破骨细胞的形成和活化研究进展

陈晓虎 孙瑜隆 骞爱荣 李京宝* 商 澎

(西北工业大学生命学院, 西北工业大学特殊环境生物物理学研究所,
空间生物实验模拟技术国防重点学科实验室, 西安 710072)

摘要 破骨细胞是骨髓系细胞经细胞因子RANKL和M-CSF共同刺激后融合而成, 在维持骨代谢平衡中发挥重要作用。破骨细胞的“形成”和“活化”是破骨细胞生理活动的两个重要方面。该文综述了最近关于破骨细胞的“形成”和“活化”方面的研究进展。从转录因子、细胞因子、酸性环境、蛋白激酶和淋巴细胞等方面详述了对破骨细胞形成的调节, 从整合素、溶酶体、Src蛋白、破骨相关基因、骨保护素、Ephrin/Eph和Semaphorin信号通路等方面详述了对破骨细胞活化的调节, 并总结了破骨细胞凋亡方面的最新进展。最后, 该文阐述了力学刺激对破骨细胞形成和活化的影响, 为以破骨细胞为靶点的药物研发提供了新的思路。

关键词 破骨细胞; 骨吸收; 形成; 活化; NFATc1; NF-κB; RANKL; 凋亡

Recent Advances in the Formation and Activation of Osteoclasts

Chen Xiaohu, Sun Yulong, Qian Airong, Li Jingbao*, Shang Peng

(*Key Laboratory for Space Bioscience and Biotechnology, Institute of Special Environmental Biophysics, School of Life Sciences, Northwestern Polytechnical University, Xi'an 710072, China*)

Abstract Osteoclasts are giant multinucleated cells formed from myeloid lineage cells activated by receptor activator of NF-κB ligand (RANKL) and macrophage cology stimulating factor (M-CSF). It is well known that osteoclasts play pivotal role in bone metabolic balance. The “formation” and “activation” of osteoclasts are two important physiological aspects of the osteoclasts and this review outlines the latest advances of these two aspects. On the one hand, many molecules are involved in the regulation of osteoclast formation, including transcription factors, cytokines, acidosis, protein kinases and lymphocytes. On the other hand, the activation of osteoclast is modulated by diverse factors such as integrins, lysosome, Src protein, osteoclast-related genes, osteoprotegerin, Ephrin/Eph and Semaphorin signaling pathways. Moreover, the recent advances in osteoclast are also reviewed. In addition, we disscuss the influence of mechanical stimulation in osteoclast formation and activation. Furthermore, this article also provides potential clues for the potential drug targets against osteoclast.

Key words osteoclast; bone resorption; formation; activation; NFATc1; NF-κB; RANKL; apoptosis

破骨细胞的骨吸收功能在维持骨代谢平衡中具有关键作用, 它有助于维持骨骼系统的完整性和矿物质的稳态, 并且与局部或全身性骨质疏松密切相关。破骨细胞来源于特定的破骨细胞前体(osteo-

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*通讯作者。Tel: 029-88491840, E-mail: lijingbao@nwpu.edu.cn
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*Corresponding author. Tel: +86-29-88491840, E-mail: lijingbao@nwpu.edu.cn
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clast precursors, OCPs)。OCPs产生于骨髓, 随后进入血循环, 并在一系列信号分子(趋化因子、细胞因子等)的作用下迁移至骨吸收单元(bone remodeling units, BRUs)并发挥骨吸收作用。

破骨细胞的“形成”和“活化”是其发挥生理作用的两个重要方面[1]。破骨细胞的形成受到转录因子、细胞因子和淋巴细胞等方面的调节; 而整合素、Src蛋白、破骨相关基因、骨保护素、Ephrin/Eph和Semaphorin信号通路等在破骨细胞的活化过程中具有关键调控作用。力学刺激在调节破骨细胞形成、活化方面具有重要的作用, 成骨细胞骨形成与破骨细胞骨吸收动态平衡对维持生理状态骨代谢平衡具有关键作用, 一旦平衡被打破可导致骨质疏松、骨硬化病(osteopetrosis)等多种骨代谢性疾病。因此, 破骨细胞是骨质疏松和骨折的预防和治疗方面的重要靶点, 而二膦酸盐是这方面使用最广泛的药物[2]。然而, 研究表明长期使用该药物与非典型股骨骨折具有密切相关性, 临床静脉注射二膦酸盐的患者容易出现颌骨坏死[3]。因此, 具有全新靶点的抗骨吸收药物的研发具有迫切的现实意义。本文围绕破骨细胞的“形成”和“活化”这两个方面, 对其机制研究及对应的潜在药物靶点的最近进展作一综述。

1 破骨细胞形成的调节

1.1 转录因子对破骨细胞形成的调节

破骨细胞的成熟过程受到众多转录因子的调控, 而转录因子NFATc1(nuclear factor of activated T cells cytoplasmic 1)即为其中的关键分子。NFATc1是NFAT转录因子家族成员之一, 该家族首先发现于T淋巴细胞中, 具有调节多种生理活动的作用[4]。在OCPs中, NFATc1通过钙调磷酸酶的去磷酸化作用被激活, 并参与破骨细胞的形成、活化的所有方面, 是抗破骨细胞疗法的一个首要靶向目标[5-6]。在治疗方面, NFATc1抑制剂已被用于治疗炎症性关节炎引起的骨质流失[7]。

此外, 转录因子PU.1、MITF(microphthalmia-associated transcription factor)也在骨髓生成OCPs的前期过程中具有重要作用[8]。研究表明, PU.1和MITF能促进OCPs上M-CSF受体(c-fms)的表达[8], 而缺乏这两种转录因子的小鼠易患骨硬化病[9], 这提示以上转录因子可作为抗骨吸收的潜在靶点。

1.2 细胞因子对破骨细胞形成的影响

1.2.1 巨噬细胞集落刺激因子(macrophage colony stimulating factor, M-CSF) 包括M-CSF在内的细胞因子在破骨细胞成熟过程中具有不可或缺的调控作用。M-CSF最初由成骨细胞分泌产生, 可与髓系细胞上的相应受体结合并促进破骨细胞形成。M-CSF对于破骨细胞形成过程中基因谱的表达具有关键的调控作用[10]。在信号传导方面, 它可通过ERK(extracellular signal-regulated kinase, ERK)/Grb-2(growth factor receptor bound protein 2, Grb-2)和Akt/PI3K(phosphoinositide 3-kinase, PI3K)信号通路调节OCPs的增殖、分化和存活[11]。此外, M-CSF也可通过DAP12(DNAX-activating protein 12, DAP12)和Syk(spleen tyrosine kinase, Syk)调节破骨细胞的骨吸收功能[11]。

1.2.2 NF-κB受体激活蛋白配体(receptor activator of NF-κB ligand, RANKL) RANKL是肿瘤坏死因子(tumor necrosis factor, TNF)超家族成员之一, 主要由成骨细胞系、T细胞和B细胞分泌[12]。但也有一系列研究表明, 成骨细胞并不在破骨细胞的形成过程担当必要角色, 而骨细胞在破骨细胞的形成和活化过程中可能具有重要作用, 进而影响骨重建过程[13-16]。最近发现, 在松质骨中骨细胞分泌的RANKL才是调节破骨细胞形成的主要来源[17-18], 因此也有学者认为骨细胞对破骨细胞具有重要的调节作用[19]。

研究发现, 如果阻断RANKL下游的信号分子NF-κB和c-Fos, 会引起OCPs数量增加[20-21]并促使OCPs分化为巨噬细胞系细胞[22]。因此, 使用抗RANKL的药物可增加OCPs的数量, 而在中断药物治疗后, 引起OCPs分化为破骨细胞并导致破骨细胞数量增加。这一机制可解释在临床试验中, 停止使用狄诺塞麦后患者血液中骨吸收标志物增加的现象[23]。

RANKL介导的信号通路分为经典与非经典途径两种。在经典信号通路中, RANKL与RANK结合后引起IKKβ的磷酸化, 后者引起IκB的降解, 最终导致NF-κB释放入核, 防止破骨细胞凋亡, 并维持其正常分化[24-25]。动物实验表明, 敲除*IKKβ*基因可引起小鼠的破骨细胞形成抑制并最终导致骨硬化病[25]。

RANKL引起的非经典信号通路起效较慢。处理3~4 h后, RANKL在NIK(NF-κB inducing kinase)等介导下激活NF-κB信号通路[26], 并导致前体分

子p100加工为p52。在病理状态下, NIK、IKKα和p100可调控RANKL或TNF引起的破骨细胞形成过程。例如, 静脉注射小鼠黑色素肉瘤细胞, 引其野生型小鼠局部骨质溶解, 而*NIK*$^{-/-}$小鼠则未受影响[25]。相反, TNF转基因小鼠(TNF-transgenic TNF-Tg)与*p100*$^{-/-}$鼠杂交后代比TNF转基因小鼠父代更容易出现关节炎及骨质侵蚀, 这表明p100抑制了TNF诱导的破骨细胞形成和炎症反应[27]。在药物靶点方面, 抑制NIK或增加p100均可抑制因炎症反应或转移性骨疾病引起的骨质流失。Jimi等[28]用抑制NEMO的肽抑制NF-κB信号通路后, 发现破骨细胞形成降低以及关节炎中骨质侵蚀减少。因此, NF-κB信号系统在破骨细胞形成过程中具有关键作用, 该信号系统可作为破骨细胞中的潜在药物靶点。

1.2.3 转化生长因子-β(transforming growth factor-beta, TGF-β) TGF-β是一种广泛分布于骨表面的细胞因子, 调节多种细胞生长和分化。TGF-β结合到两种不同类型的丝氨酸/苏氨酸激酶受体(I型和II型受体)。II型受体与相应配体结合后, 通过下游Smad家族信号蛋白引起I型受体的磷酸化。TGF-β对破骨细胞的形成具有双向调节作用。一方面, TGF-β直接与骨髓巨噬细胞作用并促进破骨细胞形成; 另一方面, TGF-β通过骨髓巨噬细胞周围的间充质细胞抑制破骨细胞形成[29]。最新研究表明, TGF-β可以通过Smad3和TRAF6这两个信号分子调节RANKL引起的破骨细胞形成[30]。

1.2.4 基质衍生因子SDF-1(stroma-derived factor-1, SDF-1) SDF-1是破骨细胞前体迁移至骨吸收单位的过程中的关键细胞因子。在破骨细胞成熟过程中, 位于血液循环中OCPs细胞迁移至骨吸收单位并完成活化, 这是破骨细胞成熟的重要环节。SDF-1(stroma-derived factor-1)可以调节白细胞的迁移, 并且其局部浓度可以决定白细胞的定位, 由此调节OCPs的形成。例如, 在由TNF介导的炎症性关节炎中, TNF抑制间质细胞产生SDF-1[31], 导致来源于骨髓的OCPs进入血循环, 引起外周血循环过程中OCPs的数量增多[32]。

1.2.5 酸性环境与破骨细胞形成的影响 酸性环境可以促进破骨细胞的形成, 尤其有利于形成体积巨大的破骨细胞[33-34]。研究发现, 酸性环境在破骨细胞分化过程中既发挥促进作用[35]。在pH不同的培养体系中, 研究人员将破骨细胞与1,25(OH)$_2$VD3和PGE2在胶原平板进行共培养, 发现破骨细胞在低pH条件下的数量和骨吸收能力明显高于其在生理状态下(pH7.4)的表现[34]。

1.2.6 鞘氨醇-1-磷酸(sphingosine-1 phosphate, S1P) S1P是一种可以调节破骨细胞形成的细胞因子。它是一种具有多种生物活性的鞘脂, 主要由红细胞内鞘氨醇激酶催化鞘氨醇产生, 可吸引OCPs进入血液循环。OCPs表达S1P受体(sphingosine-1 phosphate receptors, S1PRs)1和2, 信号通过这些受体可产生不同作用。例如, S1PR1信号吸引骨髓中的OCPs到血液, 而S1PR2信号使得OCPs返回到骨髓[36]。在临床药物方面, 专门针对于S1PR1而非 S1PR2的拮抗剂——FTY720可以阻止小鼠卵巢切除所诱发的骨吸收, 然而在*S1PR1*$^{-/-}$小鼠体内, 研究人员发现更多的OCPs被吸引到骨表面, 以增加OC的形成和骨吸收[36]。

1.2.7 蛋白激酶C(protein kinase C, PKC) 蛋白激酶C可以调节多种细胞的增殖、分化和存活。PKC家族具有十种异构体。其中, PKC-β具有两种异构体: PKC-βI和PKC-βII。在破骨细胞分化过程中, PKC-β的两种异构体的表达均上调。研究表明, PKC-β在调节破骨细胞分化过程中发挥关键作用, 它是通过参与RANKL和M-CSF引起的下游ERK信号通路发挥作用的[37-38]。

1.3 淋巴细胞对破骨细胞形成的作用

淋巴细胞对破骨细胞的形成也具有调控作用。随着骨免疫学的兴起, 研究人员逐步发现免疫细胞尤其是淋巴细胞也具有调控破骨细胞的作用[39]。研究发现, 除成骨细胞外, T、B淋巴细胞以及炎症性骨疾病中的滑膜细胞也表达RANKL, 并且RANK信号通路涉及免疫反应、淋巴结形成和B细胞成熟等过程[40-41]。在卵巢切除动物模型中, 发现破骨细胞具有抗原递呈细胞的功能, 可活化T细胞, 并表达FcRγ(Fc receptor common γ subunit)、MHC(major histocom-patibility complex)、CD40、CD80以及其他细胞因子。有趣的是, Grassi等[42]发现, 破骨细胞能抑制T细胞增殖并抑制T细胞产生TNF和IFNγ等细胞因子。由此可见, T、B淋巴细胞对破骨细胞的调节作用呈现出多重调节, 其详细机制尚待深入研究。

2 破骨细胞活化的调节

2.1 整合素对破骨细胞活化的影响

在破骨细胞活化过程中, 破骨细胞在暴露的骨

表面形成一个称为伪足小体的密闭区域, 继而发挥骨吸收作用[43-44]。在破骨细胞迁移并附着到骨表面的过程中, 整合素受体、αVβ3整合素[45]以及kindlin-3[46]都发挥了重要的作用。整合素是αβ跨膜异二聚体, 是识别细胞基质的主要分子。在整合素家族中, αVβ3在破骨细胞丰度较高, 且它可以介导破骨细胞的骨吸收功能[47]。此外, 研究发现人属*kindlin-3*基因突变和*kindlin-3*$^{-/-}$小鼠由于自身破骨细胞不能形成伪足小体[48]而发生骨硬化。此外, β3 *integrin*$^{-/-}$小鼠也可发生骨硬化[49]。由于以上步骤都可影响破骨细胞的活化过程, 因此所涉及的分子可望成为抑制破骨细胞的潜在靶点。

2.2 溶酶体在破骨细胞骨吸收中的作用

溶酶体在破骨细胞行驶骨吸收功能中的关键细胞器[50]。依其对破骨细胞骨吸收功能的影响进行分类, 溶酶体可以分为两类。第一类主要对骨吸收陷窝的酸化环境相关, 主中涉及的关键蛋白包括TCIRG1(T cell immune regulator 1)[51-52]、ATP6V0D2(ATPase, H^+ transporting, lysosomal V0 subunit D2)[53-54]、ATP6V1C1(ATPase, H^+ transporting, lysosomal V1 subunit C1)[55]、CLCN7(chloride channel, voltage-sensitive 7)[56-57]、OSTM1(osteopetrosis associated transmembrane protein 1)[58-61]。第二类主要调节细胞外基质, 其中的关键蛋白包括CTSK(cathepsin K)[62-63]、MMPs(matrix metallo-proteinases)[64-66]、TRAP(tartrate acid-resistant phosphatase)[67-69]。因此, 这些蛋白也可作为破骨细胞的潜在靶点。

2.3 Src蛋白对破骨细胞活化的影响

Src蛋白可以通过影响破骨细胞伪足小体的形成来调节其活化。Src属非受体酪氨酸激酶家族, 该家族成员可以以直接或间接方法结合到细胞表面受体(如RANK), 通过磷酸化相应信号蛋白介导相应信号通路。它参与破骨细胞活化过程, 同时也调节体外RANKL介导的破骨细胞生存信号通路。Src在多种肿瘤中存在高表达, 并且在肿瘤扩散、入侵以及新陈代谢方面有着正性调控作用, 被认为是骨代谢疾病中破骨细胞和肿瘤细胞的治疗靶点[70]。

2.4 破骨细胞相关基因突变对破骨细胞活化的影响

骨基质去矿化和溶解相关基因的突变是导致骨硬化的遗传因素。这些基因包括: 与质子生成相关并且能编码H^+ATP酶α3亚基的T细胞免疫调节子1(T-cell immune regulator 1, TCIRG1); 能催化CO_2形成H_2CO_3并提供H^+的碳酸酐酶II; 介导氯离子通过的ClCN7; 可编码连接小GTPase信号的小泡蛋白的普列克底物蛋白同源结构域M家族蛋白1, 以及组织蛋白酶K[9,71-72]。此外, 人类组织蛋白酶K的突变可引起软骨骨质化发育异常(亦称致密成骨不全症), 主要症状包括骨硬化、矮小以及颅面部骨骼的缺陷。

目前, 以这些靶点为基础的药物研发中, 破骨细胞的质子泵抑制剂和组织蛋白酶K抑制剂开展较多, 值得注意的是组织蛋白酶K抑制剂(奥达卡替)已进入治疗绝经后骨质疏松症的二期临床[73-74]。奥达卡替能抑制骨吸收, 但是与其他药物一样不能抑制骨形成, 其机制与破骨细胞刺激骨形成有关[75]。

2.5 骨保护素对破骨细胞活化的影响

骨保护素(osteoprotegerin, OPG)是骨吸收的主要负调节物[40,76]。它由成骨细胞和其他类型细胞分泌。OPG的N-端具有半胱氨酸富集区域, C-端可以形成二聚体, OPG与RANKL结合进而阻止RANKL诱导的破骨细胞成熟。值得注意的是, 这方面的代表药物狄诺塞麦已于2012年被FDA批准用于治疗骨质疏松[77]。在遗传突变方面, 编码OPG的TNFRSF11B基因功能缺失性突变可引起人类以及大多数青少年Paget's病[78], 这种突变可导致OPG缺乏、骨质疏松以及儿童长骨、脊椎骨畸形等[79]。

2.6 Ephrin/Eph和Semaphorin信号通路对破骨细胞活化的影响

Ephrins和Semaphorins是控制成骨细胞和破骨细胞间相互作用的关键蛋白分子[80-82]。采用mRNA芯片对前列腺癌[83]和巨细胞骨瘤[84]患者的骨进行分析后发现, EphrinA1和EphA1表达下调, 即溶骨性骨疾病中Ephrin-Eph信号传递降低。

Semaphorins是最近新发现的一个蛋白分子, 由于其对成骨细胞和破骨细胞独特的双向调节作用而吸引众多研究者的注意[85]。由成骨细胞和破骨细胞分泌的Sema3A与OCPs的Nrp1结合, 随后通过抑制ITAM和RhoA信号进而抑制RANKL介导的OC形成[86]。与此同时, 它也能结合到间充质前体的Nrp1上并通过Wnt/β-catenin信号通路促进成骨细胞的分化、抑制脂肪细胞的分化。相应的动物实验表明, Sema3A和*Nrp*$^{-/-}$小鼠患有骨质疏松症伴随着骨形成的降低。使用Sema3A处理正常小鼠, 发现其骨吸收被抑制, 骨形成增加, 并且皮质骨缺损模型小鼠的骨重建活动明细增强[86]。

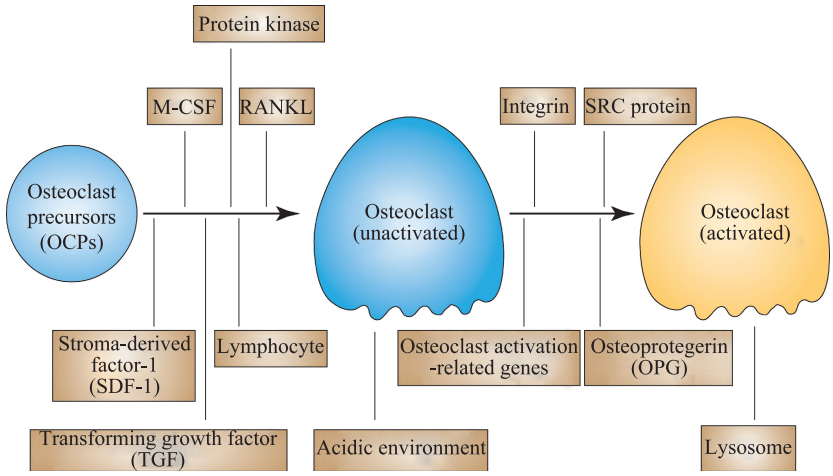

图1 破骨细胞形成和活化的调控

Fig.1 Schematic representation of the modulation of osteoclasts

进一步研究发现, 由破骨细胞和成骨细胞表达的Sema7A可诱导单核细胞产生自由基、IL-6和TNF, 说明Sema7A在炎性骨疾病中起着重要作用[82]。此外, 研究发现, Sema7A不仅促进了OC的形成, 并且增强OCPs的融合, 这些因素导致体外成骨细胞的迁移[87]。以上研究结果都为破骨细胞靶点研究提供了新的思路。

3 破骨细胞的凋亡

3.1 促进破骨细胞的凋亡

雌激素能上调破骨细胞Fas配体的表达进而诱导其凋亡[88]。而雌激素α受体信号的激活可在不影响破骨细胞前体的增殖和融合的情况下调节破骨相关标志基因的表达[89], 这表明雌激素有可能通过影响破骨细胞细胞周期和活性来抑制骨吸收[87]。

二膦酸盐是目前临床广泛用于治疗骨质疏松的药物, 其作用机制包括抑制甲羟戊酸途径中的酶活性从而诱导体内外破骨细胞凋亡[90-91]。但是也有部分研究表明, 二膦酸氨盐可能通过抑制骨吸收而非诱导破骨细胞凋亡发挥治疗作用[92]。值得注意的是, 二膦酸盐在风湿性关节炎患者体内只有轻微的抑制骨吸收活性。研究表明, 这可能与关节和血液中糖皮质激素以及高浓度TNF有关[92-93]。狄诺塞麦[94]和雷洛昔芬[95]可诱导破骨细胞凋亡, 而进入临床试验的其他抗骨吸收药物如降钙素、组织蛋白酶K抑制剂(奥达卡替)、ONO-5334却未发现此作用[75]。

3.2 抑制破骨细胞的凋亡

在破骨细胞前体分化至破骨细胞的过程中, RNAKL信号的早期作用是激活c-Jun氨基末端激酶信号(c-Jun N-erminal kinase, JNK), 后来发现它可以通过激活BH3相互作用域(BH3 interacting domain, Bid)和caspase 3通路, 导致NF-κB p65蛋白缺失的前破骨细胞凋亡[24], 这表明p65蛋白在防治破骨细胞凋亡方面具有重要调控作用。研究发现, 一些细胞因子如TNF、IL-1和血管内皮生长因子A(vascular endothelial growth factor A, VEGF-A)都在抑制破骨细胞凋亡方面发挥各自作用, 这表明以上细胞因子也可成为针对破骨细胞的潜在药物靶点[96-97]。

4 力学刺激对破骨细胞形成和活化的影响

力学刺激在调节骨骼重塑和维持骨量方面具有重要的作用。以往研究已证明, 力学刺激能促进成骨细胞骨形成和或抑制破骨细胞骨吸收[98], 去负荷大鼠的成骨活动减弱, 破骨活动明显增强, 而给予力刺激可有效改善后肢去负荷引起的骨丢失[99-100]。

作者所在实验室开展了关于力学刺激减少或消失对破骨细胞分化和成熟的影响。分别采用抗磁悬浮和随机定位回转培养模拟失重条件, 研究不同模拟失重条件下RANKL诱导破骨细胞分化成熟的变化, 发现模拟失重条件增强了前破骨细胞的增殖能力, 并促进其向成熟破骨细胞的分化[101-105]。这表明力学刺激减少或消失可促进破骨细胞的形成和活化[106-107]。

5 总结与展望

综上所述, 作为骨代谢系统中的关键细胞, 破

骨细胞的“形成”和“活化”这两个重要方面的机制研究进一步深化了我们对破骨细胞的认识(图1)。骨免疫学方面的研究提示, 破骨细胞参与骨免疫系统的调控, 而具有双重调节作用的Semaphorin等全新信号通路的发现及阐明均可望为骨代谢平衡的机制研究提供全新的视角[108]。尽管现在骨细胞在骨代谢系统的调控作用逐渐被人们发现并认识[109-113], 但破骨细胞对骨代谢系统的多重调节作用仍不容忽视, 尤其在以破骨细胞为靶点的治疗药物研发方面, 破骨细胞依然是未来的重点[87]。相信随着研究的深入, 尤其是骨免疫学[114-115]、Ephrin/Eph和Semaphorin等新型信号通路的深入研究, 可望为破骨细胞的生物机制提供新的思路, 并为以破骨细胞为靶点的药物研发提供新的方向。此外, 由于破骨细胞在骨重塑中的重要性, 破骨细胞会成为地面人群的骨质疏松以及航天员空间骨丢失机制研究的焦点。

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