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鸢尾素与骨代谢相关性

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摘　要

鸢尾素是一种由骨骼肌分泌的肌细胞因子，在骨代谢中起主要作用。大量的试验数据表明，鸢尾素可促进骨生成，保护骨细胞免受地塞米松诱导的细胞凋亡，防止骨和肌肉质量损失，并加速骨折愈合。在绝经后女性和老年男性中观察到血清鸢尾素水平降低，与骨质疏松症和骨折的风险增加相关。本片综述将从鸢尾素的来源以及和骨的生成和代谢，分析出鸢尾素与骨代谢之间的相关性。

关键词

鸢尾素，骨代谢，骨质疏松

Correlation between Irisin and Bone Metabolism

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Abstract

Irisin is a myokine secreted by skeletal muscles and plays a major role in bone metabolism. A substantial body of experimental data suggests that irisin can promote bone formation, protect bone cells from dexamethasone-induced apoptosis, prevent the loss of bone and muscle mass, and accelerate fracture healing. Lower serum levels of irisin have been observed in postmenopausal women and elderly men, associated with an increased risk of osteoporosis and fractures. This review will cover the origins of irisin as well as its role in bone formation and metabolism, analyzing the relationship between irisin and bone metabolism.

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Keywords

Irisin, Bone Metabolism, Osteoporosis

1. 鸢尾素的来源

在骨骼肌中发现的几种其他肌因子如 IL-15、IL-6、IL-8、白血病抑制因子、FGF 21、BDNF 等，除此之外，还有一种新发现的肌细胞因子，Irisin，由 Bostrom 等人于 2012 年首次报道，据报道，它是一种能够诱导脂肪组织变化并激活产热作用的分子[1]。鸢尾素的主要来源是骨骼肌，但白色脂肪组织、胰腺、心肌和肝脏也被确定可以分泌鸢尾素[2]。

2. 鸢尾素的作用

早期研究表明，鸢尾素主要通过增加能量消耗上调 UCP 1 表达，将 WAT (白色脂肪组织)转化为 BAT (棕色脂肪组织) [1]，肌因子鸢尾素是一种在辅激活因子 1-α (PGC1α)控制下骨骼肌收缩后通过膜蛋白 5 (FNDC 5)裂解分泌到血液中的蛋白质[1]。近期有研究发现，鸢尾素参与改善葡萄糖耐量和帮助改善胰岛素抵抗[3]。鸢尾素通过促进 AMPK 磷酸化激活 AMPK 下游信号系统，从而上调 PPARα、HK2、GLUT4 等促进糖、脂分解代谢的基因表达，降低 PCK1、肌型糖原磷酸化酶、G6PC 等促进葡萄糖生成的基因表达[4]。因此，鸢尾素/AMPK 通路改善胰岛素抵抗的重要分子机制。鸢尾素在中枢神经系统中也有一些有益的作用[5] [6]，并且它激活脑组织中的 AKT 和 ERK 信号通路[5]。此外，鸢尾素调节 AD (阿尔茨海默病)的一些风险因素[7]，其包括改变的神经发生、氧化应激、胰岛素抵抗和神经营养因子的失衡。已发现鸢尾素在各种病症中具有重要作用，包括海马神经发生、炎症、衰老和其他代谢病症[8] [9]。各种研究已经发现了鸢尾素的重要生物学作用，例如调节抑郁行为[10]、增殖成骨细胞[11]和皮质骨质量[12]。由于鸢尾素在体内具有多种生理作用，因此引起了广泛的研究。本文综述了鸢尾素与骨代谢的关系。

3. 骨骼生成与代谢

骨构成主要由有机和无机化合物组成的矿化多孔结构。有机成分主要包含胶原纤维和非胶原蛋白形成的矿化细胞外基质，以及成骨细胞、破骨细胞和骨细胞[13] [14]。骨骼的主要功能包括为内部器官提供结构支撑和保护，同时作为运动系统的肌肉组织的锚固点。此外，骨骼作为钙(Ca)和磷(P)等必需矿物质的储存库，对维持矿物质体内平衡至关重要，因此发挥着重要的代谢作用。骨骼系统由钙化组织(即骨)组成，其由约 60%的无机成分(羟基磷灰石)，10%的水和 30%的有机成分(骨基质蛋白)组成[15]。骨骼含有必需的矿物质，包括钙、磷和镁，它们结合在一起以促进羟基磷灰石晶体的沉积，这一过程对骨矿化有重要作用[16]。近年来，骨骼被认为是一种内分泌器官，具有合成各种物质的能力，如成纤维细胞生长因子 23 (FGF-23)、硬化素和骨钙素[17] [18]。

骨作为一种代谢活性组织，会经历持续的重塑，其特征是通过破骨细胞去除旧骨，随后主要通过再吸收和形成过程被成骨细胞形成的新骨替代[19]。在其整个生命周期中都会经历大量的变化。一系列因素，包括遗传异常，激素紊乱和营养缺乏，干扰了强壮和健康骨骼的发育[20] [21]。在青年期，骨形成和骨吸

收之间的平衡保持相对稳定。随着个体在衰老过程中的进展，骨形成和吸收之间的平衡发生了明显的变化，倾向于增加吸收率。因此，骨密度逐渐下降，增加了骨骼脆弱性的易感性。保持最佳体重，摄入足够的 Ca 和维生素 D，以及定期的体力活动对这个阶段的骨骼健康至关重要[20]。在高龄时，骨丢失可能会加速，从而增加骨质疏松症和脆性骨折的风险，强调了旨在保持骨骼完整性和避免不良结局的积极措施的必要性[21]。

4. 骨质疏松

作为现代科学的主要成就，预期寿命的增加导致人口平均年龄的提高，从而导致老年人典型的慢性疾病发病率增加，如骨质疏松症[22]。骨质疏松症是一种多原因导致的骨骼疾病，其特征是骨微结构的恶化和骨折风险的增加[22]。通常，患有骨质疏松症的老年人群通常伴随着肌肉减少症，这会逐渐导致肌肉质量和力量的损失，从而增加骨折的风险[23]。骨质疏松症的特征是骨量和强度降低，导致骨质脆性增加进而发展为骨折，世界卫生组织给出的定义是通过双能 X 射线吸收测定法(DXA)测定的髋关节和/或脊柱骨密度(BMD)与健康年轻成人的骨量相比小于 2.5 标准差[24] [25]。其发病率随着人口老龄化而上升，影响全球超过 2 亿人，每年导致约 890 万例腰椎骨折[26]。骨质疏松性骨折导致第一年内死亡率增加(20%~40%)，并导致受影响个体丧失独立性和生活质量[27]。骨质疏松已经严重影响个体的生活质量，甚至对家庭造成了巨大的精神及财产损失，需要对骨质疏松加强关注度，避免恶性事件发生。

5. 骨代谢生物标志物

评估骨代谢的生物标志物在临床环境中广泛使用，但经典的生物标志物如钙(Ca)、磷(P)、甲状旁腺激素(PTH)、骨特异性碱性磷酸酶(BALP)、I 型前胶原延伸肽(I 型前胶原延伸肽)、骨钙素(OC)和骨特异性碱性磷酸酶(BALP)。氨基-NTX-1 和羧基－末端交联端肽具有局限性，包括低特异性(由于在骨以外的组织中合成)、低敏感性、对饮食、年龄、性别或昼夜节律影响的敏感性，以及肾衰竭时的潜在变化。一些，如半乳糖基羟基赖氨酸[28]，由于缺乏简单的常规测定方法，临床应用仍然有限。此外，在不同的研究中评估其作为骨质疏松症或血管钙化生物标志物的作用的相互矛盾的结果构成了挑战。例如，考虑骨桥蛋白(OPN) (骨吸收的经典生物标志物)对成骨细胞的影响：某些研究表明 OPN 诱导成骨细胞的增殖和分化，并促进骨中的矿化[29]。相反，其他研究提出了相互矛盾的证据，提出 OPN 抑制成骨细胞中的这些过程[30]。也有研究报告 OPN 对成骨细胞发育无明显影响[31]。尽管存在这些缺点，但经典生物标志物在临床实践中对于监测和分析患者进展仍然是非常宝贵的。

6. 鸢尾素与骨代谢的关系

Irisin 可增加疾病相关骨质减少症中皮质组织的骨量和矿物质密度[32]。通过促进成骨细胞基因的表达、降低成骨细胞抑制基因的表达和减少破骨细胞来实现[12] [33]。在骨髓中，通过给予鸢尾素，基质细胞可以更有效地分化为成熟的成骨细胞[34]。鸢尾素治疗以剂量依赖性方式增加血浆 sclerostin (骨细胞的一种特异性产物，可引起骨吸收并启动骨重塑)水平以及骨细胞培养物中 sclerostin 的 mRNA 水平[35]。所有这些结果可以说明，鸢尾素能够在体外作用于骨细胞使其减少凋亡，并可以在体内促进 sclerostin 表达水平[35]。体外研究表明，鸢尾素促进成骨细胞的增殖，并提高成骨细胞转录调节因子如 osterix/sp 7、Runt 相关转录因子 2，增加成骨细胞分化标志物包括碱性磷酸酶、I 型胶原 α-1、骨桥蛋白和骨钙蛋白的表达水平[33]。此外，鸢尾素可以增加培养的成骨细胞中的钙沉积和碱性磷酸酶的活性[33]。鸢尾素通过激活 ERK 和 p38 MAPK 途径发挥其成骨作用。这得到了以下研究的支持，即用特异性抑制剂抑制这些途径导致降低鸢尾素对碱性磷酸酶活性和 Runx 2 表达的上调作用。表明鸢尾素可以直接作用于成骨细胞，

并激活 P38/ERK MAPK 信号通路诱导成骨细胞的分化和增殖[33]，这些发现与 Colaianni 最近的研究结果一致，该研究表明鸢尾素通过 ERK 信号通路诱导骨髓基质细胞的成骨分化[12]。除了刺激骨重塑外，鸢尾素还作为一种反调节激素发挥作用，因为它直接作用于破骨细胞前体细胞以增强分化并促进骨吸收。RNA 序列显示，鸢尾素刺激差异基因表达，包括上调破骨细胞的再吸收和分化标志物[36]。鸢尾素的临床试验表明对骨形成有积极作用。Serbest 等人报告称，在骨折愈合过程中，血液中的鸢尾素浓度增加，并且由于鸢尾素受体存在于人体骨组织中，因此骨折愈合受到影响[37]。在另一项研究中，发现女性运动员(没有月经)的鸢尾素水平低于月经失调的运动员和非运动员[38]。此外，在所有运动员中，鸢尾素浓度与体积骨矿物质密度(BMD)之间呈正相关[38]。最近，已证明鸢尾素缺乏会导致骨代谢紊乱[39]。在成骨细胞谱系中，FNDC 5/irisin 缺失，从而产生 FNDC 5/irisin KO 小鼠。在骨骼的基因和蛋白质水平上，鸢尾素的表达显著降低，导致骨密度降低和骨发育延迟[39]。

7. 结论

鸢尾素在骨代谢方面是一个新的、具有关键作用的因子，它可以促进骨吸收，与骨形成呈正相关，与骨质破坏呈负相关。它正在成为一个潜在的治疗剂，用于治疗骨骼疾病。此外，这些发现在人类上的扩展将鼓励使用鸢尾素作为治疗剂用于治疗和预防骨质疏松症和其他骨相关疾病。

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