中国骨质疏松杂志 2011 年 11 月第 17 卷第 11 期 Chin J Osteoporos, November 2011, Vol 17, No. 11
Published online www.wanfangdate.com.cn doi:10.3969/j.issn.1006-7108.2011.11.022

· 综述 ·

骨细胞对破骨细胞形成和功能的影响

张冬燕 扈英伟

中图分类号：R336 文献标识码：A 文章编号：1006-7108(2011)11-1031-03

摘要：破骨细胞的骨吸收作用和成骨细胞骨形成作用的交替进行维持了骨量的平衡。破骨细胞可以选择性吸收损伤部位的骨质，其激活和定位机制目前还未阐明。近年来的研究认为骨细胞是感知骨环境的基本单位，而且骨细胞还可以将所感知的信号传递给其它骨细胞，骨衬细胞，成骨细胞及破骨细胞等。对骨细胞和破骨细胞的研究中发现骨细胞可能在破骨细胞的激活和定位中起到了重要的作用，但是具体机制还有待研究。

关键词：骨细胞；破骨细胞

The effect of the osteocyte on the formation and function of the osteoclast

ZHANG Dongyan[1], *HU Yingwei*[2]. [1]*Department of Dental Biomedical Laboratory, Institute of Dental Medicine of Shandong University*; [2]*Department of Dental, Qilu Hospital of Shandong University, Jinan* 250012, China
Corresponding author: HU Yingwei, Email: huyingwei@sdu.edu.cn

Abstract: The balance of bone mass is maintained by osteoclastic bone resorption and osteoblastic bone formation. Osteoclasts can selectively resorb bone at damaged sites. The mechanism of activation and localization ave not been clarified yet. Recent research finds that the osteocyte is the basic unit to sense the bone environment and they can transfer the sensed singles to other osteocytes, lining cells, osteoblasts, and osteoclasts. It has been found that the osteocyte may play an important role in the activation and localization of the osteoclast. However, the specific mechanism need to be studied.

Key words: Osteocyte; Osteoclast

在正常情况下，骨组织是承受机械负荷的主要结构，并且骨组织有自我检测、清除并修复受损或机械承受力不强的骨质[1]。机械负荷过重导致的骨骼结构损害或者激素紊乱导致的骨组织内环境平衡的破坏，都会引发骨质的重塑过程[2]。具体的机制是什么，目前的了解还不够充分，不少学者把目光放在了骨细胞的研究上。

1 骨细胞

骨细胞是骨组织中含量最多的细胞类型。在骨形成的晚期，成骨细胞嵌入骨基质中终末分化为骨细胞，位于充满基质(90% ~95%)的骨陷窝中[3]。这些骨细胞与具有活跃的形成并分泌蛋白能力的成骨细胞相比较，骨细胞胞质中含有更少量的细胞器，分泌合成蛋白质的能力更低。但是骨细胞的生存时间为 10 ~20 年，相对于成骨细胞(几个月)和破骨细胞(两周以内)要长的多[4]。

2 骨细胞对骨组织有保护作用

骨细胞对骨基质具有保护作用，对骨结构的完善和机械强度的维持有重要作用。骨细胞会产生转移生长因子 β(TGF-β)[5]和一氧化氮[6]，对骨组织有保护作用。有研究证实 PFF 处理的骨细胞能通过释放因子抑制破骨细胞的形成和骨吸收活性，而且这些因子发挥作用至少部分的依赖于 NO 通路的激活[7]。骨细胞缺陷会导致骨机械强度下降和动力传导能力的降低，内皮质骨的多孔性增加，小梁骨含量减低，皮质骨变薄，骨质的矿化作用减弱，髓腔脂肪含量增高，同时，因为缺少对骨组织的检测能力导致骨微裂和破骨性骨吸收的增加[8]。有学者构建转基因骨细胞溶解的动物模型(大鼠)研究证实，

作者单位：济南，山东大学 口腔医学院，山东大学 口腔医学研究所，山东省口腔生物医学重点实验室，Email: dongyan1126@yahoo.com.cn，电话：13665317724
通讯作者：扈英伟，山东大学 齐鲁医院，Email: huyingwei@sdu.edu.cn

在骨细胞溶解后短期可以观察到有破骨细胞出现在骨表面开始吸收活动，之后成骨细胞加入行使骨形成的功能。长期骨细胞溶解的动物模型实验观察到，动物管状骨的厚度变薄，骨机械强度降低，骨髓腔的脂肪含量增多[9]。

3 骨细胞的凋亡对破骨细胞的影响

体外实验应用小鼠的骨样细胞（MLO-Y_4）的凋亡碎片可以刺激新生大鼠颅骨的吸收[10]。高机械负荷造成的大鼠骨劳损模型中发现皮质骨有大量的骨细胞凋亡，在内皮质骨也发现有破骨细胞及骨陷窝的出现，而且骨吸收发生在凋亡骨细胞的附近[11]。大鼠负荷实验显示抑制骨细胞凋亡会使大鼠尺骨皮质骨微裂增加 600% 以上[12]。通过对行卵巢切除术的小鼠的股骨的观察发现，骨吸收激活发生在骨细胞凋亡之后，并且吸收部位与骨细胞凋亡部位一致[13]。另外糖皮质激素引起的人类和小鼠的骨质流失也被证实与骨细胞的凋亡有关[14]。因此我们认为骨细胞的凋亡也许是机械刺激和激素失调引起的骨吸收的共同通路。

前面讲到骨细胞可以产生转移生长因子 β，TGF-β 可以降低成骨细胞核因子 kappaB 受体活化因子配基（RANKL）的表达，从而抑制破骨细胞的发生[5]。骨骼承受的机械压力可刺激骨细胞产生一氧化氮（NO），一氧化氮可以防止成骨细胞发生进入起始阶段[6]。也许骨细胞的凋亡使得局部的骨保护因素下降，降低了对破骨细胞前体或者破骨细胞的抑制作用而导致骨吸收。另外，骨细胞可以感知力的变化，并将这种变化转化为细胞信号激发骨重塑的过程[15]。有研究认为当骨组织因正常压力负荷积聚产生骨微裂或者因外界的超负荷及激素等因素导致的骨损伤发生时，骨细胞可以通过间隙连接传递信号给成骨细胞，成骨细胞表达粘着分子引导破骨前体细胞的附着，同时成骨细胞表达 RANKL，与破骨细胞前体表面受体 RANK 结合，促进破骨细胞的分化和功能[16]。也有对 MLO-Y4 三维模式培养模型的微损伤研究中发现，300～400μm 损伤的模型上清中的 RANKL 明显增加，这不但说明了凋亡的骨细胞对破骨细胞的活化有部分直接作用而且也说明了为什么体内骨组织的微小微裂不被修复[17]。然而在一些研究中发现已凋亡的骨细胞周围的健康骨细胞表现出积极的抗凋亡现象，说明这些健康的骨细胞在骨重塑的过程中也不是旁观者[18]。

骨细胞在骨组织重塑中的作用已被学者所认可，其活性可以直接和（或）间接调节破骨细胞的发生和功能的激活，但凋亡的骨细胞对破骨细胞及其前体细胞的直接作用还有待研究。

【参考文献】

[1] Brendon Noble. Bone microdamage and cell apoptosis. European Cells and Materials, 2003, 6: 46-56

[2] RaggattLJ, Partridge NC. Cellular and Molecular Mechanisms of Bone Remodeling. The Journal of biological chemistry, 2010, 285 (33): 25103-108.

[3] Bonewald LF. Osteocytes as dynamic multifunctional cells. Annals of the New York Academy of Sciences, 2007, 1116: 281-290.

[4] Kyoji Ikeda. Osteocytes in the pathogenesis of osteoporosis. Geriatr Gerontol Int, 2008, 8: 213-217.

[5] Heino TJ, Hentunen TA, Vaananen HK. Osteocytes inhibit osteoclastic bone resorption through transforming growth factor-beta: Enhancement by estrogen. Journal of Cellular Biochemistry, 2002, 85: 185-197.

[6] TanSD, Bakker AD, Semeins CM, et al. Inhibition of osteocyte apoptosis by fluid flow is mediated by nitric oxide. Biochem Biophys Res Commun, 2008, 369: 1150-1154.

[7] ASantos, AD Bakker, J Klein - Nulend. The role of osteocytes in bone mechanotransduction. Osteoporosis International, 2009, 20: 1027-1031.

[8] Kyoji Ikeda. Osteocytes in the pathogenesis of osteoporosis. Geriatr Gerontol Int, 2008, 8: 213-217.

[9] Tatsumi S, Ishii K, Amizuka N et al. Targeted ablation of osteocytes induces osteoporosis with defective mechanotransduction. Cell Metabolism, 2007, 5: 464-475.

[10] Kogianni G, Mann V, Noble BS. Apoptotic bodies convey activity capable of initiating osteoclastogenesis and localized bone destruction. Journal of Bone and Mineral Research, 2008, 23 (6): 915-927.

[11] Noble BS, Peet N, Stevens HY, et al. Mechanical loading: biphasic osteocyte survival and targeting of osteoclasts for bone destruction in rat cortical bone. Am J Physiol Cell Physiol, 2003, 284: C934-C943.

[12] Luis Cardoso, Brad C Herman, Olivier Verborgt, et al. Osteocyte Apoptosis Controls Activation of Intracortical Resorption in Response to Bone Fatigue. Journal of Bone and Mineral Research, 2009, 24(4): 597-605.

[13] KB Emerton, B Hu, AA Woo, et al. Osteocyte apoptosis and control of bone resorption following ovariectomy in mice. Bone, 2010, 46: 577-583.

[14] Weinstein R S, Nicholas RW, Manolagas SC. Apoptosis of osteocytes in glucocorticoid-induced osteonecrosis of the hip. J Clin Enocrinol Metab, 2000, 85: 2907-2912.

（下转第 1036 页）

of survival after osteoporotic fractures. Am J Epidemiol, 1993, 137:1001-1005.

[13] Engelen MP, Schols AM, Heidendal GA, et al. Dual-energy X-ray Absorptiometry in the clinical evaluation of body composition and bone mineral densiy in patients with chronic pulmonary disease. Am J Clin Nutr, 1998, 68(6):1298-1303.

[14] 朱砚萍,朱汉民,徐怀玉,等.63 例老年男性慢性阻塞性肺病患者骨密度和骨代谢的改变.中国骨质疏松杂志,2000,(6)1:44-47.

[15] Kumedu Y, Lanba M, NlishizawaY. Secondary osteoporosis and its treatment diabetes mellitus. Japan Clini Med, 1998, 56: 1579-1586.

[16] Dimai HP, Domej W, Leb G, et al. Bone less in patients with untreated chonic obstructive pulmonary disease is mediated by an increase in bone resorption associated with hypercapnia. Bone Miner Res, 2001, 16:2132-2141.

[17] Cooper C, A tkinson EJ, Jacobsen SJ et al. Population-based study of survival after osteporotic fractures. Am J Epidemiol, 1993, 137:1001-1005.

[18] Incalzi RA, et al. Association between corticosteroid use and vertebral fractures in old men with chronic obstructive pulmonary diseases. AM J Respir Crit Care Med, 2000, 94(11):1079.

[19] GanWQ, Man SF, Senthilselvan A, et al. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax, 2004, 59: 574-580.

[20] EidAA, Ionescu AA, Nixon LS, et al. Inflammatory response and body composition in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2001, 164: 1414-1418.

[21] Nishimura Y, Nakata H, Tsussumi M, et al. Relationship between changes of bone mineral content and twelve-minute walking distance in men with chronic obstructive pulmonary disease: a longitudinal study. Intern Med, 1997, 36(7):450-453.

[22] 中华医学会呼吸病学分会,慢性阻塞性肺疾病学组,慢性阻塞性肺疾病诊治指南(2007 年修订版)中华结核与呼吸杂志,2007,1(1):8-17.

[23] 刘和娣,李恩.糖皮质激素继发骨质疏松的机理.中华骨科杂志,1994,4(14):233.

[24] 李恩,薛延,王洪复,等.骨质疏松鉴别诊断与治疗北京:人民卫生出版社,2005:505.

[25] Scanlon PD. Loss of bone density with inhaled triamcinolone in Lung Health Study. Am J Resoir Cirt Care Med, 2004, 170 (12)2-9.

[26] Ananda rajah AP, Schwarz EM. Anti-RANKL therapy for inflammatory bone disorders: mechanisms and potential clinical applications. J Cell Bichem. 2006, 97: 226-342.

[27] SabitR, Bolton CE, Edwards PH, et al. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2007, 175: 1259-1265.

[28] Vogelme ier C, Bals R. Chronic obstructive pulmonary disease and premature aging. Am J Respir Crit Care Med. 2007, 175: 1217-21.

[29] 王志文.慢性阻塞性肺病和骨质疏松. 四川医学,2003,24(3):363-364.

[30] Shane E, Silverberg SJ, Donovan D, et al. Osteeoporosis in patients with chonic obstructive airways disease. Thorax, 2004, 59 (7):574-580.

[31] 杨福荫,李国忠,黄苗清等. 肺癌病人血清降钙素水平变化的临床意义.北京大学,1991,13(3):132.

[32] Shane E, Silverberg SJ, Donovan, et al. Osteoporsis in lung transplantation candidates with end - stage pulmonary disease. The Am J Med 1996, 101(3):262-269.

[33] A. G. N Agusa, A. Noguera, J. Sauleda, et al. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J, 2003, 21:347-360.

(收稿日期: 2011-05-27)

(上接第 1032 页)

[15] O Verborgt, GJ Gibson, MB Schaffler, et al. Loss of osteocyte integrity in association with microdamage and bone remodeling after fatigue *in vivo*. Journal of Bone and Mineral Research, 2000, 15:60-67.

[16] Donahue HJ. Gap junctions and biophysical regulation of bone cell differentiation. Bone, 2000, 26:417-422.

[17] LE Mulcahy, D Taylor, TC Lee, et al. RANKL and OPG activity is regulated by injury size in networks of osteocyte - like cells. Bone, 2011, 48:182-188.

[18] Verborgt O, Tatton NA, Majeska RJ, et al. Spatial distribution of Bax and Bcl-2 in osteocytes after bone fatigue: complementary roles in bone remodeling regulation? Journal of Bone and Mineral Research, 2002, 17(5):907-914.

(收稿日期: 2011-06-30)

骨细胞对破骨细胞形成和功能的影响

作者： 张冬燕， 扈英伟， ZHANG Dongyan， HU Yingwei
作者单位： 济南,山东大学口腔医学院,山东大学口腔医学研究所,山东省口腔生物医学重点实验室
刊名： 中国骨质疏松杂志ISTIC
英文刊名： Chinese Journal of Osteoporosis
年，卷(期)： 2011,17(11)