剂采用 CT 扫描测定肌肉含量的方法可广泛用于小鼠肌肉含量测定。DXA 法可以在无创条件下测定小鼠的肌肉与脂肪含量[59],此方法对人体辐射小,实验结果精确,测试时间短[60]。MRI 测定小鼠也是通过无创的方式进行,对软组织分辨率高,可以准确的测定肌肉含量[61]。其中 CT 与 MIR 可以最直接、最准确地测量骨骼肌质量,但使用方法成本较高。与人体不同,小鼠还可以通过解剖的方式对肌肉质量进行测量。

2.3 肌肉功能

通过测量步行 4 或 6 m 所使用的时间可以测量小鼠的肌肉功能[66],可以采用小鼠转棒式疲劳仪、小鼠跑步机间接测量小鼠的步速,小鼠跑步实验是指将小鼠放置于跑步机上,每 2 min 增加 0.2 m/s 的速度直至小鼠在电网停留超过 10 s 记录跑步时间和距离[67]。转棒式疲劳仪是通过测定小鼠在机器上掉落时的速度来测定小鼠步数[63]。水迷宫法也可以在很大程度上反映肌肉功能,多用来测量小鼠的学习记忆能力[68],也可做为评估肌少症小鼠的肌肉功能检测方法。

3 小结与展望

肌少症小鼠模型的建立对于研究肌少症的生理病理变化具有重大意义。肌少症小鼠模型的建立包括药物注射、衰老模型、转基因模型及骨骼肌萎缩模型等各有优缺点。需针对实验需求确定合适的建模方法。模型建造成功与否需要正确的评判标准,目前的评价标准主要从肌肉力量、质量及功能 3 个方面出发。模型建造的研究有一定进展,但对肌少症作用机制、治疗方案仍存在问题,因此需对肌少症的造模方法进行进一步探究,探究适用于各类型的造模方法,并制定统一的评价标准。

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