中国骨质疏松杂志 2015 年 11 月第 21 卷第 11 期 Chin J Osteoporos, November 2015, Vol 21, No. 11
Published online www. wanfangdate. com. cn doi:10. 3969/j. issn. 1006-7108. 2015. 11. 025

·综述·

内质网应激与骨细胞及相关骨病的研究进展

张宇昂[1,2] 鲁艳芹[1,2] 任秀智[3*] 韩金祥[1,2*]
1. 山东省医药生物技术研究中心,山东省医学科学院,济南 250062
2. 济南大学-山东省医学科学院医学与生命科学学院,济南 250200
3. 天津市武清区人民医院,天津 301700

中图分类号: R681 **文献标识码**: A **文章编号**: 1006-7108(2015) 11-1407-05

摘要: 内质网(endoplasmic reticulum, ER)作为细胞内重要的膜性结构,负责分泌蛋白与膜蛋白的折叠加工,脂类的生物合成以及钙平衡的调节。当 ER 环境发生改变,如缺血、缺氧、突变蛋白的大量堆积时,内质网应激(endoplasmic reticulum stress, ERS)启动,并引发未折叠蛋白反应、内质网超负荷反应和固醇调节级联反应。在应激状态下,ER 对维持细胞内稳态起到至关重要的作用。一方面 ERS 有助于成骨细胞、破骨细胞和软骨细胞的生长,可以促进骨髓间充质干细胞向成骨细胞的分化,并抑制细胞凋亡的发生。另一方面在高强度长时间应激状态下,ERS 无法维持细胞稳态,会通过多种信号通路诱导细胞凋亡的发生,加速细胞更新。根据近几年已有报道的文献研究整理,在骨质疏松、成骨不全、氟骨症等相关骨病的研究中,ERS 同样发挥着重要的调节作用。特别是在发病早期,ERS 通过对多种骨细胞的调节,缓解病情。当病情严重 ERS 会触发内质网凋亡信号,导致细胞凋亡和生物体的损伤。本文就近年来国内外对 ERS 与骨细胞及相关骨病的研究进展进行综述。

关键词: 内质网应激;骨病;骨髓间充质细胞;成骨细胞;破骨细胞;软骨细胞

Research progress in endoplasmic reticulum stress and osteocytes and the relevant bone diseases

ZHANG Yuang[1,2], LU Yanqin[1,2], REN Xiuzhi[3], HAN Jinxiang[1,2]
1. Shandong Medicinal Biotechnology Centre, Shandong Academy of Medical Sciences, Jinan 250062, China
2. University of Jinan-Shandong Academy of Medical Sciences, Jinan 250200, China
3. The People's Hospital of Tianjin Wuqing District, Tianjin 301700, China
Corresponding author: HAN Jinxiang, Email: samshjx@ sina. com; REN Xiuzhi, Email: xiuzhiren@ hotmail. com

Abstract: Endoplasmic reticulum (ER) is an important intracellular membrane structure. It is responsible for folding process of the secreted protein and membrane protein, the biosynthesis of lipids, and calcium balance. When the endoplasmic reticulum environmental changes, such as ischemia, hypoxia, an substantial accumulation of misfolded proteins, ER stress is activated, accompanying with unfolded protein response (UPR), the endoplasmic reticulum overload (EOR) and cholesterol regulation cascade reaction. Under stress, ER plays an important role in cellular homeostasis. On the one hand, ER stress promotes the growth of osteoblasts, osteoclasts, chondrocytes, and the differentiation of osteoblasts from mesenchymal stem cells and restrain apoptosis. On the other hand, ER stress loses the control of cellular homeostasis and induces apoptosis to accelerate cell turnover when the stress is strong and continuous. According to the literature reported in recent years, ER stress plays a vital modulator role in a variety of bone diseases, including osteoporosis, osteogenesis, imperfect, and skeletal fluorosis. Especially during the early stage of these diseases, ER stress alleviates the patients' condition by regulating osteocytes. Apoptosis can be activated by long-term ER stress, which can result in cell apoptosis and damage on organism. In this review, we summarize the relationship between ER stress and bone diseases and the related cells.

Key words: Endoplasmic reticulum stress; Osteopathy; BMSC; Osteoblast; Osteoclast; Chondrocyte

内质网是细胞内蛋白质折叠修饰的主要场所,根据 Bonfanti 等提出的内质网管腔成熟模型[1],修饰后的蛋白在内质网中聚合,经高尔基体由分泌小泡分泌到细胞外[2]。内质网应激(endoplasmic reticulum stress, ERS)是指在缺氧、缺血、钙离子紊乱、功能蛋白基因突变等原因下,造成大量未折叠蛋

*通讯作者: 韩金祥 Email: samshjx@ sina. com;任秀智 Email: xiuzhiren@ hotmail. com

白在内质网中聚集,引起的内质网功能紊乱和细胞内稳态失衡[3,4]。此时,ERS 会通过启动未折叠蛋白反应(unfolded protein response, UPR)[5]、内质网超负荷反应(endoplasmic reticulum overload, EOR)[6]和固醇调节级联反应[7]三条信号通路缓解应激压力,对维持细胞稳态,促进细胞生长起到至关重要的作用。目前,随着研究的深入,人们发现 ER 在成骨细胞、破骨细胞、软骨细胞和骨间充质干细胞及相关骨病中也发挥着不同生理和病理作用,对病情的发展有直接影响,现分述如下:

1 ERS 与骨细胞

1.1 ERS 与骨髓间充质干细胞

骨髓间充质干细胞可以分化成多种细胞系并且可以产生一个或多个定向祖细胞[8,9]。目前,很多研究证实,ERS 在骨髓间充质干细胞向成骨细胞分化过程中起到十分重要的作用。

一方面,ERS 通过调高传感器蛋白的表达量,影响 BMP2、BMP9 等多条信号通路,促进骨细胞的生成,参与骨的生成和伤后修复[10,11]。ERS 诱导因子 Creld2 蛋白在内质网中的作用尚不明确,但在内质网应激中发现 Creld2 表达量明显变化[12]。Jiye Zhang 等通过对 Creld2 的定位研究表明,其通过影响 BMP9 信号途径介导骨髓间充质干细胞向成骨细胞的分化[13]。此外,ERS 还可以通过内质网自噬的激活增强骨髓间充质干细胞向成骨细胞分化的能力[14]。

另一方面,Yueping Chen 等的研究发现,骨髓间充质干细胞在酒精环境下可引发高强度的 ERS 并激活 ATF4 信号通路,提高 CHOP 凋亡因子的表达量,加速骨髓间充质干细胞向成脂细胞的转化,同时,抑制成骨细胞的生成[15]。上述研究表明,ERS 对骨髓间充质干细胞的分化有双向调节作用。

1.2 ERS 与成骨细胞

成骨细胞分泌大量的胶原蛋白和骨细胞生长因子,与钙、磷等无机质结合后生成骨组织。近几年的研究发现,ERS 与成骨细胞的生长有着密切的联系。Hiroki Yokota[16] 等的研究发现,ERS 通过调节 ATF4/CHOP 信号通路增强成骨细胞的分化和生长能力。实验用衣霉素和毒胡萝卜素来诱发成骨细胞的 ERS,发现在不同强度的 ERS 反应下,对成骨细胞有双向调控作用。在高浓度和长时间的诱导剂作用下,成骨细胞内 ATF4 表达量提高并与 ATF3 的结合能力加强,使下游 CHOP 转录因子表达量增高。CHOP 是 ERS 的特异转录因子,属于碱性亮氨酸锌指结构(bZIP)蛋白样转录因子蛋白家族中的一员能加速成骨细胞凋亡。在低水平的 ERS 下,伴随 ATF4 的表达量增高,Runx2 等骨形成因子的表达量很快提升。Runx2[17] 作为 Runxx 家族成员之一,是骨细胞的特异转录因子,对促进骨组织的形成和重建起着重要作用。Hiroki Yokota 后期研究证实除 ATF4,多种细胞生长因子的表达也同时上调[18]。此外,YU Shou-He 等人[19] 发现 Runx2 不仅促进成骨细胞生长,它还可以抑制 LC3II 的转化及 Beclin1 的表达量,使得自噬体膜的延伸减慢,阻断了自噬流,减小细胞因为自噬过度而导致的细胞凋亡。上述研究证实,ERS 对成骨细胞的生长具有双向调节作用。

1.3 ERS 与破骨细胞

骨的重构是一个高度协调的过程,由破骨细胞和成骨细胞共同完成,破骨细胞负责骨的重吸收,成骨细胞完成骨的构建[20]。破骨细胞的成熟与分化与 RANK/RANKL/OPG 系统调控有关,包括:骨保护素(OPG)、核因子 κB 受体活化因子(RANK)和核因子 κB 受体活化因子配体(RANKL),三者均属肿瘤坏死因子受体超家族[21]。研究证明,ERS 通过细胞白介素(IL-1β)介导 RANKL 途径调控破骨细胞的增殖分化,ERS 被抑制后,破骨细胞的生长也明显放缓[22,23]。因此,深入探寻成骨细胞和破骨细胞协调增殖分化的有效方法十分重要,它将会对治疗某些骨相关疾病起到重要作用。

1.4 ERS 与软骨细胞

软骨组织是结缔组织的一种,由软骨细胞和胞外基质组成,在机体中起到支撑作用。研究证明 ERS 的 IRE1 和 ATF6 信号通路在软骨细胞分化过程中被激活,结合后的 XBP1s 作为辅助因子与 Runx2 促进软骨细胞的肥大性分化[24]。同时,ERS UPR 信号通路中的剪切酶 S1P,在软骨细胞的骨化及生长板的形成中发挥重要作用[25]。

ERS 参与正常软骨细胞的分化,然而过度的 ERS 作用会引起软骨发育异常。Z. J. Han 等将小鼠 IRE1 基因敲除后,ERS 信号通路受到干扰,导致 caspase3, CHOP 和 JNK 表达量增高[26]。ERS 通过提高 Chop、BMP2 等因子表达量介导软骨细胞凋亡,加速软骨退变进程[27,28]。

此外,ERS 介导的细胞自噬对生长板中的软骨细胞的生存起到重要作用。软骨细胞中,自噬的调节主要依赖于 HIF, mTOR 和 AMP 激酶等[29]。在

自噬障碍的小鼠模型中，内质网数量增多体积变大，BIP 和 CHOP 表达量提高，软骨细胞凋亡率上升，会观察到严重的软骨发育异常[30]。同样，研究发现，在小鼠体内 Sumf1 因子的无义突变，引起 LC3-自噬溶酶体的激增，加速 ERS 介导的细胞自噬，造成软骨细胞大量减少[31]。

2 ERS 与相关骨病

2.1 ERS 与骨质疏松

骨质疏松即骨质疏松症（osteoporosis），是一种单位体积骨量减少和骨组织退化的的骨代谢疾病，严重患者极易发生骨折。在正常骨组织中，成骨细胞产生新的骨组织，破骨细胞吸收陈旧的骨组织，这是一种不断重建的骨平衡。Manolagas 等的研究表明[32]，ROS 表达水平提高引起氧化应激，打破骨重建平衡，抑制骨髓间充质干细胞向成骨细胞的转化并抑制生长，并通过 PKC/p53/p66shc/JNK 途径加速成骨细胞的凋亡，同时加快破骨细胞的分化，从两个方向加速了骨量的流失[33]。

在 Malhotra[34] 等的研究报道中，明确指出高浓度活性氧可导致蛋白错误折叠引发 ERS，同时阐明了 ERS、氧化应激和自噬三者间的紧密联系。近期 Yue-Hua Yang 等[35]在研究 ERS 对骨质疏松的调控作用时进一步证实了 Malhotra 等的观点。Yue-Hua Yang 等用不同浓度的 H_2O_2 诱发细胞氧化应激反应，同时检测 ERS 的标记蛋白、自噬标记蛋白的表达量和成骨细胞凋亡情况。结果显示低浓度活性氧通过 ERS 途径促进成骨细胞生存，而高浓度活性氧直接导致成骨细胞凋亡。同样的结果在酵母实验中得到证实[36]。

2.2 ERS 与成骨不全

成骨不全（Osteogenesis Imperfecta，OI）又称为脆骨病，是一种结缔组织异常可遗传疾病，由于基因突变造成胶原形成障碍和骨纤维结构异常[37]。临床表现包括骨质脆弱、鸡胸、蓝巩膜和牙本质发育不全[38, 39]。异常胶原蛋白大量堆积在内质网中引发 ERS 和细胞自噬[40-42]。ERS 通过内质网相关蛋白降解途径（ERAD）和内质网自噬（ER-phagy）对异常的胶原分子和前胶原蛋白进行降解[43]。

近期 Reich A 等研究发现，VI 型成骨不全患者的成骨细胞在细胞分化的早期和晚期，细胞生长速度明显快于正常成骨细胞，其矿化能力相对于正常细胞也有所增加。但在细胞的中晚期，其分泌 I 型胶原蛋白的能力明显低于正常的成骨细胞[44]。这可能与 ERS 通过调节 ATF4/CHOP 信号通路增强成骨细胞的分化和生长能力有关。

成骨不全患者中软骨细胞同样发生异常，主要表现在软骨细胞数量的下降和骨化不全，特别是在 II 型成骨不全中表现更为明显[45]。Kunito Kawasaki 等人发现[46]，在 ERS 条件下，Hsp47 的表达量与 I 型胶原蛋白的分泌密切相关，Hsp47 表达量过低，不仅引起胶原蛋白合成量减少，还会引发细胞的凋亡。

2.3 ERS 与氟骨症

地方性氟骨症，是通过水长时间摄入大量氟元素造成的一种慢性骨代谢疾病。氟可以影响骨组织的代谢平衡，较高的骨转换率和其对成骨细胞的双重作用是研究氟骨症的关键[47]。最近研究发现，氟元素通过 ERS 调节成骨细胞分化[48]。在低剂量的氟的刺激下，成骨细胞加速分化和增殖，转录因子 Runx2 表达量增高。特别是在器官水平，骨量增加快。但高剂量的氟存在细胞毒性，通过 ERS 途径加速成骨细胞凋亡。Xi-ning Li 等在小鼠实验中发现[49]，氟会激活体内的 ERS，通过调高 PERK 的表达量促进成骨细胞的分化。而在敲除 PERK 基因的模型小鼠中，成骨细胞快速凋亡，皮质骨和骨小梁的骨质迅速流失。Lu 等的研究中也证实，GRP78，XBP1，caspase－12 和 CHOP 等因子的表达及 ERS 的强度均与氟量存在剂量效应关系[50]。ERS 发生后，PERK 信号通路不仅可以加速胶原蛋白的合成，同时促进骨髓间充质细胞向成骨细胞的分化[51]。

3 结语

随着 ERS 研究的不断深入，其对各类相关骨细胞的成熟、分化、代谢等过程中的激活作用逐步得到证实。通过不同系统的定位实验，对各种信号传导逐步明确的基础上，也对不同影响因子进行了大量的实验观察。ERS 在骨病早期能维持骨细胞生长，特别是加速成骨细胞的分化和生长，调高分子伴侣的表达量，帮助细胞应对环境的急剧变化，但病程晚期 ERS 已无法应对，只能启动细胞凋亡致病情逐步加重。总之，ERS 与骨细胞及相关骨病的各项体内、体外研究，分别从信号通路、作用机制等方面取得的一定进展，将为今后深入探讨有关防控措施和治疗方法提供了重要参考。

【参考文献】

[1] Bonfanti L MAJ, Martínez-Menárguez JA, et al. Procollagen traverses the Golgi stack without leaving the lumen of Cisternae

Evidence for cisternal maturation [J]. Cell Stress and Chaperones, 1998, 95(7): 993-1003.

[2] Canty EG KK. Procollagen trafficking, processing and fibrillogenesis[J]. Journal of cell science, 2005, 118(7):1341-53.

[3] RJ. K. Stress signaling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls[J]. Genes & development, 1999, 13(10):1211-33.

[4] Ron. D. Translational control in the endoplasmic reticulum stress response[J]. J Clin Invest, 2002, 110(10):1383-8.

[5] Inagi. R. Endoplasmic Reticulum: The Master Regulator of Stress Responses in Glomerular Diseases. In book: An Update on Glomerulopathies - Etiology and Pathogenesis[J]. 2011:247-66.

[6] HL. P. Signal transduction from the endoplasmic reticulum to the cell nucleus[J]. Physiol Rev, 1999, 79(3):683-701.

[7] PJ. E. SREBPs: sterol-regulated transcription factors [J]. Journal of cell science, 2006, 119(6):973-6.

[8] Potier E NJ, Ito K. Directing bone marrow-derived stromal cell function with mechanics[J]. Journal of biomechanics, 2010, 43(5):807-17.

[9] Derubeis AR CR. Bone marrow stromal cells (BMSCs) in bone engineering: limitations and recent advances [J]. Annals of biomedical engineering, 2004, 32(1):160-5.

[10] Funamoto T ST, Murakami T, et al. Roles of the endoplasmic reticulum stress transducer OASIS in fracture healing[J]. Bone, 2011, 49(4):724-32.

[11] Saito A OK, Kondo S. Endoplasmic reticulum stress response mediated by the PERK-eIF2 (alpha)-ATF4 pathway is involved in osteoblast differentiation induced by BMP2[J]. The Journal of biological chemistry, 2011, 286(6):4809-18.

[12] Maslen CL BD, Redig JK. CRELD2: gene mapping, alternate splicing, and comparative genomic identification of the promoter region[J]. Gene, 2006, 382:111-20.

[13] Zhang J WY, Liu X, et al. Endoplasmic reticulum (ER) stress inducible factor cysteine-rich with EGF-like domains 2 (Creld2) is an important mediator of BMP9-regulated osteogenic differentiation of mesenchymal stem cells[J]. PLoS One, 2013, 8(9): e73086.

[14] Gioia R PC, Besio R. Impaired osteoblastogenesis in a murine model of dominant osteogenesis imperfecta: a new target for osteogenesis imperfecta pharmacological therapy, Stem cells, 2012, 30(7):1465-76.

[15] Chen Y GH, Yin Q. ER stress activating ATF4/CHOP-TNF-alpha signaling pathway contributes to alcohol-induced disruption of osteogenic lineage of multipotential mesenchymal stem cell. Cellular physiology and biochemistry[J]. international journal of experimental cellular physiology, biochemistry, and pharmacology, 2013, 32(3):743-54.

[16] Hamamura K YH. Stress to endoplasmic reticulum of mouse osteoblasts induces apoptosis and transcriptional activation for bone remodeling[J]. FEBS Lett, 2007, 581(9):1769-74.

[17] Wysokinski D PE, Blasiak J. RUNX2: A Master Bone Growth Regulator That May Be Involved in the DNA Damage Response [J]. DNA Cell Biol, 2015, 34(5):305-15.

[18] Hamamura K LY, Yokota H. Microarray analysis of thapsigargin-induced stress to the endoplasmic reticulum of mouse osteoblasts [J]. J Bone Miner MeTab, 2008, 26(3):231-40.

[19] YU Shou-he, HONG An. Runx2 promotes osteogenic differentiating C2C12 cells through inhibiting macroautophagy [J]. Chin J Pathophysiol, 2013, 29(3):481-7.

[20] Lee HY JH, Song EK. CD40 ligation of rheumatoid synovial fibroblasts regulates RANKL-mediated osteoclastogenesis: evidence of NF-kappaB-dependent, CD40-mediated bone destruction in rheumatoid arthritis[J]. Arthritis and rheumatism, 2006, 54(6):1747-58.

[21] TJ. M. Historically significant events in the discovery of RANK/RANKL/OPG[J]. World journal of orthopedics, 2013, 4(4): 186-97.

[22] Lee EG SM, Yoo HG. Increased RANKL-mediated osteoclastogenesis by interleukin-1beta and endoplasmic reticulum stress[J]. Joint, bone, spine: revue du rhumatisme, 2014, 81(6):520-6.

[23] Wang K NJ, Kim H. Osteoclast precursor differentiation by MCPIP via oxidative stress, endoplasmic reticulum stress, and autophagy[J]. Journal of molecular cell biology, 2011, 3(6): 360-8.

[24] Liu Y ZJ, Zhao W. XBP1S associates with RUNX2 and regulates chondrocyte hypertrophy. The Journal of biological chemistry [J]. 2012, 287(41):34500-13.

[25] Patra D DE, Hayashi S. Site-1 protease is essential to growth plate maintenance and is a critical regulator of chondrocyte hypertrophic differentiation in postnatal mice[J]. The Journal of biological chemistry, 2011, 286(33):29227-40.

[26] Han X ZJ, Zhang P. IRE1α dissociates with BiP and inhibits ER stress-mediated apoptosis in cartilage development [J]. Cell Signal, 2013, 25(11):2136-46.

[27] Uehara Y Hirose J, Yamabe S. Endoplasmic reticulum stress-induced apoptosis contributes to articular cartilage degeneration via C/EBP homologous protein [J]. Osteoarthritis Cartilage, 2014, 22(7):1007-17.

[28] X Han PZR, Jiang. Explore on the effect of ATF6 on cell growth and apoptosis in cartilage development[J]. Histochem Cell Biol, 2014, 142(5):497-509.

[29] Srinivas V Bohensky J, Shapiro IM. Autophagy: a new phase in the maturation of growth plate chondrocytes is regulated by HIF, mTOR and AMP kinase[J]. Cells Tissues Organs, 2009, 189(1-4):88-92.

[30] Hall-Glenn F AA, Akopyan L. CCN2/CTGF is required for matrix organization and to protect growth plate chondrocytes from cellular stress[J]. Journal of cell communication and signaling, 2013, 7(3):219-30.

[31] Settembre C A-SE, McKee MD. Proteoglycan desulfation determines the efficiency of chondrocyte autophagy and the extent of FGF signaling during endochondral ossification[J]. Genes & development, 2008, 22(19):2645-50.

[32] SC. M. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis [J]. Endocrine reviews, 2010, 31(3):266-300.

[33] Coipeau P RP, Langonne A, et al. Impaired differentiation potential of human trabecular bone mesenchymal stromal cells

from elderly patients[J]. Cytotherapy, 2009, 11(5):584-94.
[34] Malhotra JD KR. Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword[J]? Antioxidants & redox signaling, 2007, 9(12):2277-93.
[35] Yang YH LB, Zheng XF, et al. Oxidative damage to osteoblasts can be alleviated by early autophagy through the endoplasmic reticulum stress pathway-Implications for the treatment of osteoporosis[J]. Free radical biology & medicine, 2014, 77:10-20.
[36] Marobbio CM PI, Porcelli V, et al. Rapamycin reduces oxidative stress in frataxin-deficient yeast cells[J]. Mitochondrion, 2012, 12(1):156-61.
[37] Pope FM NA, McPheat J, et al. Collagen genes and proteins in osteogenesis imperfecta[J]. Medical Genetics, 1985, 22(6): 466-78.
[38] Frank Rauch FHG. Osteogenesis Imperfecta[J]. Seminar, 2004, 363(9418):1377-85.
[39] Arponen H, Mäkitie O, Waltimo-Sirén J. Association between joint hypermobility, scoliosis, and cranial base anomalies in paediatric Osteogenesis imperfecta patients: a retrospective cross-sectional study[J]. BMC Musculoskelet Disord, 2014, 15:428.
[40] Forlino A, Kuznetsova NV, Marini JC., et al. Selective retention and degradation of moleeules with a single mutant alpha1(I) chain in the Brtl IV mouse model of OI. Matrix Biol, 2007, 26(8):604-14.
[41] Ishida Y YA, Kitamura A, et al. Autophagic elimination of misfolded procollagen aggregates in the endoplasmic reticulum as a means of cell protection[J]. Molecular biology of the cell, 2009, 20(11):2744-54.
[42] Pieri M SC, Zaravinos A. Evidence for activation of the unfolded protein response in collagen IV nephropathies. Journal of the American Society of Nephrology: JASN. 2014; 25(2):260-75.
[43] Ishida Y NK. Autophagy eliminates a specific species of misfolded procollagen and plays a protective role in cell survival against ER stress[J]. AutophAgic puNctum, 2009, 5(8): 1217-9.
[44] Fratzl-Zelman N SI, Roschger P. Unique micro- and nano-scale mineralization pattern of human osteogenesis imperfecta type VI bone[J]. Bone, 2015, 73:233-41.
[45] Vianna MF, Taciro D, Lazarini PR, et al. Osteogenesis imperfecta—a human temporal bone case study. Otol Neurotol, 2013, 34(7):e113-4.
[46] Kawasaki K UR, Ito S. Deletion of the Collagen-specific Molecular Chaperone Hsp47 Causes Endoplasmic Reticulum Stress-mediated Apoptosis of Hepatic Stellate Cells[J]. The Journal of biological chemistry, 2014, 290(6):3639-46.
[47] Li G RL. Effects of excess fluoride on bone turnover under conditions of diet with different calcium contents[J]. Zhonghua bing li xue za zhi Chinese journal of pathology, 1997, 26(5): 277-80.
[48] Zhou YL SH, Li XN. Role of endoplasmic reticulum stress in aberrant activation of fluoride-treated osteoblasts[J]. Biological trace element research, 2013, 154(3):448-56.
[49] Li XN LP, Sun Z. Role of unfolded protein response in affecting osteoblast differentiation induced by fluoride[J]. Biological trace element research, 2014, 158(1):113-21.
[50] Liu L ZY, Gu H. Fluorosis Induces Endoplasmic Reticulum Stress and Apoptosis in Osteoblasts In Vivo[J]. Biological trace element research, 2014, 164(1):64-71.
[51] Wei J SX, Feng D. PERK is essential for neonatal skeletal development to regulate osteoblast proliferation and differentiation [J]. Journal of cellular physiology, 2008, 217(3):693-707.

(收稿日期: 2015-04-03)

(上接第 1388 页)

[22] Sinaki M, Pfeifer M, Preisinger E, et al. The role of exercise in the treatment of osteoporosis[J]. Current osteoporosis reports, 2010, 8(3):138-144.
[23] Sinaki M. Yoga spinal flexion positions and vertebral compression fracture in osteopenia or osteoporosis of spine: case series[J]. Pain practice, 2013, 13(1):68-75.
[24] Lee MS, Pittler MH, Shin BC, et al. Tai chi for osteoporosis: a systematic review[J]. Osteoporosis international, 2008, 19(2): 139-146.
[25] Bemben D, A. Bemben, M, G. Dose-respones effect of 40 weeks of resistance training on bone mineral density in older adults. Osteoporosis international[J]. 2011, 22:179-186.
[26] MCAEGKMKPMBDMLCHAM T. Does frequency of resistance training affect tibial cortical bone density in older women? A randomized controlled trial[J]. Osteoporosis international, 2013, 24:623-632.
[27] 李颖,姜媛媛,宋宏伟. 老年有氧健身操对绝经女性骨密度的影响[J]. 辽宁师范大学学报:自然科学版, 2006, 29(4): 502-504.
LI Ying, JIANG Yuan-yuan, SONG Hong-wei. The Effect of the Senior Aerobics on Density of Menopause Women's Bone[J]. Journal of Liaoning Normal University (Natural Science Edition), 2006, 29(4):502-504.
[28] Fuchs RK, Bauer JJ. Snow CM. Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial[J]. J Bone Miner Res, 2001, 16(1):148-156.
[29] 赵法章,韩雪松,苏凤荣,等. 应用鲑鱼降钙素及物理疗法联合治疗原发性骨质疏松症[J]. 中国骨质疏松杂志, 2007, 13(4):281-283.
ZHAO Fazhang, HAN Xuesong, SU Fengrong, et al. Calcitonin combined with physical therapy for primary osteoporosis[J]. Chinese Journal of Osteoporosis, 2007, 13(4):281-283.
[30] Needham-Shropshire BM, Broton JG, Klose KJ, et al. Evalution of a training program for persons with SCI paraplegia using the Parastep 1 ambulation system: part 3. Lack of effect on bone mineral density[J]. Arch Phys Med Rehabil, 1993, 74:73-78.
[31] 张美娟. 运动疗法对绝经期女性骨质疏松骨折的预防作用. 中国老年学杂志 2013, 33(9):2188-2189.

(收稿日期: 2014-11-22)