中国骨质疏松杂志 2017 年 12 月第 23 卷第 12 期 Chin J Osteoporos, December 2017,Vol 23, No. 12
Published online www.wanfangdate.com.cn doi:10.3969/j.issn.1006-7108.2017.12.029

·综述·

自噬在绝经后骨质疏松中作用的研究进展

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中图分类号: R681 **文献标识码:** A **文章编号:** 1006-7108(2017) 12-1675-06

摘要: 绝经后骨质疏松症是临床上较为常见的疾病,严重影响许多老年女性生活质量。研究表明,自噬参与了绝经后骨质疏松的发生与发展。在机体衰老、雌激素水平下降及氧化应激水平增高等多种因素的影响下,骨组织细胞的自噬活性发生改变,进而导致了骨代谢及骨稳态的调节失控,并进一步导致骨质疏松的发生。自噬在细胞增殖、分化、凋亡及维持细胞稳态等多方面发挥重要作用,尤其也参与了促骨形成及促骨吸收的过程。近年来随着对自噬研究的不断深入,自噬活性的调控通路及其在细胞中作用的研究取得了众多进展。在查阅大量国内外的相关文献后,本文对自噬在绝经后骨质疏松症发病机制中所发挥的作用进行综述,并对自噬与骨形成、骨吸收的关系进行总结。

关键词: 自噬;绝经后;骨质疏松;综述

Research progress on the role of autophagy in postmenopausal osteoporosis

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Abstract: Postmenopausal osteoporosis is a common clinical disease which threatens the improvement of quality of life in majority of elderly females. Current research shows that autophagy plays an important role in the occurrence and development of postmenopausal osteoporosis. The activation of autophagy changes under the impact of factors such as senility, estrogen deficiency, oxidative stress, etc., and could disturb bone homeostasis and metabolism which leads to osteoporosis. Autophagy takes part in the process of bone formation and bone resorption, and also plays an important role in cells' multiplication, differentiation, apoptosis, homeostasis, etc. In recent years, significant progress has been made on research related to the regulatory pathway of autophagy activation and its function in cells. After reviewed a number of domestic and foreign literatures, this article summarizes the impact of autophagy on the pathogenesis of postmenopausal osteoporosis as well as the relationship between autophagy and bone formation and bone resorption.

Key words: Autophagy; Postmenopausal; Osteoporosis; Review

骨质疏松症是一种骨组织骨量减低和微结构退化的全身性骨骼疾病,并伴随着骨脆性增加及骨折的风险增高[1]。造成骨质疏松的原因复杂而多变,常与年龄、性别、种族、激素水平、饮食及药物副作用等多方面因素有关[2]。骨质疏松症常见于绝经后妇女,由于机体卵巢功能减退及雌激素水平下降,直接影响了骨骼细胞的活性并导致骨密度降低[3]。自噬是维持细胞稳态的重要机制,参与调节成骨细胞主导的骨形成与破骨细胞主导的骨吸收的动态平衡,并影响了绝经后骨质疏松(postmenopausal osteoporosis,PMOP)的发生与发展[4]。本文就自噬在 PMOP 中发挥的作用及其影响作一综述。

基金项目:云南省科技厅应用基础研究——昆明医科大学联合专项资金项目(2017FE467-063)

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1　PMOP

PMOP 临床上常常伴有身高缩短、脊柱畸形等症状，已成为绝经后妇女骨折风险增加，生活质量下降的重要因素[5]。雌激素是体内参与骨代谢调节的激素之一，骨组织细胞表面具有雌激素受体，在绝经后妇女中，雌激素水平下降直接促进了破骨细胞分化，诱导了骨细胞凋亡，并使成骨细胞受到抑制；同时由骨细胞及成骨细胞分泌调节破骨细胞分化的核因子 B 配体（receptor activator of nuclear factor-B ligand，RANKL）和巨噬细胞集落刺激因子（macrophage colony-stimulating factor，M-CSF）表达增加、骨保护素（osteoprotegerin，OPG）水平降低，进一步促进了破骨细胞的分化[1]。此外，在 PMOP 的发病中雌激素还能作为一种抗氧化剂起到防止骨质疏松的作用，而氧化应激是关键性起始因子，活性氧（reactive oxygen species，ROS）则可能是其主要根源[6]。当机体在衰老及雌激素水平下降时，体内清除氧自由基的能力下降，进一步导致了 ROS 的蓄积及线粒体的损伤，并诱导了成骨细胞及骨细胞凋亡，导致骨微结构破坏和骨质疏松的发生[7]。ROS 的积累还能增加破骨细胞及其祖细胞中的 RANKL 和 M-CSF 并抑制叉头蛋白 O（fork head box O Fox D）的转录，进一步刺激了破骨细胞祖细胞的增殖，延长了破骨细胞的寿命，增加了骨吸收并使骨量丢失[8]。

2　自噬与 PMOP

2.1　自噬的生物学作用

自噬是一种细胞对构象错误的蛋白质和受损的细胞器等进行包裹后，通过与溶酶体结合将其降解并再次循环利用的自我生存机制，对于细胞的存活、分化及维持细胞内环境稳态至关重要[9]。在整个自噬的过程中，自噬相关基因（Atg）及其编码的蛋白质与自噬调控通路相互构建了复杂的自噬调节网络并负责细胞的新陈代谢。哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）是自噬活性调节的关键性分子，它能与几种蛋白质相互作用形成 mTORC1 复合物及 mTORC2 复合物[10]。在发生自噬的复杂机制过程中 mTORC1 能被氨基酸、生长因子、ROS、炎症和 Wnt 信号等激活，并在溶酶体降解长寿蛋白和去除受损细胞器的过程中起到负调节作用，而 mTORC2 主要涉及生长因子信号的传导[11,12]。

在骨骼的发育过程中，mTOR 及信号通路在控制成骨细胞分化过程中均发挥了不同的作用，腺苷酸活化激酶（adenosine monophosphate-actived protein kinase，AMPK）依赖 mTOR 产生的早期自噬抑制以及 AMPK/Akt/mTOR 信号途径介导的晚期 mTOR 活化都是最佳分化途径所必需的，mTORC1 则在成骨细胞分化晚期通过调节细胞自噬活性促进细胞成熟[13,14]。敲除小鼠成骨细胞自噬相关基因 FIP200（focal adhesion kinase family interacting protein of 200kD）及 Atg7 后抑制了自噬，造成了细胞自噬障碍、氧化应激水平增高、成骨细胞和骨细胞生成障碍以及骨量减低[15,16]。同时，在成骨细胞分化为骨细胞期间，早期抑制自噬造成了细胞质成分改变及细胞形态成熟障碍并进一步影响了骨细胞网络结构的生成，造成了骨量减少[17]。此外，自噬相关蛋白 WDFY3 基因的敲除增加了破骨细胞的分化及其活性，而自噬基因的缺失或组织处于缺氧状态时将会造成破骨细胞数量和活性增加、体积增大、核增多等一系列变化[18,19]。

2.2　自噬活性调节与 PMOP

近几年研究证实，自噬作为细胞的自我保护机制，能够减轻氧化应激导致的细胞损伤并维持细胞功能，以延缓或减轻骨量丢失。在 PMOP 中，随着年龄的增长和雌激素水平下降，氧化应激造成的 ROS 蓄积可以损伤细胞膜、线粒体和转录因子等细胞成分，并可进一步触发自噬来清除受损成分使细胞得以存活，但 ROS 对线粒体的损伤也可能导致细胞积累更多 ROS，过度的自噬则可能直接引起细胞凋亡[20,21]。过量蓄积的 ROS 还可以通过 Wnt/β-catenin[22]、RANKL/RANK/OPG[23]、JNK/c-Jun[24]、MAPK 和 PI3K[25] 等信号通路影响核内基因表达，通过抑制成骨细胞谱系增殖和活性、抑制骨祖细胞的成骨分化、刺激破骨细胞前体细胞和破骨细胞的增殖及分化等，最终打破骨吸收和骨形成之间的平衡，引起骨质疏松。

在 PMOP 中氧化应激能使自噬活性改变并进一步导致骨稳态的失衡，因此一些抗氧化剂通过调节细胞自噬活性显示出对治疗或预防骨质疏松症具有良好的效果。白藜芦醇是具有代表性的抗氧化剂之一，在卵巢切除（ovariectomized，OVX）后的大鼠中它能够触发自噬并增强成骨细胞分化，通过 ROS 抑制来减少 RANKL 诱导的破骨细胞生成以抵抗骨吸收[26]。此外，山奈酚作为一种黄酮醇类抗氧化物在 OVX 大鼠中也表现出良好的抗骨质疏松效果[27]，

它通过激活Atg5、beclin-1、SQSTM1/p62和LC3诱导成骨细胞自噬体形成，促进成骨细胞分化及骨矿化，同时抑制破骨细胞的骨吸收[28]。茶多酚不仅能对抗绝经后因雌激素缺乏引起的氧化应激，还具有保护溶酶体膜和稳定溶酶体酶的能力，它通过增加beclin-1和LC3的表达促进自噬，对成骨细胞的分化、存活及骨矿化起到积极作用，并有效抑制破骨细胞的形成和分化[29,30]。除了一些植物性抗氧化剂，研究人员还发现人体自身分泌的褪黑素不仅是一种良好的抗氧化剂，其夜间褪黑激素峰的恢复对围绝经期妇女骨骼健康也有积极的影响[31]。褪黑素能通过抑制ROS产生，增加MAPK活性，还能通过ERK通路抑制自噬，提高成骨细胞增殖活性，对于破骨细胞则通过刺激成骨细胞成骨作用减少RANKL的释放而起到间接调节作用[32]。

3 自噬与骨形成、骨吸收的关系

在骨组织内，成骨细胞主导骨矿化形成，破骨细胞主导骨吸收，骨细胞参与骨形成、骨吸收和传导信号并启动骨微结构的修复，这三种细胞类型相辅相成，并在骨形态结构的改造与破坏中共同完成旧骨的吸收和新骨的生成。自噬参与到成骨细胞分化、破骨细胞活性调节及骨细胞的骨改造等方面，并进一步影响到骨形成与骨吸收的平衡。

3.1 自噬与成骨细胞

成骨细胞由骨髓间充质干细胞分化而来，这一过程需要经历多个阶段的转化，并受到雌激素、细胞因子和基因表达等多方面的调控。转录因子FOXO3在间充质干细胞中能诱导细胞的自噬，从而减少成骨细胞分化过程中因线粒体呼吸增加而引起的ROS水平增高，促进成骨细胞分化的顺利完成[33]。在分化成熟的成骨细胞中，雌二醇可以直接通过ERs-ERKmTOR通路显著增强自噬以减少成骨细胞凋亡所造成的骨量丢失[34]。这样的保护机制可能与减少ROS的产生、刺激谷胱甘肽还原酶的活性以及降低p66shc磷酸化等有关[35]。而雌激素水平下降引起的氧化应激并造成的成骨细胞损伤，可以通过内质网应激激发的早期自噬得以缓解，这可能是成骨细胞对ROS攻击的保护性反应[36]。Lai等[37]通过过氧化氢诱导成骨细胞自噬水平升高，发现能显著提高成骨细胞成活率，免于因氧化应激导致的细胞凋亡。此外，雷洛昔芬作为一种选择性雌激素受体调节剂应用于临床治疗PMOP，它能通过激活AMPK/ULK1通路提高细胞自噬水平、促进成骨细胞分化、增加成骨作用并抑制骨吸收[38,39]。在骨形成的过程中自噬空泡还能作为介质帮助成骨细胞分泌磷灰石晶体至细胞外参与成骨[40]。这说明自噬在维持成骨细胞功能上是一个保护性因素，能起到抗氧化、抗凋亡、参与成骨等功能，对于抗雌激素缺乏性骨质疏松及促进骨形成具有积极作用。

3.2 自噬与破骨细胞

破骨细胞是由骨髓巨细胞分化为前破骨细胞并相互融合而成的高分化多核巨细胞，能在细胞外侧形成刷状缘并通过释放溶酶体酶和HCl等物质使骨质及胶原降解并形成骨吸收陷窝。目前对于自噬在破骨细胞中的作用尚存在争议。有研究发现雷帕霉素及其类似物作为经典的自噬诱导剂在OVX大鼠中通过对PFTAIRE1蛋白激酶的上调及减少组织蛋白酶K的含量，能有效抑制破骨细胞的形成和活性并预防骨量丢失约60%[41]。另外鞘氨醇-1-磷酸（sphingosine-1-phosphate，S1P）作为破骨细胞的化学诱导物，能与破骨细胞表面相应受体结合并调节mTOR活性降低自噬[4]。而在一项对绝经后妇女外周循环血S1P的测量中也证实S1P含量增高与骨密度呈现负相关，S1P增强破骨细胞的生成并导致了骨吸收增加[42]。同时，二氢青蒿素能抑制RANKL诱导的NF-κB的活性，增加细胞中ROS的积累并激活自噬程序，使破骨细胞产生受限，进而逆转OVX小鼠的骨丢失[43,44]。由此推测，在PMOP中破骨细胞自噬水平的增加能抑制其自身的分化及活性，减少骨量丢失。另外的研究则与上述结论相反，在敲除Atg7的OVX小鼠中，研究者们发现自噬的抑制对OVX小鼠的成骨细胞没有影响，反而能抑制破骨细胞活性并减少骨丢失[45]。同时，在OVX小鼠中Atg5和Atg7基因的缺失使破骨细胞刷状缘产生受阻，使骨吸收陷窝的深度变浅[46]。而使用雷帕霉素则能逆转三氧化二铁介导的破骨细胞自噬低活性状态，使破骨细胞数量及活性显著增加[47]。破骨细胞中的自噬相关基因Beclin-1通过RANKL也介导了线粒体产生大量ROS并促进破骨细胞分化成熟[48]。这说明自噬的抑制或缺失使得破骨细胞的溶骨功能受限，提高自噬活性则能改善破骨细胞活性。在对破骨细胞的研究中由于使用不同的动物模型及干预措施的差异，以及破骨细胞来源的特殊性和其活性受到多种因子的调节，自噬在破骨细胞中发挥的作用尚不十分明确，仍需进一步研究。

3.3 自噬与骨细胞

在骨骼发育的过程中一部分成骨细胞经过剧烈

的形态转化后分化成为骨细胞并埋于骨矿化的基质中,之后通过分泌硬骨素及 RANKL 等来调节成骨细胞和破骨细胞比例并参与到骨重建修复中[49]。骨细胞能通过提高自噬水平帮助其在分化过程中完成细胞形态的改变和细胞器的回收储能,以适应相对缺氧及营养缺失的状态,自噬的增加也帮助骨细胞抵御来自骨基质中的氧化应激并保持细胞活力[50]。Yang 等[51]在 OVX 大鼠中使用雌激素治疗后发现骨细胞在雌激素缺失的状态下可能因为氧化应激水平的增高导致自噬水平的增加,而恢复雌激素水平则对自噬没有显著影响。而更多研究指出抑制骨细胞自噬导致的骨量下降可能更接近于年龄相关的骨质疏松[15,53]。一项研究比较了在骨质疏松的发生过程中性激素及年龄对自噬的影响[52],发现了骨细胞的自噬水平可能更多受年龄及细胞自身衰老的影响,雌激素对骨细胞的自噬起到了负调节作用。而随着年龄的增长骨细胞的自噬水平下降、凋亡增加,导致了局部微环境及结构的变化并进一步使骨组织退化。相比成年大鼠,在老年大鼠的骨细胞中一些重要的自噬基因如 LC3、Beclin-1 和 Ulk-1 表达出现下降,而与其相应的表现是骨细胞的凋亡和骨密度的下降,自噬增加则对于骨细胞延缓衰老、抗凋亡及抗氧化应激有一定作用[53]。在 PMOP 中受到氧化应激的影响,骨细胞自噬活性的上调可能作为抗骨质疏松的反应性保护因素,但随着年龄的增加,骨细胞凋亡开始增多、自噬水平下降,这进一步促进了骨质疏松的发生发展。

4　总结与展望

自噬是细胞生存的重要机制,也在 PMOP 中发挥着不可替代的作用,但对于目前的研究来说其具体机制尚不是十分清楚。人体中细胞的自噬具有普遍性,而对于 PMOP 中细胞自噬水平的改变可能不仅仅简单的涉及到雌激素水平下降和氧化应激,可能还与机体随着年龄增加伴随的各器官的逐渐衰老和功能下降有关。在体内衰老的开始一般都能诱导自噬,但自噬的抑制也能促进衰老,这可能是细胞自噬在抵抗逐步积累的有害物达到一定限度并严重受损时,促进了细胞的衰老及凋亡[54]。而在成骨细胞和骨细胞中自噬的下降也可能是细胞衰老的标志之一。因此自噬与衰老为将来进一步研究治疗 PMOP 提供了更加清晰的思路与目标。同时,随着对于自噬在骨质疏松中所发挥作用的不断深入探索和研究,以及不断发现的各种激素或药物对自噬活性产生的影响,或许能通过自噬活性的改变保持骨骼细胞之间的相互平衡并抵御细胞衰老以达到预防和治疗骨质疏松症的目的,从而降低脆性骨折的发生概率并改善绝经后妇女的生活质量。

【参考文献】

[1] Mcnamara LM. Perspective on post-menopausal osteoporosis: establishing an interdisciplinary understanding of the sequence of events from the molecular level to whole bone fractures. J R Soc Interface, 2010, 7(44): 353-372.

[2] 王方, 邹德威, 吴继功, 等. 原发性骨质疏松症的病因学研究进展. 中国骨质疏松杂志, 2012, 18(7): 675-679.
Wang F, Zou DW, Wu JG, et al. Research progress in etiology of primary osteoporosis. Chin J Osteoporosis, 2012, 18(7): 675-679. (in Chinese)

[3] Cauley JA. Estrogen and bone health in men and women. Steroids, 2015, 99(Pt A): 11-15.

[4] Shapiro IM, Layfield R, Lotz M, et al. Boning up on autophagy: the role of autophagy in skeletal biology. Autophagy, 2014, 10(1): 7-19.

[5] 白颖, 杨雪, 王蕾, 等. 中老年妇女骨质疏松健康教育现状调查与分析. 中国骨质疏松杂志, 2012, 18(10): 946-948.
Bai Y, Yang X, Wang L, et al. The investigation and analysis of health education status of osteoporosis in middle-aged women. Chin J Osteoporosis, 2012, 18(10): 946-948. (in Chinese)

[6] 孙振双, 耿元卿, 张丽君, 等. 氧化应激介导绝经后骨质疏松发病机制的研究进展. 中国骨质疏松杂志, 2016, 22(8): 1063-1067.
Sun ZS, Geng YQ, Zhang LJ, et al. Research progress on the pathogenesis of oxidative stress mediated osteoporosis. Chin J Osteoporosis, 2016, 22(8): 1063-1067. (in Chinese)

[7] Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr Rev, 2010, 31(3): 266-300.

[8] Bartell SM, Kim HN, Ambrogini E, et al. FoxO proteins restrain osteoclastogenesis and bone resorption by attenuating H_2O_2 accumulation. Nat Commun, 2014, 5: 3773.

[9] Kroemer G. Autophagy: a druggable process that is deregulated in aging and human disease. J Clin Invest, 2015, 125(1): 1-4.

[10] Perl A. mTOR activation is a biomarker and a central pathway to autoimmune disorders, cancer, obesity, and aging. Ann N Y Acad Sci, 2015, 1346(1): 33-44.

[11] Laplante M, Sabatini D M. Regulation of mTORC1 and its impact on gene expression at a glance. J Cell Sci, 2013, 126(Pt 8): 1713-1719.

[12] Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell, 2011, 147(4): 728-741.

[13] Chen J, Long F. mTORC1 signaling promotes osteoblast differentiation from preosteoblasts. PLoS One, 2015, 10(6): e0130627.

[14] Pantovic A, Krstic A, Janjetovic K, et al. Coordinated time-dependent modulation of AMPK/Akt/mTOR signaling and

autophagy controls osteogenic differentiation of human mesenchymal stem cells. Bone, 2013, 52(1): 524-531.

[15] Onal M, Piemontese M, Xiong J, et al. Suppression of autophagy in osteocytes mimics skeletal aging. J Biol Chem, 2013, 288(24): 17432-17440.

[16] Liu F, Fang F, Yuan H, et al. Suppression of autophagy by FIP200 deletion leads to osteopenia in mice through the inhibition of osteoblast terminal differentiation. J Bone Miner Res, 2013, 28(11): 2414-2430.

[17] She C, Zhu LQ, Zhen YF, et al. Activation of AMPK protects against hydrogen peroxide-induced osteoblast apoptosis through autophagy induction and NADPH maintenance: new implications for osteonecrosis treatment. Cell Signal, 2014, 26(1): 1-8.

[18] Bozec A, Bakiri L, Hoebertz A, et al. Osteoclast size is controlled by Fra − 2 through LIF/LIF-receptor signalling and hypoxia. Nature, 2008, 454(7201): 221-225.

[19] Wu DJ, Gu R, Sarin R, et al. Autophagy-linked FYVE containing protein WDFY3 interacts with TRAF6 and modulates RANKL-induced osteoclastogenesis. J Autoimmun, 2016, 73: 73-84.

[20] Kaushik S, Cuervo AM. Autophagy as a cell-repair mechanism: activation of chaperone-mediated autophagy during oxidative stress. Mol Aspects Med, 2006, 27(5-6): 444-454.

[21] Ott C, Grune T. Protein oxidation and proteolytic signalling in aging. Curr Pharm Des, 2014, 20(18): 3040-3051.

[22] Monroe DG, Mcgee-Lawrence ME, Oursler MJ, et al. Update on Wnt signaling in bone cell biology and bone disease. Gene, 2012, 492(1): 1-18.

[23] Kobayashi Y, Udagawa N, Takahashi N. Action of RANKL and OPG for osteoclastogenesis. Crit Rev Eukaryot Gene Expr, 2009, 19(1): 61-72.

[24] Ikeda F, Matsubara T, Tsurukai T, et al. JNK/c-Jun signaling mediates an anti-apoptotic effect of RANKL in osteoclasts. J Bone Miner Res, 2008, 23(6): 907-914.

[25] Yang J, Zhang X, Wang W, et al. Insulin stimulates osteoblast proliferation and differentiation through ERK and PI3K in MG-63 cells. Cell Biochem Funct, 2010, 28(4): 334-341.

[26] Pierrefite-Carle V, Santucci-Darmanin S, Breuil V, et al. Autophagy in bone: Self-eating to stay in balance. Ageing Res Rev, 2015, 24(Pt B): 206-217.

[27] 丁淑琴, 杨风琴, 张玮, 等. 山奈酚治疗去卵巢大鼠骨质疏松的实验研究. 中国新药杂志, 2014, 23(24): 2925-2930. Ding SQ, Yang FQ, Zhang W, et al. Anti-osteoporotic activity of kaempferol in ovariectomized rats. Chin J New Drugs, 2014, 23(24): 2925-2930. (in Chinese)

[28] Kim IR, Kim SE, Baek HS, et al. The role of kaempferol-induced autophagy on differentiation and mineralization of osteoblastic MC3T3-E1 cells. BMC Complement Altern Med, 2016, 16(1): 333.

[29] Shen CL, Chyu MC, Wang JS. Tea and bone health: steps forward in translational nutrition. Am J Clin Nutr, 2013, 98(6 Suppl): 1694S-1699S.

[30] Zhang PW, Tian C, Xu FY, et al. Green tea polyphenols alleviate autophagy inhibition induced by high glucose in endothelial cells. Biomed Environ Sci, 2016, 29(7): 524-528.

[31] Kotlarczyk MP, Lassila HC, O´neil CK, et al. Melatonin osteoporosis prevention study (MOPS): a randomized, double-blind, placebo-controlled study examining the effects of melatonin on bone health and quality of life in perimenopausal women. J Pineal Res, 2012, 52(4): 414-426.

[32] Maria S, Witt-Enderby PA. Melatonin effects on bone: potential use for the prevention and treatment for osteopenia, osteoporosis, and periodontal disease and for use in bone-grafting procedures. J Pineal Res, 2014, 56(2): 115-125.

[33] Gomez-Puerto MC, Verhagen LP, Braat AK, et al. Activation of autophagy by FOXO3 regulates redox homeostasis during osteogenic differentiation. Autophagy, 2016, 12(10): 1804-1816.

[34] Yang YH, Chen K, Li B, et al. Estradiol inhibits osteoblast apoptosis via promotion of autophagy through the ER-ERK-mTOR pathway. Apoptosis, 2013, 18(11): 1363-1375.

[35] Almeida M, Martin-Millan M, Ambrogini E, et al. Estrogens attenuate oxidative stress and the differentiation and apoptosis of osteoblasts by DNA-binding-independent actions of the ERalpha. J Bone Miner Res, 2010, 25(4): 769-781.

[36] Yang YH, Li B, 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. Free Radic Biol Med, 2014, 77: 10-20.

[37] Lai EH, Hong CY, Kok SH, et al. Simvastatin alleviates the progression of periapical lesions by modulating autophagy and apoptosis in osteoblasts. J Endod, 2012, 38(6): 757-763.

[38] Taranta A, Brama M, Teti A, et al. The selective estrogen receptor modulator raloxifene regulates osteoclast and osteoblast activity in vitro. Bone, 2002, 30(2): 368-376.

[39] Kim DE, Kim Y, Cho DH, et al. Raloxifene induces autophagy-dependent cell death in breast cancer cells via the activation of AMP-activated protein kinase. Mol Cells, 2015, 38(2): 138-144.

[40] Nollet M, Santucci-Darmanin S, Breuil V, et al. Autophagy in osteoblasts is involved in mineralization and bone homeostasis. Autophagy, 2014, 10(11): 1965-1977.

[41] Kneissel M, Luong-Nguyen NH, Baptist M, et al. Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts. Bone, 2004, 35(5): 1144-1156.

[42] Lee SH, Lee SY, Lee YS, et al. Higher circulating sphingosine 1-phosphate levels are associated with lower bone mineral density and higher bone resorption marker in humans. J Clin Endocrinol Metab, 2012, 97(8): E1421-E1428.

[43] Zhou L, Liu Q, Yang M, et al. Dihydroartemisinin, an anti-malaria drug, suppresses estrogen deficiency-induced osteoporosis, osteoclast formation, and RANKL-induced signaling pathways. J Bone Miner Res, 2016, 31(5): 964-974.

[44] Hu W, Chen SS, Zhang JL, et al. Dihydroartemisinin induces autophagy by suppressing NF-kappaB activation. Cancer Lett, 2014, 343(2): 239-248.

[45] Lin NY, Chen CW, Kagwiria R, et al. Inactivation of autophagy

ameliorates glucocorticoid-induced and ovariectomy-induced bone loss. Ann Rheum Dis, 2016, 75(6): 1203-1210.

[46] Deselm CJ, Miller BC, Zou W, et al. Autophagy proteins regulate the secretory component of osteoclastic bone resorption. Dev Cell, 2011, 21(5): 966-974.

[47] Cheng X, Zhu L, Zhang J, et al. Anti-osteoclastogenesis of mineral trioxide aggregate through inhibition of the autophagic pathway. J Endod, 2017, 43(5): 766-773.

[48] Chung YH, Jang Y, Choi B, et al. Beclin-1 is required for RANKL-induced osteoclast differentiation. J Cell Physiol, 2014, 229(12): 1963-1971.

[49] Jilka RL, O'brien CA. The role of osteocytes in age-related bone loss. Curr Osteoporos Rep, 2016, 14(1): 16-25.

[50] Florencio-Silva R, Sasso GR, Simoes MJ, et al. Osteoporosis and autophagy: What is the relationship? Rev Assoc Med Bras (1992), 2017, 63(2): 173-179.

[51] Yang Y, Zheng X, Li B, et al. Increased activity of osteocyte autophagy in ovariectomized rats and its correlation with oxidative stress status and bone loss. Biochem Biophys Res Commun, 2014, 451(1): 86-92.

[52] Camuzard O, Santucci-Darmanin S, Breuil V, et al. Sex-specific autophagy modulation in osteoblastic lineage: a critical function to counteract bone loss in female. Oncotarget, 2016, 7(41): 66416-66428.

[53] Chen K, Yang YH, Jiang SD, et al. Decreased activity of osteocyte autophagy with aging may contribute to the bone loss in senile population. Histochem Cell Biol, 2014, 142(3): 285-295.

[54] Capasso S, Alessio N, Squillaro T, et al. Changes in autophagy, proteasome activity and metabolism to determine a specific signature for acute and chronic senescent mesenchymal stromal cells. Oncotarget, 2015, 6(37): 39457-39468.

(收稿日期: 2017-05-11,修回日期:2017-07-13)

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[23] Wu L, Qi H, Zhong Y, et al. 11beta-hydroxysteroid dehydrogenase type 1 selective inhibitor Bvt. 2733 protects osteoblasts against endogenous glucocorticoid induced dysfunction. Endocrine Journal, 2013, 60(9): 1047-1058.

[24] Espina B, Liang M, Russell RG, et al. Regulation of bim in glucocorticoid-mediated osteoblast apoptosis. Journal of Cellular Physiology, 2008, 215(2): 488-496.

[25] Xie H, Tang LL, Luo XH, et al. Suppressive effect of dexamethasone on Timp - 1 production involves murine osteoblastic Mc3t3-E1 cell apoptosis. Amino Acids, 2010, 38(4): 1145-1153.

[26] Chang JK, Li CJ, Liao HJ, et al. Anti-inflammatory drugs suppress proliferation and induce apoptosis through altering expressions of cell cycle regulators and pro-apoptotic factors in cultured human osteoblasts. Toxicology, 2009, 258(2-3): 148-156.

[27] Plotkin LI, Manolagas SC, Bellido T. Glucocorticoids induce osteocyte apoptosis by blocking focal adhesion kinase-mediated survival, evidence for inside-out signaling leading to anoikis. The Journal of Biological Chemistry, 2007, 282(33): 24120-24130.

[28] Almeida M, Han L, Ambrogini E, et al. Glucocorticoids and tumor necrosis factor alpha increase oxidative stress and suppress wnt protein signaling in osteoblasts. The Journal of Biological Chemistry, 2011, 286(52): 44326-44335.

[29] Rossini M, Gatti D, Adami S. Involvement of Wnt/Beta-catenin signaling in the treatment of osteoporosis. Calcified Tissue International, 2013, 93(2): 121-132.

[30] Ohnaka K, Tanabe M, Kawate H, et al. Glucocorticoid suppresses the canonical Wnt signal in cultured human osteoblasts. Biochemical and Biophysical Research Communications, 2005, 329(1): 177-181.

[31] Sato AY, Cregor M, Delgado-Calle J, et al. Protection from glucocorticoid-induced osteoporosis by anti-catabolic signaling in the absence of sost/sclerostin. Journal of Bone and Mineral Research, 2016, 31(10): 1791-1802.

[32] Butler JS, Queally JM, Devitt BM, et al. Silencing Dkk1 expression rescues dexamethasone-induced suppression of primary human osteoblast differentiation. BMC Musculoskeletal Disorders, 2010, 11:210.

[33] Kim J, Lee H, Kang KS, et al. Protective effect of korean red ginseng against glucocorticoid-induced osteoporosis in vitro and in vivo. Journal of Ginseng Research, 2015, 39(1): 46-53.

[34] Lin H, Wei B, Li G, et al. Sulforaphane reverses glucocorticoid-induced apoptosis in osteoblastic cells through regulation of the Nrf2 pathway. Drug Design, Development and Therapy, 2014, 8:973-982.

[35] Li H, Qian W, Weng X, et al. Glucocorticoid receptor and sequential P53 activation by dexamethasone mediates apoptosis and cell cycle arrest of osteoblastic Mc3t3 - E1 cells. PloS One, 2012, 7(6): e37030.

[36] Sato AY, Tu X, Mcandrews KA, et al. Prevention of glucocorticoid induced-apoptosis of osteoblasts and osteocytes by protecting against endoplasmic reticulum (Er) stress in vitro and in vivo in female mice. Bone, 2015, 73:60-68.

[37] Ding H, Wang T, Xu D, et al. Dexamethasone-induced apoptosis of osteocytic and osteoblastic cells is mediated by Tak1 activation. Biochemical and Biophysical Research Communications, 2015, 460(2): 157-163.

[38] Gohel A, Mccarthy MB, Gronowicz G. Estrogen prevents glucocorticoid-induced apoptosis in osteoblasts in vivo and in vitro. Endocrinology, 1999, 140(11): 5339-5347.

[39] Wang X, Simpson ER, Brown KA. P53: Protection against tumor growth beyond effects on cell cycle and apoptosis. Cancer Research, 2015, 75(23): 5001-5007.

[40] Liu W, Xu C, Zhao H, et al. Osteoprotegerin induces apoptosis of osteoclasts and osteoclast precursor cells via the Fas/Fas ligand pathway. PLoS One, 2015, 10(11): e0142519.

[41] Kogianni G, Mann V, Ebetino F, et al. Fas/Cd95 Is associated with glucocorticoid-induced osteocyte apoptosis. Life Sciences, 2004, 75(24): 2879-2895.

(收稿日期: 2017-05-28,修回日期:2017-07-24)