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肌源性因子参与骨与脂肪形成的研究进展及其应用前景

刘登峰[1]，田宝方[2,3*]

[1]济宁医学院临床医学院，山东 济宁
[2]济宁市第一人民医院急诊创伤外科，山东 济宁
[3]济宁市医学科学院创伤研究所，山东 济宁

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摘 要

肌源性因子是一种由肌肉分泌的细胞因子或蛋白质，具有调控肌肉发育和生长的作用。最新研究发现，肌源性因子在骨与脂肪的形成中也发挥了重要作用。本文综述了肌源性因子在骨与脂肪形成中的功能及其应用前景，为该领域的进一步探索提供参考。

关键词

肌源性因子，骨形成，脂肪形成，应用前景

Research Progress and Application Prospects of Myogenic Factors Involved in Bone and Fat Formation

Dengfeng Liu[1], Baofang Tian[2,3*]

[1]School of Clinical Medicine, Jining Medical University, Jining Shandong
[2]Emergency Trauma Surgery, Jining No. 1 People's Hospital, Jining Shandong
[3]Trauma Institute of Jining Medical Research Academy, Jining Shandong

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Abstract

Muscle derived factors are cytokines or proteins secreted by muscles that regulate muscle devel-

*通讯作者。

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opment and growth. The latest research has found that myogenic factors also play an important role in the formation of bone and fat. This article reviews the functions and application prospects of myogenic factors in bone and fat formation, providing reference for further exploration in this field.

Keywords

Muscle Derived Factors, Bone Formation, Fat Formation, Application Prospects

1. 引言

骨骼和肌肉是运动系统中的主要构成部分，共同接受内外环境等多种因素的调节控制。学术界通常认为肌肉与骨骼的相互影响的纽带主要是力学调控。随着研究的逐步深入，骨骼肌的内分泌功能日益得到重视[1] [2]。肌肉组织所产生的肌源性因子(Muscle-derived factors)能够通过旁分泌或内分泌方式影响临近组织以及肝脏、胰腺、大脑等多器官的生长与修复[3]。本文旨在综述几种典型的肌源性因子在骨骼与脂肪形成中的调控作用并对其应用前景进行了详细的探讨。

2. 骨与脂肪形成

骨组织的形成需经过间充质干细胞－成骨细胞－骨细胞等细胞分化及生长过程。在此过程中，成骨细胞和破骨细胞相互协作发挥作用。整个骨骼形成过程需要许多细胞内信号以及相互作用的分子来促进增殖和分化[4]。

脂肪形成是间充质干细胞向成脂方向分化，逐步积累甘油三酯，最终成为成熟脂肪细胞的过程，主要分为成脂分化的相关受体表达阶段和脂质积累阶段[5]。

3. 肌肉的内分泌功能

既往的研究认为，肌肉与骨骼的相互影响的纽带主要是力学作用，然而肌肉的内分泌功能近年来逐渐得到重视。肌肉能够分泌多种肌源性因子，这些因子通过旁分泌或血液循环的方式到达各种器官，并发挥特定的功能[6] [7]。通过对多篇文献的查询与归纳，对于骨形成与脂肪形成作用比较明显的肌源性因子主要有肌生长抑制素(myostatin, MSTN)、鸢尾素(irisin)、胰岛素样生长因子-1 (insulinlike growth factor-1, IGF-1)、成纤维细胞生长因子-2 (fibroblast growth factor-2, FGF-2)、成纤维细胞生长因子-21 (fibroblast growth factor-21, FGF-21)、白血病抑制因子(leukemia inhibitory factor, LIF)等[8]。

4. 对骨脂形成具有调控作用的肌源性因子

多种肌源性因子对骨骼形成与脂肪形成具有不同程度的调控作用，且效能不一。下面将列举几种比较经典的肌源性因子，并详细探讨其对骨骼与脂肪形成的效用机制。

4.1. 鸢尾素(Irisin)

鸢尾素是由骨骼肌合成并分泌的一种多肽片段。Bostrom 等研究人员于 2012 年首次发现鸢尾素可由

运动的骨骼肌产生和释放[9]。运动的肌肉组织可通过氧化物酶激活受体共激活物-1α (PPARγ coactivator-1α, PGC-1α)促进纤连蛋白 III 型结构域蛋白 5 (fibronectin type-III domain-containing protein 5, FNDC5)过量表达，最终形成鸢尾素[9]。鸢尾素对成骨分化的调控作用主要体现在以下方面：通过激活 αV 整合素诱导的蛋白激酶/信号传导及转录激活蛋白(ERK/STAT)通路，增强骨形态发生蛋白 2 (BMP2)信号促进成骨[10]；通过 AMP 依赖的蛋白激酶(Adenosine 5’-monophosphate (AMP)-activated protein kinase, AMPK)介导的巨噬细胞极化和 Wnt/β-连环蛋白通路(Wnt/β-catenin pathway)激活自噬，促进骨髓间充质干细胞成骨分化[11] [12] [13]。此外，Oranger 等人的研究表明，鸢尾素还通过血管等骨周围组织生长，从而间接促进骨质形成[14]。对于成脂分化，Yuan Zhang 的实验结果证实鸢尾素可以减少成脂基因的表达从而抑制脂肪细胞形成[15]。Eun Bi Ma 团队的研究结果显示外源性和内源性鸢尾素都能通过 Wnt 蛋白抑制脂肪形成[16]。值得注意的是 Wnt 通路，鸢尾素可通过此通路同时对间充质干细胞产生抑制成脂分化和促进成骨分化的作用，是影响脂肪形成和骨骼形成的作用途径交叉点[12] [16]。

4.2. 白血病抑制因子(Leukemia Inhibitor Factor, LIF)

白血病抑制因子，又称分化刺激因子或分化诱导因子，是白细胞介素-6 (interleukin, IL-6)蛋白家族的成员，其受体在多种组织或器官中广泛表达[17]。LIF 通常与其受体复合物及糖蛋白 130 结合，从而产生生物学作用[18]。尽管也有部分实验显示某些特殊环境下(高糖)，LIF 会抑制早期的成骨分化进程[19]，然而更多结果趋向于 LIF 促进骨髓基质细胞向成骨细胞谱系的分化。LIF 主要通过以下途径影响成骨分化进程：① 通过抑制骨细胞中硬化蛋白的表达来促进骨形成[20] [21]。② LIF 可以激活丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路，诱导生长因子受体结合蛋白 2 (Growth Factor Receptor Binding Protein 2, GRB2)的表达，促进 Runt 相关转录因子 2 (Recombinant Runt Related Transcription Factor 2, RUNX2)和碱性磷酸酶(alkaline phosphatase, ALP)的表达，而 RUNX2 与 ALP 均是成骨分化的标记物[22]。③ LIF 通过暴露后立即和成骨细胞分化过程中激活(signal transducer and activator of transcription 3, Stat3)信号，然后激活 Mapk/Erk 和丝氨酸/苏氨酸蛋白激酶(Serine/Threonine Kinase, Akt)信号来改善成骨细胞分化[23]。LIF 对于脂肪形成的研究较少，许多研究人员发现，LIF 在脂肪细胞分化的早期和晚期均抑制了 Wnt 信号分子的表达水平，提示 LIF 可能作为 Wnt 信号通路的负调控因子，介导其对脂肪细胞分化的抑制作用[24]。不过，也有研究发现在脂肪细胞中，LIF 通过 MAPK 通路促进前脂肪细胞表达早期成脂肪转录因子 CCAAT 增强子结合蛋白 β (CCAAT enhancer binding proteins, CLEBPβ)和 CCAAT 增强子结合蛋白 δ (CCAAT enhancer binding proteins, CLEBPδ)，从而诱导脂肪细胞分化[25]。这些不一致的结果可能与细胞和组织的不同发育阶段有关[26]。总体来说，LIF 的生物学作用仍然是促进骨髓基质细胞向成骨细胞谱系的分化，同时抑制其成脂分化，但其生物学作用受细胞生长发育阶段等因素影响。

4.3. 胰岛素样生长因子-1 (Insulinlike Growth Factor-1, IGF-1)

IGF-1 主要激活两条主要的下游信号通路——磷酸肌醇 3-激酶(PIK3/AKT)通路和丝裂原活化蛋白激酶(RAS/MAPK)通路，从而发挥促进细胞增殖、分化等效应[27]。在骨骼形成以及脂肪形成领域，IGF-1 的研究较为成熟。Ran, G、Jiang, H 等的实验已经可以表明 IGF-1 可通过 P38/JNK 通路、PI3K/AKT/COX-2 通路、Wnt/β-catenin 通路等促进骨骼形成[28] [29] [30]。在骨再生修复组织工程领域中，经过实验研究，工程嵌合钛材料、3D 打印钛等支架等工程材料可以有效地介导胰岛素样生长因子-1 及其受体的生物效用，从而促进骨骼的生成和修复[31] [32]。对于脂肪形成方面，IGF-1 在骨髓肥胖的调节中起负向作用[33]，血浆 IGF-1 与骨髓脂肪组织形成呈负相关[34]。在一项横断面研究中，IGF-1 水平较高的绝经前肥胖女性

的脊椎骨髓脂肪含量较低，与年龄和身体质量指数无关[35]。此外，有实验研究表明，从血清 IGF-1 减少的小鼠中获得的间充质干细胞显示了比对照组更大的成脂潜能[36]。由此可见，IGF-1 对于脂肪生成的抑制作用以及对成骨分化的促进作用比较确切，但其作用机制仍未明确。

4.4. 肌生长制抑素(Myostatin, MSTN)

肌生长抑制素又称为生长分化因子 8 (growth differentiation factor-8, GDF-8)，属于转化生长因子 β (TGFβ)细胞因子家族，其分泌水平与肌肉废用、损伤和骨骼肌减少症的状态相关[37]。肌肉生长抑制素可抑制 Wnt/β-catenin 通路，从而减少成骨细胞的分化和减少 RUNX2 等成骨相关转录因子的分泌[38]。Suh 及其同事的实验结果显示，MSTN 基因敲除的小鼠细胞具有更高的分化潜能[39]。对于脂肪形成方面，Shifeng Pan,等人发现 MSTN 能够通过激活 ERK1/2 信号通路和抑制 PPAR-γ 等相关成脂基因的表达来抑制脂肪形成[40]。Wen Guo 等人的研究显示，肌肉生长抑制素可以促进 Smad 蛋白 3-β-连环蛋白-T 细胞因子复合物(Smad3-β-catenin-TCF4)的形成从而对脂肪生成的产生抑制作用[41]。综上，与以往的骨骼与脂肪的分化平衡不同，肌肉生长抑制素对于这两种分化方向的影响并没有此消彼长的趋势，其对于骨骼形成以及脂肪形成均有抑制作用。

4.5. 肿瘤坏死因子-α (Tumor Necrosis Factor-α, TNF-α)

TNF-α 是一种促炎细胞因子，与调节炎症、凋亡、趋化因子产生和代谢相关，也属于肌源性因子家族中的一员[42]。以往的研究表明，高水平的 TNF-α 可以通过 Wnt/β-catenin 信号通路降低成骨细胞的活性[43] [44] [45]。有趣的是，Qi Yuping 的实验结果显示，低浓度的 TNF- α 可以通过抑制 AKT/mTOR 通路激活自噬，促进人牙周韧带干细胞成骨分化[46]。Qingyun Mo 等整合了以往 TNF-α 对骨骼形成的结论与争议，发现肿瘤坏死因子 α 对骨髓间充质干细胞成骨分化的促进或抑制作用主要取决于其剂量浓度：低浓度的 IL-1β 和 TNF-α 可刺激骨髓间充质干细胞在体外成骨分化；高浓度的 IL-1β 和 TNF-α 是成骨过程中的负调节剂[47]。在不同物种或者细胞类型中，TNF-α 促进成骨分化及抑制成骨分化的界限值也有所不同[47]。在脂肪形成方面，有研究表明，与未刺激的对照组相比，TNF-α 刺激组表现脂肪细胞的特异性染色效果不佳[48]。不过 TNF-α 对于脂肪分化是否也随着剂量浓度的不同而变化仍未可知。总之，TNF-α 对于脂肪形成及骨骼形成的影响主要为：低剂量的 TNF-α 促进骨质形成，抑制脂肪形成，介导骨/脂分化平衡；而高剂量的 TNF-α 对于二者的分化方向均为抑制作用。

5. 肌源性因子的应用前景

5.1. 作为骨骼健康度的检测指标

骨质疏松是常见的全身代谢性骨骼疾病，绝经后的老年女性全体尤为多见。其发病机制与骨髓微环境中的骨脂信号网络密切相关[49]。作为调控脂肪形成与骨骼形成的重要因素，肌源性因子在预防骨质疏松及监测骨骼健康度领域具有极高的潜力。彭竑程等对 184 例绝经后女性骨质疏松患者进行骨折风险与肌源性因子的相关性研究，结果显示患者骨折概率与肌源性因子 MSTN 等含量成正相关，与鸢尾素等呈负相关关系[50]。Hu Wei 等学者发现，FGF21 与中国绝经后女性的骨密度相关，与腰椎压缩性骨折风险成正相关[51]。由这些结论可以得出，肌源性因子对于骨质疏松及骨折风险具有一定的相关性，可以考虑作为疾病的监测指标之一，然而骨质疏松与肌源性因子的生物学机制仍待探究。

5.2. 辅助骨缺损修复

骨缺损的定义为骨的结构完整性被破坏，常由创伤、感染、肿瘤以及先天性疾病等因素造成。目前

骨缺损的主要治疗方法有自体骨移植、骨搬运手术、膜诱导成骨等。近些骨组织工程技术发展迅速，为骨缺损疾病的治疗提供了新的治疗思路[31]。支架、细胞、生长因子是骨组织工程的三要素。而本文探讨的肌源性因子是极具潜力的调节骨骼形成的细胞因子。Sandra Stamnitz 的团队曾探究过 FGF-2 和 BMP-2 对接种于纳米羟基磷灰石涂层聚己内酯/羟基磷灰石/β-磷酸三钙(nHAP 涂层 PCL/HAP/β-TCP)支架上的绵羊骨髓间充质干细胞体外成骨能力的影响，发现 FGF-2 和 BMP-2 增强了在支架上生长的 MSCs 的成骨分化潜能[52]。这种组织工程构建物很有希望用于较大的骨缺损疾病的治疗。虽然目前肌源性因子相关的支架研究和体内应用较少，这类因子作为生长因子参与骨组织工程治疗骨缺损具有很大的应用潜力与前景。

5.3. 辅助诊断肥胖症等代谢性疾病

肥胖症通常被概括为身体脂肪的过度或异常积累超过理想体重 20%以上，是一种由遗传因素、环境因素等多种原因相互作用而引起的慢性代谢性疾病[53]。肥胖症患者机体中的脂肪组织功能障碍导致低度慢性炎症，促炎性途径的激活和脂肪因子释放等是其发病机制之一[54]。肌源性因子的分泌异常可能在其中发挥作用[55]。肌肉生长抑制素(MSTN)在肥胖动物模型中上调，并且在女性肥胖这中观察到肌生长抑制素水平升高[56]。Jan Baczek 等人的研究指出肌生长抑制素和 TNF-α 是肌减少性肥胖症一种可行的生物标志物，但这两种肌源性因子的合成与分泌易受到身体活动、年龄等因素影响[57]。此外，IL-6、肌肉生长抑制素、鸢尾素等肌源性因子是 2 型糖尿病、骨骼肌减少症等年龄相关和代谢性疾病发病机制的重要参与者[58] [59]。因此，肌源性因子可以考虑作为肥胖症等代谢性疾病的动态观察指标之一。

6. 展望与总结

肌肉作为运动系统的重要组成部分，其内分泌功能不容小觑。骨骼、脂肪与肌肉之间存在错综复杂的调节网络系统。肌肉收缩诱发的肌细胞分泌的一系列肌源性因子，对骨骼与脂肪的形成起着重要作用。鉴于肌源性因子在成骨分化和脂肪形成中的效能，其在评估骨质健康状态、修复骨缺损以及辅助评估肥胖症等代谢病等领域展示出广阔的应用前景。然而，肌源性因子仍然面临许多亟待解决的问题。部分肌源性因子在不同物种及剂量条件下表现出特异的生物效应。作为一种繁杂的细胞因子体系，肌源性因子之间的相互作用尚需进一步探索。目前，各类肌源性因子在骨骼生成及脂肪形成中的效能评估尚未建立标准化的评价体系。对于骨再生领域，寻求促进骨形成的肌源性因子及生长因子的最佳比例可以作为未来研究的重点之一。

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