

· 综述 ·

探讨 PM_{2.5} 暴露的肺外毒理效应对绝经后骨代谢的影响机制

刘宗玉 黄惠娟* 杨帆 曾小娟

厦门大学附属东方医院妇产科, 福建 福州 350025

中图分类号: R36 文献标识码: A 文章编号: 1006-7108(2020) 04-0595-05

摘要: 骨代谢是骨吸收和骨形成两方面动态过程,其分子机制涉及氧化应激、炎症因子、雌激素及相关受体(如 AhR)等多种因素、多途径调节,在骨重塑方面起到至关重要的作用。大气细颗粒物(airborne particulate matter, PM_{2.5})因其粒径小、表面积大、活性强,是有毒、有害物质吸附在其表面的有效载体,且气溶胶在大气中的沉降速率低、搬运距离远,对人体危害更大。PM_{2.5} 可随呼吸吸入肺泡中聚集,破坏肺泡毛细血管屏障而进入循环系统作用于全身各个脏器,造成各个脏器不同程度受损,并激活一系列全身的或局部的炎症因子、氧化作用和相关受体(如 AhR)等对成骨细胞及破骨细胞的分化增殖起到调控作用,参与骨代谢。

关键词: PM_{2.5}; 氧化应激及活性氧; 炎症因子; 雌激素; 芳香烃受体(AhR); 绝经后骨质疏松

To explore the mechanism of extrapulmonary toxicological effects of PM_{2.5} exposure on postmenopausal bone metabolism

LIU Zongyu, HUANG Huijuan*, YANG Fan, ZENG Xiaojuan

Department of Obstetrics and Gynecology, Dongfang Hospital Affiliated to Xiamen University, Fuzhou 350025, China

* Corresponding author: HUANG Huijuan, Email: hhj352@163.com

Abstract: Bone metabolism is a dynamic process of bone resorption and bone formation. Its molecular mechanism involves oxidative stress, inflammatory factors, estrogen and related receptors (such as AhR). It plays an important role in bone remodeling. Atmospheric fine particulate matter (airborne particulate matter, PM_{2.5}) because of its small particle size, large surface area and strong activity, is an effective carrier for toxic and harmful substances adsorbed on its surface, and the deposition rate of aerosols in the atmosphere is low and the transport distance is long, so it is more harmful to human beings. PM_{2.5} can accumulate in the alveoli of respiratory tract, destroy the alveolar capillary barrier and enter the blood system to act on all organs of the whole body, Resultsing in different degrees of damage to each organ, and activating a series of systemic or local inflammatory factors, oxidation and related receptors (such as AhR), which regulate the differentiation and proliferation of osteoblasts and osteoclasts and participate in bone metabolism.

Key words: PM_{2.5}; oxidative stress and reactive oxygen species; inflammatory cytokines; estrogen; aromatic hydrocarbon receptor(AHR); postmenopausal osteoporosis

绝经后骨质疏松症(postmenopausal osteoporosis, PMOP)是衰老相关性低雌激素效应,导致高效骨重塑向骨吸收方向进行致骨脆性增加、易于骨折的全身性骨病,是骨质丢失中最常见的一种类型^[1]。我国人口基数大,人口老龄化严峻,上

海部分地区调查发现,骨质疏松造成髋部骨折中,中老年女性是男性3倍多,人均住院费用高达3万余元,平均住院天数近18 d^[2]。骨质疏松的高发病率及其并发症的高致残率、高致死率及高消耗医疗、经济资源问题,使得PMOP成为我国医疗卫生面临的重大挑战。PM_{2.5}易吸附大量氧化还原特性的过渡金属、持久的自由基、多环芳烃(PAHs)等有害物质,并具有极强的穿透力,极易破坏肺泡毛细血管屏障随血液作用于全身脏器,改变机体多种生物活性,

基金项目: 国家自然科学基金:PM_{2.5}暴露对绝经后骨质疏松症的影响及其机制的实验研究(81771547)

* 通信作者: 黄惠娟, Email: hhj352@163.com

包括炎症细胞的招募,释放大量炎症因子和活性氧(ROS)等,对人体毒害最强^[3-5]。我国京津冀、长三角,珠三角年平均PM_{2.5}分别为70、72、53 $\mu\text{g}/\text{m}^3$ ^[6]均高于我国规定的二级年均水平限值35 $\mu\text{g}/\text{m}^3$,提示我国环境污染严峻。环境污染对破骨/成骨细胞的杀伤作用与氧化应激及活性氧等相关,其可使RANK/RANKL/OPG比值失衡和下调抗氧化酶,引起骨质丢失^[7]。现就氧化应激、炎症因子、雌激素及相关受体(如AhR)等对骨质疏松的影响进行综述。

1 PM_{2.5}暴露的毒性效应与绝经后骨代谢密切相关

1.1 氧化应激及活性氧

PM_{2.5}参与机体生物活性转化过程,可诱导炎症和氧化损伤产生具有协同效应的活性氧或氮(如ROS、RNS)和炎症介质^[8]。氧化应激及活性氧被广泛认为是许多病理条件下的致病因素,包括骨质疏松。缺氧可使骨髓基质细胞中的线粒体产生大量活性氧,其在低雌激素水平能强有力促进骨吸收^[9-11]。此外,雌激素缺乏可致相关组织主要抗氧化剂、抗氧化酶水平显著下降,活性氧(如H₂O₂)水平升高,降低骨的抗氧化防御能力,运用抗氧化剂可阻止卵巢切除后引起的骨质疏松^[11-14]。Altindag等^[15]通过测定血浆TAS、TOS水平获得OSI时,发现血浆中TOS和OSI值在绝经后骨质疏松症患者中明显升高,血浆TAS水平明显降低,而腰椎和股骨颈部位骨密度与OSI呈显著负相关。Baek等^[16]通过测定血清DNA氧化损伤的标志物8-羟基-2'-脱氧鸟苷(8-OH-DG)水平,同样发现8-OH-DG水平与腰椎、全髋关节、股骨颈和粗隆部的骨密度水平呈负相关。

另外,职业性暴露于低水平PM_{2.5}(12.4 $\pm$ 6.9 $\mu\text{g}/\text{m}^3$)和BaP(1.0 $\pm$ 0.6 ng/ m^3)的出租车司机血清炎症生物标志物水平明显升高,活性氧和相关氧化损伤标志物增加,抗氧化酶和抗炎介质(IL-10)下降^[17]。反过来,升高的活性氧又可增加吸收性炎症因子的表达间接刺激破骨细胞^[18-19]。雌激素缺乏致骨髓微环境中负调控炎症因子、氧化物等系统地、局部地增加,并通过TGF- β 的表达延缓破骨细胞的凋亡,诱导破骨细胞分化,引发骨质疏松^[20]。促炎细胞因子被证明能提高不同类型细胞内的ROS水平^[21]。而外源性ROS或内源性ROS均可刺激破骨细胞的形成和吸收活动,但其细节尚不清楚。PM_{2.5}可促进细胞内活性氧生成和NF- κ B磷酸化,

ROS(主要H₂O₂)可刺激M-CSF和RANKL的表达,提高RANKL/OPG的比值,使低雌激素水平妇女骨吸收增加和骨量降低^[15-16,22]。最新研究指出,RANKL能参与Bach 1的核易位,抑制Nrf 2依赖的抗氧化酶的表达,并通过与Bach 1核蓄积竞争,从而增强破骨细胞内的ROS信号^[23]。应用抗氧化剂能减少RANKL诱导的Akt、NF- κ B和ERK活化,显著降低RANKL诱导的骨吸收活性和破骨细胞存活率,促进破骨发生^[22]。此外,ROS还可通过MAPK和Ca²⁺介导的信号通路参与骨代谢^[21]。

1.2 炎症细胞因子

目前国内关于PM_{2.5}诱发促炎因子直接或间接引发绝经后骨质疏松的相关研究并不多见。Zheng等^[24]发现绝经后妇女腰椎骨密度与血清炎症细胞因子IL-1、IL-6和TNF- α 呈负相关性,提示雌激素可调节各种细胞因子的分泌或释放阻止骨质丢失。Terauchi等^[25]指出骨髓中Th细胞分泌的IL-1、IL-6和TNF- α 等均可促进骨髓破骨细胞的发生、增殖,引发骨质疏松。PM_{2.5}在肺中的沉积可引起全身炎症反应,并能刺激骨髓产生广谱的促炎细胞因子,且颗粒直径越小,血清中产生的炎症细胞因子越多,引发相应脏器病理损害越严重^[26]。研究发现慢性暴露于PM_{2.5}可使血清中的TNF- α 、IL-1、IL-6、IFN- γ 等炎症生物标志物水平明显升高,导致血清RANKL值增加41%,OPG下降22%,引起该群体骨量减少^[17,27-28]。

炎症细胞因子在缺氧、感染和炎症期间对骨破坏发挥着关键作用。雌激素缺乏可通过抗原提呈细胞和细胞因子IFN- γ 、IL-7和TGF- β 介导的复杂细胞机制诱导系统地、局部地增加炎症细胞因子分泌或释放^[25]。强效骨吸收因子(TNF- α 、IL-1、IL-6)能通过分布在破骨细胞前体上相应的受体(如TNFR、IL-1 R和IL-6R)发挥其生物学效应,在对其相应受体缺陷小鼠的分析表明,TNFR 1、IL-1 RI、sIL-6R促进破骨细胞分化,而TNFR 2、IL-1 RII抑制破骨细胞分化,TNF- α 、IL-1、IL-6能增强TNFR 1、IL-1 RI、sIL-6R破骨发生,降低TNFR 2、IL-1 RII功能,促进破骨发生^[29-31]。研究发现敲除TNF- α 、IL-1 R、IL-6基因的动物可抑制卵巢切除后骨质丢失,证实细胞因子对绝经后骨代谢的影响是必不可少的、多途径的^[32-34]。

最后,炎症介质直接或间接通过激活共同信号通路OPG/RANKL/RANK调节骨代谢。这些细胞因子可提高RANKL mRNA的表达和RANKL/OPG

的比值,激活下游信号磷酸化(如 JNK、p38、MAPK、JAK2、ERK 和 Akt)促进成骨细胞介导的破骨细胞分化、成熟;还可直接强烈激活 NF- κ B、p38、ERK 和应激激活蛋白激酶/c-Jun NH2-末端激酶活性,并显著降低 ALP 活性及成骨细胞基因(RunX 2、Osterix 和骨钙素)的表达,且呈剂量依赖性抑制骨矿化和成骨细胞分化,从而导致女性骨质丢失加重^[34-38]。炎症因子还能强烈抑制成骨细胞的生成,这种抑制成骨细胞活性的途径是通过影响细胞因子下游信号通路,诸如 MAPK、Stats、SMURF 1/2、PGE2 等^[36,38-43],使新骨形成无法代偿骨吸收。

1.3 芳香烃受体(AhR)

芳香烃受体(AhR)广泛分布于人体组织器官中(如骨),与 ER 以复杂的方式相互起干扰作用,且具有类雌激素或抗雌激素样作用。TCDD、PAHs、BaP 等是典型芳基烃受体(AhR)激动剂和 CYP1A1 诱导剂,并通过 AHR 与 ER α 之间相互干扰来共同竞争激活 Arnt 核蛋白,干扰雌激素信号传导,促进破骨细胞基因表达^[44]。多环芳烃(PAHs)介导 NF- κ B 诱导巨噬细胞和破骨细胞表达 CYP1B1(一种雌激素代谢酶)增加,使骨中雌激素水平降低,导致骨成积率降低,影响骨重塑^[45]。Iqbal 等^[46]指出,破骨细胞作用在 Cyp1a1/1a2/1b1^{-/-}三重 KO 小鼠骨吸收减少,并且在 AhR^{-/-}的小鼠,骨量显著增加。Hýžd' alová 等^[47]利用雌激素敏感的人乳腺癌 MCF-7 细胞

的 AhR 基因敲除变异体,观察到芳香烃化合物及代谢物在 MCF-7 AhRKO 细胞中的雌激素样作用减弱,而 CYP1A1 和 CYP1B1 酶的异位表达部分恢复了 BAP 代谢及其对细胞增殖的影响。另外,在对敲除 AhR(RANK Δ Oc/ Δ Oc)的骨髓巨噬细胞培养中,也发现 B 淋巴细胞诱导 CYP1B1、CYP1A2 表达下调,呈现破骨功能受损和分化抑制^[48]。

此外,芳香烃化合物通过激活 AhR 来抑制 SMAD 依赖的信号通路 TGF- β 1/Smad4 和 SMAD 非依赖的 TGF- β 1/ERK/AKT 信号通路,使其下游相应蛋白磷酸化降低,成骨细胞基因 Runx2 和 OPN 明显降低,导致成骨分化和成熟均受抑制,骨生成减少^[49]。同时,激活 AhR 还能通过 RANK/c-Fos 信号轴调控髓系前体向破骨细胞的分化,在 AhR 过表达的 BMMS 中,骨吸收面积和 CTX-1 的释放均明显升高,促进破骨作用^[50]。激活 AhR 还可介导影响 NF- κ B、Wnt、MAPK 等信号通路蛋白的转录促进破骨作用^[51]。

2 其他介导途径

垂体-骨轴具有内分泌骨重塑调节的功能。垂体激素(FSH)能通过破骨细胞及其前体物上的 Gi 2 α 偶联 FSH 受体(FSHR)来增强 ERK、Akt、I κ B α (核因子 κ B-轻链增强子)的磷酸化,从而增强 ERK/c-Fos 和 NF- κ B 信号转导,介导 RANKL 的促骨吸收

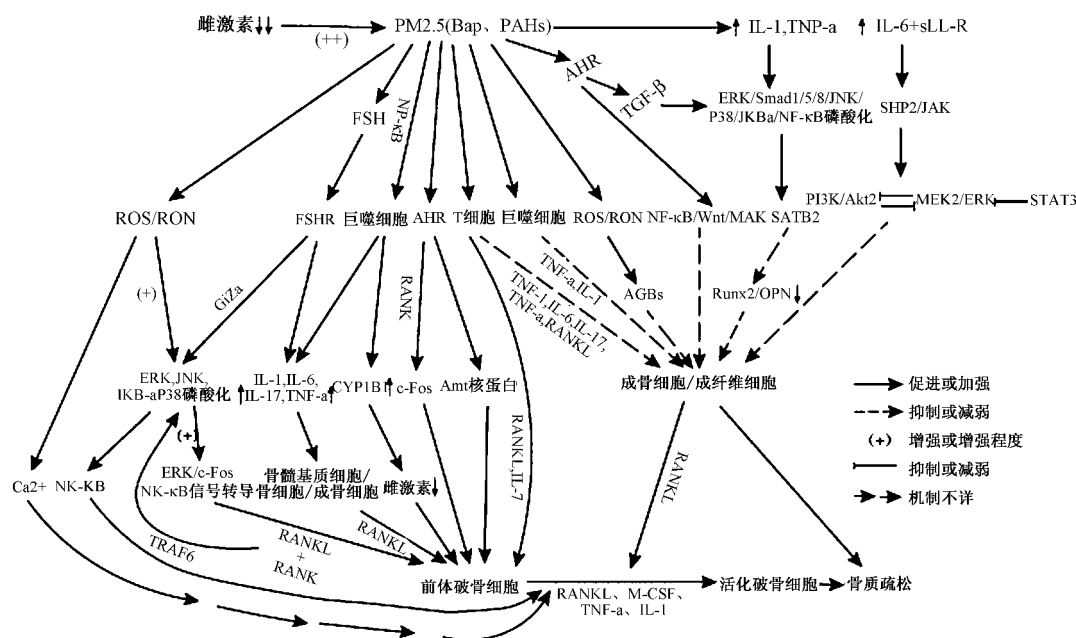


图1 PM2.5在低雌激素水平中对骨代谢影响的机制(具体机制详见文中参考文献)。

Fig.1 The mechanism of PM2.5 affecting bone metabolism at low estrogen levels

作用^[52]。另外, FSH 可直接刺激骨髓微环境产生 TNF α 、IL-1 β 、IL-6, 而 FSH β 基因缺陷小鼠骨髓巨噬细胞产生炎症因子减少, 即使雌激素缺乏, 仍可免于骨量丢失^[53-54]。PM2.5 暴露诱导下丘脑炎症因子释放, 从而抑制下丘脑-垂体-性腺轴, 影响垂体 LH 和 FSH 释放, 影响相应功能^[55]。应用 FSH 特异性抗体可增加骨量^[56]。

3 结语

PM2.5 可通过多途径、多通路促进雌激素缺乏症的骨质丢失。近年来, 国内有关学者越来越注意到环境污染对骨侵蚀的作用。笔者有望通过在体水平或细胞水平建模探讨 PM2.5 暴露对年龄相关性雌激素缺乏介导骨质丢失发生、发展的研究。

【参 考 文 献】

- [1] Radominski SC, Bernardo W, Paula AP, et al. Brazilian guidelines for the diagnosis and treatment of postmenopausal osteoporosis[J]. Rev Bras Reumatol Engl Ed, 2017, 57(Suppl 2): 452-466.
- [2] 中华医学会骨质疏松和骨矿盐疾病分会, 中华医学会骨科学分会骨质疏松学组. 骨质疏松性骨折患者抗骨质疏松治疗与管理专家共识[J]. 中华骨质疏松和骨矿盐疾病杂志, 2015, 8(3): 189-195.
- [3] 环境空气质量标准[S]. (GB3095-2012).
- [4] 葛良全, 刘合凡, 郭生良, 等. 大气颗粒物浓度与重金属元素分析研究进展[J]. 科技导报, 2014, 32(33): 67-74.
- [5] Falcon-Rodriguez CI, Osorio-Vargas AR, Sada-Ovalle I, et al. Aeroparticles, composition, and lung diseases [J]. Front Immunol, 2016, 7: 3.
- [6] 环境保护部发布 2018 年 1 月重点区域和 74 个城市空气质量状况[J]. 节能与环保, 2018, (3): 14.
- [7] Scimeca M, Feola M, Romano L, et al. Heavy metals accumulation affects bone microarchitecture in osteoporotic patients[J]. Environ Toxicol, 2017, 32(4): 1333-1342.
- [8] Valavanidis A, Vlachogianni T, Fiotakis K, et al. Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms[J]. Int J Environ Res Public Health, 2013, 10(9): 3886-3907.
- [9] Knowles HJ. Hypoxic regulation of osteoclast differentiation and bone resorption activity[J]. Hypoxia (Auckl), 2015, 3: 73-82.
- [10] Bax BE, Alam AS, Banerji B, et al. Stimulation of osteoclastic bone resorption by hydrogen peroxide[J]. Biochem Biophys Res Commun, 1992, 183(3): 1153-1158.
- [11] Garrett I R, Boyce BF, Oreffo RO, et al. Oxygen-derived free radicals stimulate osteoclastic bone resorption in rodent bone in vitro and in vivo[J]. J Clin Invest, 1990, 85(3): 632-639.
- [12] Lean JM, Davies JT, Fuller K, et al. A crucial role for thiol antioxidants in estrogen-deficiency bone loss[J]. J Clin Invest, 2003, 112(6): 915-923.
- [13] Lean JM, Jagger CJ, Kirstein B, et al. Hydrogen peroxide is essential for estrogen-deficiency bone loss and osteoclast formation [J]. Endocrinology, 2005, 146(2): 728-735.
- [14] Muthusami S, Ramachandran I, Muthusamy B, et al. Ovariectomy induces oxidative stress and impairs bone antioxidant system in adult rats[J]. Clin Chim Acta, 2005, 360(1-2): 81-86.
- [15] Altindag O, Erel O, Soran N, et al. Total oxidative/antioxidative status and relation to bone mineral density in osteoporosis[J]. Rheumatol Int, 2008, 28(4): 317-321.
- [16] Baek KH, Oh KW, Lee WY, et al. Association of oxidative stress with postmenopausal osteoporosis and the effects of hydrogen peroxide on osteoclast formation in human bone marrow cell cultures[J]. Calcif Tissue Int, 2010, 87(3): 226-235.
- [17] Brucker N, Moro AM, Charao MF, et al. Biomarkers of occupational exposure to air pollution, inflammation and oxidative damage in taxi drivers[J]. Sci Total Environ, 2013, 463-464: 884-893.
- [18] Ferguson MD, Migliaccio C, Ward T. Comparison of how ambient PM₁₀ and PM2.5 influence the inflammatory potential[J]. Inhal Toxicol, 2013, 25(14): 766-773.
- [19] Ha H, Kwak HB, Lee SW, et al. Reactive oxygen species mediate RANK signaling in osteoclasts[J]. Exp Cell Res, 2004, 301(2): 119-127.
- [20] Pietschmann P, Mechtcheriakova D, Meshcheryakova A, et al. Immunology of Osteoporosis: A Mini-Review[J]. Gerontology, 2016, 62(2): 128-137.
- [21] Callaway DA, Jiang JX. Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases[J]. J Bone Miner Metab, 2015, 33(4): 359-370.
- [22] Li B, Guo L, Ku T, et al. PM2.5 exposure stimulates COX-2-mediated excitatory synaptic transmission via ROS-NF-kappaB pathway[J]. Chemosphere, 2018, 190: 124-134.
- [23] Kanzaki H, Shinohara F, Itohiya K, et al. RANKL induces Bach1 nuclear import and attenuates Nrf2-mediated antioxidant enzymes, thereby augmenting intracellular reactive oxygen species signaling and osteoclastogenesis in mice[J]. FASEB J, 2017, 31(2): 781-792.
- [24] Zheng SX, Vrindts Y, Lopez M, et al. Increase in cytokine production (IL-1 beta, IL-6, TNF-alpha but not IFN-gamma, GM-CSF or LIF) by stimulated whole blood cells in postmenopausal osteoporosis [J]. Maturitas, 1997, 26(1): 63-71.
- [25] Terauchi M. Role of the immune system in the pathophysiology of postmenopausal osteoporosis[J]. Nihon Rinsho, 2011, 69(7): 1215-1219.
- [26] van Eeden SF, Tan WC, Suwa T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM 10) [J]. Am J Respir Crit Care Med, 2001, 164(5): 826-830.
- [27] Calderon-Garciduenas L, Mora-Tiscareno A, Francolira M, et al. Exposure to urban air pollution and bone health in clinically healthy six-year-old children[J]. Arh Hig Rada Toksikol, 2013,

- 64(1): 23-34.
- [28] Saha H, Mukherjee B, Bindhani B, et al. Changes in RANKL and osteoprotegerin expression after chronic exposure to indoor air pollution as a result of cooking with biomass fuel [J]. *J Appl Toxicol*, 2016, 36(7): 969-976.
- [29] Abu-Amer Y, Erdmann J, Alexopoulou L, et al. Tumor necrosis factor receptors types 1 and 2 differentially regulate osteoclastogenesis [J]. *J Biol Chem*, 2000, 275 (35): 27307-27310.
- [30] Akira S, Takeda K. Toll-like receptor signalling [J]. *Nat Rev Immunol*, 2004, 4(7): 499.
- [31] Lazzaro L, Tonkin BA, Poulton IJ, et al. IL-6 trans-signalling mediates trabecular, but not cortical, bone loss after ovariectomy [J]. *Bone*, 2018, 112: 120-127.
- [32] Lorenzo JA, Naprta A, Rao Y, et al. Mice lacking the type I interleukin-1 receptor do not lose bone mass after ovariectomy [J]. *Endocrinology*, 1998, 139(6): 3022-3025.
- [33] Roggia C, Tamone C, Cenci S, et al. Role of TNF-alpha producing T-cells in bone loss induced by estrogen deficiency [J]. *Minerva Med*, 2004, 95(2): 125-132.
- [34] Wong PK, Quinn JM, Sims NA, et al. Interleukin-6 modulates production of T lymphocyte-derived cytokines in antigen-induced arthritis and drives inflammation-induced osteoclastogenesis [J]. *Arthritis Rheum*, 2006, 54(1): 158-168.
- [35] Lam J, Takeshita S, Barker JE, et al. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand [J]. *J Clin Invest*, 2000, 106 (12): 1481-1488.
- [36] Zuo C, Zhao X, Shi Y, et al. TNF-alpha inhibits SATB2 expression and osteoblast differentiation through NF-kappaB and MAPK pathways [J]. *Oncotarget*, 2018, 9(4): 4833-4850.
- [37] Kaneshiro S, Ebina K, Shi K, et al. IL-6 negatively regulates osteoblast differentiation through the SHP2/MEK2 and SHP2/Akt2 pathways in vitro [J]. *J Bone Miner Metab*, 2014, 32(4): 378-392.
- [38] Wu Q, Zhou X, Huang D, et al. IL-6 Enhances osteocyte-mediated osteoclastogenesis by promoting JAK2 and RANKL activity in vitro [J]. *Cell Physiol Biochem*, 2017, 41 (4): 1360-1369.
- [39] Kaneki H, Guo R, Chen D, et al. Tumor necrosis factor promotes Runx2 degradation through up-regulation of Smurf1 and Smurf2 in osteoblasts [J]. *J Biol Chem*, 2006, 281 (7): 4326-4333.
- [40] Huang RL, Yuan Y, Tu J, et al. Opposing TNF-alpha/IL-1beta- and BMP-2-activated MAPK signaling pathways converge on Runx2 to regulate BMP-2-induced osteoblastic differentiation [J]. *Cell Death Dis*, 2014, 5: e1187.
- [41] Park H, Noh AL, Kang JH, et al. Peroxiredoxin II negatively regulates lipopolysaccharide-induced osteoclast formation and bone loss via JNK and STAT3 [J]. *Antioxid Redox Signal*, 2015, 22(1): 63-77.
- [42] Huang H, Veien ES, Zhang H, et al. Skeletal Characterization of Smurf2-deficient mice and in vitro analysis of smurf2-deficient chondrocytes [J]. *PLoS One*, 2016, 11(1): e0148088.
- [43] Liu XH, Kirschenbaum A, Yao S, et al. Interactive effect of interleukin-6 and prostaglandin E2 on osteoclastogenesis via the OPG/RANKL/RANK system [J]. *Ann N Y Acad Sci*, 2006, 1068: 225-233.
- [44] Swedenborg E, Kotka M, Seifert M, et al. The aryl hydrocarbon receptor ligands 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin and 3-methylcholanthrene regulate distinct genetic networks [J]. *Mol Cell Endocrinol*, 2012, 362(1): 39-47.
- [45] Voronov I, Li K, Tenenbaum HC, et al. Benzo [a] pyrene inhibits osteoclastogenesis by affecting RANKL-induced activation of NF-kappaB [J]. *Biochem Pharmacol*, 2008, 75 (10): 2034-2044.
- [46] Iqbal J, Sun L, Cao J, et al. Smoke carcinogens cause bone loss through the aryl hydrocarbon receptor and induction of Cyp1 enzymes [J]. *Proc Natl Acad Sci U S A*, 2013, 110 (27): 11115-11120.
- [47] Hyzd' alova M, Pivnicka J, Zapletal O, et al. Aryl Hydrocarbon receptor-dependent metabolism plays a significant role in estrogen-like effects of polycyclic aromatic hydrocarbons on cell proliferation [J]. *Toxicol Sci*, 2018, 165(2): 447-461.
- [48] Yu TY, Pang WJ, Yang GS. Aryl hydrocarbon receptors in osteoclast lineage cells are a negative regulator of bone mass [J]. *PLoS One*, 2015, 10(1): e0117112.
- [49] Zhou Y, Jiang R, An L, et al. Benzo [a] pyrene impedes self-renewal and differentiation of mesenchymal stem cells and influences fracture healing [J]. *Sci Total Environ*, 2017, 587-588: 305-315.
- [50] Izawa T, Arakaki R, Mori H, et al. The nuclear receptor AhR controls bone homeostasis by regulating osteoclast differentiation via the RANK/c-Fos signaling axis [J]. *J Immunol*, 2016, 197 (12): 4639-4650.
- [51] Yu H, Jiang L, Wan B, et al. The role of aryl hydrocarbon receptor in bone remodeling [J]. *Prog Biophys Mol Biol*, 2018, 134: 44-49.
- [52] Sun L, Peng Y, Sharrow AC, et al. FSH directly regulates bone mass [J]. *Cell*, 2006, 125(2): 247-260.
- [53] Iqbal J, Sun L, Kumar TR, et al. Follicle-stimulating hormone stimulates TNF production from immune cells to enhance osteoblast and osteoclast formation [J]. *Proc Natl Acad Sci U S A*, 2006, 103(40): 14925-14930.
- [54] Cannon JG, Cortez-Cooper M, Meaders E, et al. Follicle-stimulating hormone, interleukin-1, and bone density in adult women [J]. *Am J Physiol Regul Integr Comp Physiol*, 2010, 298 (3): R790-798.
- [55] Qiu L, Chen M, Wang X, et al. Exposure to concentrated ambient PM2.5 compromises spermatogenesis in a mouse model: role of suppression of hypothalamus-pituitary-gonads axis [J]. *Toxicol Sci*, 2018, 162(1): 318-326.
- [56] Ji Y, Liu P, Yuen T, et al. Epitope-specific monoclonal antibodies to FSHbeta increase bone mass [J]. *Proc Natl Acad Sci U S A*, 2018, 115(9): 2192-2197.

(收稿日期: 2019-02-11; 修回日期: 2019-06-21)