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·综述·

铁调素与骨质疏松鼠

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中图分类号：R68 **文献标识码**：A **文章编号**：1006-7108(2017)02-0256-03

摘要：骨质疏松是一种骨代谢异常，成骨、破骨功能失衡所致的全身性疾病，骨质疏松常见于绝经后女性，而绝经后十年的女性往往会出现铁蓄积，所以将铁蓄积与骨质疏松症联系起来的研究越来越多。铁调素(Hepcidin)作为调节机体铁稳态的一类抗菌多肽被人们重视，铁调素的相关研究有了越来越多的研究报道，作为传统的模式动物小鼠，铁调素基因在小鼠中的研究进展颇多。本综述旨在拓展了小鼠作为模式动物研究铁调素的认识。

关键词：铁调素；小鼠；基因表达

Hepcidin and osteoporosis in mice

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Abstract: Osteoporosis is a systemic bone metabolic disease caused by the imbalance function of osteoblasts and osteoclasts. Osteoporosis is common in postmenopausal women and postmenopausal women tend to have iron accumulation in the first decade after menopause. Research on the associations of iron accumulation and osteoporosis has received more and more interest. Hepcidin, an antibacterial peptide, can regulate the body's iron homeostasis, and a growing number of studies have reported its importance. This review aims to expand the use of mice as an animal model in hepcidin research.

Key words: Hepcidin; Mouse; Gene expression

骨质疏松(osteoporosis)是机体非特异性内分泌紊乱而导致的全身骨量减少的代谢性骨病[1]。骨质疏松的病理改变是骨的韧性下降，脆性增加，轻度外伤即可发生骨折。随着我国人口老龄化问题的突出，骨质疏松症的治疗也显得越来越重要。然而，关于骨质疏松症的发病机理和治疗目前尚不完全清楚和肯定，实践中仍然有许多问题尚待解决，因此研究骨质疏松的相关机理依然是一项十分有价值的工作。近几年来，许多研究发现体内铁代谢与骨的矿化有着密切联系[2-4]。那么在骨质疏松的发生过程中是否存在铁代谢异常现象就显得十分有实用价值。铁是机体必需的微量元素之一，体内许多生化反应都需要铁参与，如血红蛋白、细胞色素、各种氧化还原酶的组成。体内铁稳态需要铁调素(hepcidin)的调节，其机理为：铁调素与膜转铁蛋白结合，使其降解失去活性，从而阻断了胞内铁向胞外转移，使胞外铁降低[5-7]。铁代谢与骨代谢相关性的研究越来越深入，很多影响骨代谢的因素同时也涉及到铁代谢。Andriopoulos等[8]报道，铁调素的功能与作为重要骨代谢指标的骨形成蛋白(BMP)紧密相关。同年，Meynard等[9]报道，敲除BMP基因老鼠体内铁调素表达水平极为低下，其肝脏、心脏、胰脏的腺泡细胞和肾小管上均出现了严重的铁沉积现象。铁不足会使骨密度降低[10]，而铁超载与骨质疏松密切相关[11]。有报道股骨颈骨折、地中海贫血、血色病、吸烟、过量饮酒、感染及停经等引起的骨质疏松，有一个共同的特点，即体内铁的超载[12-15]。见图1。

关于铁调素本身的研究以及与铁调素相关的研究已取得了很多进展[16-18]，有研究提出“铁介导性

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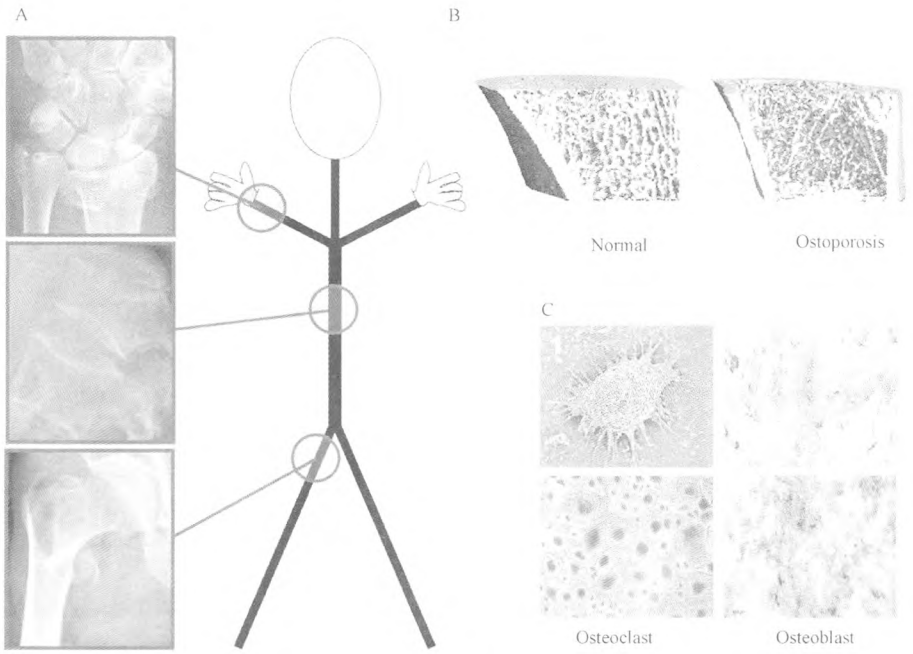

图 1 骨质疏松是一个系统性的疾病，当骨的重吸收超过骨的形成，并导致其微小的结构的改变。A 脆性骨折易发生在患者的腕关节，脊柱和髋关节。B 小鼠的骨质疏松骨与正常组的 mirco CT 的比较。C 微观的成骨细胞的骨形成和破骨细胞的吸收收；1 一个破骨细胞独特的形态；2 -破骨细胞 TRAP 染色；3 图片示多个成骨细胞矿化矩阵（白色箭头）；4 茜素红染色显示的是矿化的成骨细胞分泌细胞外基质。

Fig. 1 Osteoporosis is a systemic disease, when reabsorption of bone exceeds bone formation, a change of bone microscopic structure occurs. A. Brittle fractures occurred in osteoporotic patients at wrist, spine and hip. B. The micro CT of osteoporosis mice compared with normal group. C. Microscopic bone formation of osteoblast and bone reabsorption of osteoclast. 1 A unique form of osteoclast; 2 TRAP staining of an osteoclast; 3 Images of multiple osteoblast mineralization matrix (white arrow); 4 Alizarin red staining shows the mineralized osteoblasts secreting extracellular matrix.

骨异常”不同于以往研究的循环代谢异常，是另一类导致骨异常的因素。在这类因素中：(1)铁调素参与着体内铁的动态平衡调节；(2)体内铁的动态平衡影响着骨代谢、影响着骨矿化过程。因此，将两者结合起来，在骨质疏松研究领域，观察、研究“铁代谢调节因素（铁调素）”在“骨代谢异常（骨质疏松）”过程中的作用，对骨质疏松症的机理、治疗将有着十分积极的临床意义；这还因为铁调素已开始进行人工合成研究，已有学者正致力于将铁调素商品化；如能及早、全面了解铁调素对骨组织异常的影响机制，将对骨质疏松治疗新的干预方法研究有着十分重要的现实意义。

Liu 等[19]通过观察去势大鼠骨质疏松模型给予铁螯合剂，发现骨量丢失和骨微结构破坏得到缓解，提示绝经后骨质疏松与骨组织中铁沉积密切相关。Tsay 等[20]对铁超载小鼠模型研究发现活性氧起着重要作用，说明氧化应激可能是铁超载引起骨质疏松的一个重要机制。李君平等[21]研究发现去卵巢小鼠血清铁水平较假手术组降低，刘禄林等[22]发现去卵巢大鼠血清铁水平与假手术组的差异无统计学意义，这可能与动物周龄及干预时间有关，还需进一步研究。有文献报道，细胞内铁积累会通过氧化反应产生活性氧（ROS）[23-25]，而 ROS 能够促进破骨细胞的分化，增强骨吸收[26]。Lj 等[27]认为高铁通过诱导氧化应激及肿瘤坏死因子促进破骨细胞分化，增加骨吸收。Jia 等[28]用枸橼酸铁铵（FAC）培养 RAW264.7 发现，破骨细胞数随 FAC 浓度增加而增加，提示高铁环境下破骨细胞活性明显增强。对于成骨细胞，Yamasaki 等[25]报道铁过载会抑制其增殖，Yang 等[28]发现高铁使前成骨细胞保持在未分化状态。徐又佳等[30]和王冰等[31]发现，维甲酸及糖皮质激素所致骨质疏松模型伴有铁调素表达变化，提示铁调素在其他类型骨质疏松发生发展过程中也有一定作用。

铁调素可显著增加去卵巢大鼠的骨密度，改善力学性能。铁调素对骨代谢影响的具体机制还需进

一步研究,针对铁调素及其他去铁剂的研究可能为绝经期后骨质疏松的防治提供更多思路。

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