[DOI]10.12016/j.issn.2096-1456.2023.07.011

·综述·

AMPK通路介导骨代谢相关细胞自噬调控牙周炎骨稳态的研究进展

李炎杰[1,2]，　刘旺[1,2]，　和红兵[1,2]
1. 昆明医科大学附属口腔医院牙周科，云南 昆明(650106)；　2. 云南省口腔医学重点实验室，云南 昆明(650106)

【摘要】 破骨细胞是体内唯一负责骨吸收的细胞，成骨细胞是体内负责骨再生的主要细胞，生理情况下，二者保持动态平衡，以维持骨稳态。过去普遍认为，骨代谢的失衡主要受相关炎症因子表达影响，但随着近年来相关研究的逐渐深入，发现自噬与破骨细胞、成骨细胞的分化、凋亡及功能关系密切。腺苷酸活化蛋白激酶(AMP-activated protein kinase，AMPK)是体内能量代谢的重要调节器，同时AMPK参与了调控骨代谢相关细胞的自噬及骨稳态。牙周炎是一种慢性感染性疾病，其典型的症状为牙槽骨吸收。目前在临床上如何更有效地控制牙周炎症水平及牙槽骨的吸收依然是个难题，未来针对AMPK及骨代谢相关细胞自噬水平的检测对于牙周炎的临床防治上具有一定前景。因此，本文就AMPK介导的骨代谢相关细胞自噬调控牙周炎症水平及骨稳态作一综述。

【关键词】 腺苷酸活化蛋白激酶；　破骨细胞；　成骨细胞；　牙周炎；　自噬；　骨代谢；　骨吸收；　骨再生；　分化；　凋亡
【中图分类号】 R78　【文献标志码】 A　【文章编号】 2096-1456(2023)07-0524-05
【引用著录格式】 李炎杰, 刘旺, 和红兵. AMPK通路介导骨代谢相关细胞自噬调控牙周炎骨稳态的研究进展[J]. 口腔疾病防治, 2023, 31(7): 524-528. doi:10.12016/j.issn.2096-1456.2023.07.011.

微信公众号

Research progress on an autophagy-mediating AMPK pathway involving bone metabolism-related cells that regulate bone homeostasis in periodontitis

LI Yanjie[1,2], LIU Wang[1,2], HE Hongbing[1,2]. 1. Department of Periodontics, Kunming Medical University School and Hospital of Stomatology, Kunming 650106, China; 2. Yunnan Key Laboratory of Stomatology, Kunming 650106, China
Corresponding authors: HE Hongbing, Email: 1320058043@qq.com, Tel: 86-871-653878622

【Abstract】 Osteoclasts are the only cells responsible for bone resorption in the body, and osteoblasts are the main cells responsible for bone regeneration in the body. Under physiological conditions, these cells maintain a dynamic balance to maintain bone homeostasis. It was widely believed that the imbalance of bone metabolism is mainly affected by the expression of related inflammatory factors. However, with the gradual expansion of related studies in recent years, autophagy has been shown to be closely related to the differentiation, apoptosis and functions of osteoclasts and osteoblasts. AMP-activated protein kinase (AMPK) is an important regulator of energy metabolism *in vivo* and is involved in the regulation of autophagy and bone homeostasis in bone metabolism-related cells. Periodontitis is a chronic infectious disease, and its typical symptoms are alveolar bone resorption. At present, controlling the level of periodontal inflammation and alveolar bone resorption more effectively in clinical practice remains a challenge. The detection of AMPK and autophagy levels in bone metabolism-related cells shows certain prospects for the clinical prevention and treatment of periodontitis in the future. Therefore, this article reviews the regulation of periodontal inflammation levels and bone homeostasis through cell autophagy related to AMPK-mediated bone metabolism.

【收稿日期】2022-08-28；　【修回日期】2022-10-08
【基金项目】云南省科技厅—昆明医科大学应用基础研究联合专项资金重点项目[2019FE001(-168)]；昆明医科大学研究生创新基金项目(2022S031)
【作者简介】李炎杰，硕士研究生，Email：liyanjiekq@163.com；共同第一作者，刘旺，硕士研究生，Email：838806731@qq.com
【通信作者】和红兵，教授，博士生导师，Email: 1320058043@qq.com，Tel：86-871-653878622

【Key words】 AMP-activated protein kinase; osteoclasts; osteoblasts; periodontitis; autophagy; bone metabolism; bone resorption; bone reconstruction; differentiation; apoptosis
J Prev Treat Stomatol Dis, 2023, 31(7): 524-528.
【Competing interests】 The authors declare no competing interests.
This study was supported by the grants from the Key Project of Applied Basic Research Joint Special Fund of Yunnan Provincial Science and Technology Department and Kunming Medical University[No. 2019FE001(-168)] and Graduate Innovation Fund of Kunming Medical University (No. 2022S031).

腺苷酸活化蛋白激酶(AMP-activated protein kinase,AMPK)是一种丝氨酸/苏氨酸激酶,在自噬调控中起着关键作用[1]。自噬(autophagy)是在自噬相关基因(autophagy-related gene,ATG)编码蛋白的调控下,细胞通过次级溶酶体对自身的细胞器、生物大分子等底物进行消化分解的现象,其与破骨细胞和成骨细胞的分化、凋亡及功能密切相关[2-3]。牙周炎的主要临床症状是附着丧失及牙槽骨的骨吸收[4-5]。近期有研究发现,AMPK参与牙周炎症、骨代谢相关细胞细胞自噬水平的调控。本文拟对AMPK介导的骨代谢相关细胞自噬调控牙周炎症水平及骨稳态作综述。

1　AMPK通路主要成员

AMPK通常以异源三聚体复合物出现,内含一个催化性α亚单位、调节性β和γ亚单位,可对体内ATP不足做出反应,在其被激活后,可对补充细胞ATP的信号通路做出正向调控,这些通路包括细胞自噬[6]。哺乳动物雷帕霉素靶蛋白mTOR位于AMPK下游,通常形成2个不同的复合体,即mTOR复合体1(mTOR complex 1, mTORC1)和mTOR复合体2(mTOR complex 2,mTORC2),其中mTORC1是一个包含mTOR、雷帕霉素调节相关蛋白(regulatory-associated protein of mTOR, Raptor)、哺乳动物致死蛋白sec-13蛋白8(mammalian lethal with sec-13 protein 8, mLST8)的多蛋白复合物,其对雷帕霉素的抑制敏感,对自噬起负调控作用[7]。ULK1为酵母Atg1的哺乳动物同源基因,是mTOR下游靶点,它通常与ATG13、FIP200和ATG101组成复合体,在自噬小体的启动过程中,发挥着重要作用[8]。研究发现,在体内外可通过激活AMPK/mTOR/ULK1信号通路而激活自噬,而抑制AMPK则对自噬流起负调节作用[9-10]。

2　自噬与牙周炎

自噬是在营养缺乏或其他因素刺激下,细胞通过次级溶酶体对体内某些生物分子进行消化降解的现象。通常根据胞内物质运送至溶酶体的途径不同将自噬分为3类:巨自噬(macroautophagy)、微自噬(microautophagy)和分子伴侣介导的自噬(chaperone-mediatedautophagy)[11]。由于巨自噬是对环境和生理信号作出反应的最主要的自噬方式,一般将巨自噬简称为“自噬”[12]。细胞自噬大致分为5个阶段:①启动;②自噬泡成核;③自噬小体扩张和底物选择;④自噬小体与溶酶体融合;⑤底物被降解[13]。Bullon等[14]首次描述了牙周炎患者中的自噬水平的显著激活,他们发现,与对照组相比,牙周炎患者外周血单个核细胞的自噬基因表达水平增加,两者之间存在显著的正相关。在非灵长类动物牙周炎模型中,通过基因芯片筛查对比牙周炎侧和健康侧的牙龈组织发现,牙周炎侧牙龈组织中的自噬早期基因ULK和晚期基因ATG12在牙周炎进展期(1~3个月)明显被激活[15]。An等[16]发现在牙周炎中,牙周膜干细胞(periodontal ligament stem cells,PDL)中的自噬水平高于正常组织,表现为LC3、Beclin-1、ATG7和ATG12蛋白水平较高,且自噬小体数量明显增多。

3　自噬参与调控破骨细胞、成骨细胞的分化与凋亡

近年来,越来越多的学者发现在破骨细胞的分化和成熟过程中,自噬作用增强,自噬活性与破骨细胞活性及存活率呈正相关[17-18]。破骨细胞主要由破骨前体细胞(osteoclast precursors,OCPs)分化而来,低浓度的白细胞介素-17A(interleukin-17A,IL-17A)可通过激活Beclin1从而上调自噬水平,抑制RAW264.7的凋亡,从而促进破骨细胞的形成[19]。自噬抑制剂3-甲基腺嘌呤(3-Methyladenine,3-MA)可抑制RAW264.7向破骨细胞分化减少牙槽骨吸收,而激活自噬则会促进其向破骨细胞分化,加剧牙槽骨吸收[20-21]。成骨细胞作为维持骨稳态的另一个重要的细胞,自噬在其分化和凋

亡过程中同样发挥着的重要的作用。研究发现自噬对于人类成骨细胞的存活和矿化是必不可少的，成骨细胞在分化过程中由于自噬减少而容易发生凋亡，而雌激素可通过上调成骨细胞在分化过程中的自噬，从而提高成骨细胞的存活及成骨矿化能力[22]。

4　AMPK参与调控自噬及牙周炎症水平

4.1　AMPK调节能量代谢及自噬

三磷酸腺苷（adenosine triphosphate，ATP）是生物体内最直接的能量来源，而AMPK是体内重要的能量调节器，AMPK主要通过减少合成脂肪基因和rRNA的转录、核糖体蛋白的翻译、胆固醇和脂肪酸的合成等ATP消耗过程来维持能量平衡，同时增加葡萄糖和脂肪运输、脂肪酸氧化、自噬、线粒体合成和氧化代谢等代谢途径，以在能量不足时保护ATP[23]。自噬是通过溶酶体分解细胞内外组分并将其在自噬泡中降解为简单的分子，例如单糖、脂肪酸和氨基酸，然后这些分子可以进一步用于通过分解代谢产生ATP或为必需蛋白质的合成提供条件，所以自噬同样也是维持能量稳态的重要机制[24]。AMPK是自噬重要的上游调控因子，其主要通过3条途径激活自噬从而调节能量代谢：①AMPK活化后，通过直接激活ULK1的Ser317和Ser777位点，ULK1进一步激活ATG14在Ser29位点的磷酸化，从而促进自噬小体的形成。而mTORC1则通过抑制ULK1的Ser757位点的磷酸化，从而阻止了AMPK对ULK1的激活[25]；②AMPK可通过抑制mTOR的活化来激活自噬[26]。AMPK激活后，通过结节性硬化症复合体1/2（tuberous sclerosis complex1/2，TSC1/2）-脑Ras同源蛋白（Rashomologen-richedin brain，Rheb）途径抑制mTOR，或者通过抑制雷帕霉素（Rapamycin，RAPA）来抑制mTORC1的磷酸化，从而激活自噬[27-28]；③AMPK还可通过直接磷酸化Beclin1和液泡蛋白分类34（Vps34）来激活自噬。

4.2　AMPK与牙周炎

体外促进AMPK的磷酸化，可抑制RAW264.7细胞中肿瘤坏死因子-α（tumr necrosis factor αlpha，TNF-α）、白细胞介素-6（interleukin-6，IL-6）和白细胞介素1β（interleukin-1 beta，IL-1β）等促炎细胞因子水平的显著下调。同时，在牙周炎小鼠模型中，激活AMPK信号通路可抑制炎症反应、炎症细胞浸润和促炎因子的分泌[29]。Li等[30]在体内研究发现光生物调节（photobiomodulation，PBM）通过激活AMPK信号通路，能显著改善牙周炎症水平，减少牙槽骨的骨吸收，同时促进牙槽骨修复。AMPK除了调控牙周炎本身，在牙周炎与系统性疾病相互作用机制中也发挥着重要的调控作用。Xing等[31]体内研究发现，与正常对照组相比，牙周炎大鼠的肝细胞中AMPK磷酸化水平明显下调，同时TNF-α、IL-1β等炎症因子的mRNA及肝组织中脂肪变性程度显著升高。AMPK还可通过调节氧化应激、炎症因子及自噬等方式在糖尿病及牙周炎的相关调控机制中发挥着关键的作用[32]。

5　AMPK通过调控骨代谢相关细胞自噬水平影响骨代谢

5.1　AMPK调控破骨细胞自噬及骨吸收

破骨细胞是体内唯一负责骨吸收的细胞，在多种转录因子、细胞因子的作用下先分化成OCP，再相互融合形成的多核巨细胞[33]。AMPK基因敲低后，小鼠牙周炎症及骨吸收更加明显[34]。然而，也有学者研究发现，AMPK信号通路参与了破骨细胞自噬的调控，抑制AMPK/mTOR/途径可下调破骨细胞的自噬水平，从而降低破骨细胞骨吸收功能[35]。Tong等[36]研究发现AMPK可通过能量代谢及自噬途径降低活化T细胞相关胞浆因子-1（nuclear factor of activated T cells-1，NFATc-1）的表达从而抑制RANKL诱导的破骨细胞的分化和及骨吸收功能。自噬抑制剂3-MA可通过升高p-AMPKα水平，降低p-mTOR水平，从而抑制RAW264.7的Beclin-1、ATG5蛋白水平和LC3-II/LC3-I比值，以及自噬小体的形成，同时降低破骨细胞的形成和骨吸收功能。而自噬激动剂RAPA则可逆转3-MA对RAW264.7的影响[37]。

5.2　AMPK调控成骨细胞自噬及骨重建

骨是一种动态组织，由成骨细胞形成，并在整个生命周期中被破骨细胞再吸收，生理情况下，破骨细胞和成骨细胞保持着的骨代谢的动态平衡，使骨骼结构适应最佳功能[38-39]。在体内成骨细胞主要由骨髓间充质干细胞分化（bone marrow mesenchymal stem cells，BMSCs）而来。近期有学者发现AMPK可通过增强BMSCs自噬水平抑制成骨细胞的凋亡，从而减少骨吸收，促进骨再生。AMPK-ULK1自噬轴在负压创伤治疗时可在体内外促进成骨细胞分化，从而促进骨再生[40]。Ran等[41]研究发现转化生长因子-β活化激酶1（TGF-β-activated

kinase1，TAK1）可激活AMPK，并通过磷酸化ULK1S317位点激活ULK1，抑制mTORC1，提高LC3-II脂质化及P62降解水平，相反敲除AMPK则阻断了成骨细胞的自噬流。二甲双胍是AMPK激动剂，聚多巴胺模板羟基磷灰石（polydopamine-templated hydroxyapatite，tHA）联合二甲双胍可显著降低活性氧（reactive oxygen species，ROS）产生和凋亡，促进成骨分化。在tHA和二甲双胍处理后LC3及Beclin-1水平升高，同时AMPK和磷酸化升高，mTOR磷酸化水平降低，成骨分化增强[42]。在体内大鼠牙周炎时，AMPK通路在二甲双胍碳点（metformin carbon dots，MCDs）处理时促进成骨分化，促进牙槽骨的骨再生[43]。

6　小结与展望

牙周炎是口腔疾病中的常见病和多发病，严重的可导致大量的牙槽骨吸收，牙松动移位甚至脱落。目前临床上对于牙周炎的治疗仍然以牙周基础治疗为主，必要时牙周手术治疗，以达到控制局部炎症，促进牙周组织再生的目的，然而效果并不太理想。近年来，大量研究已证明AMPK参与了牙周炎症水平的调控，并可通过调控骨代谢相关细胞的自噬水平从而调节牙槽骨代谢，未来针对AMPK及骨代谢相关细胞自噬水平的检测具有一定的临床应用潜力。目前AMPK作用于牙周炎中骨代谢相关细胞自噬的具体机制尚未完全阐明，有待进一步的研究。

【Author contributions】 Li YJ wrote the article. Liu W revised the article. He HB reviewed the article. All authors read and approved the final manuscript as submitted.

参考文献

[1] Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis[J]. Nat Rev Mol Cell Biol, 2018, 19(2): 121-135. doi: 10.1038/nrm.2017.95.

[2] Liu W, Zhou J, Niu F, et al. *Mycobacterium tuberculosis* infection increases the number of osteoclasts and inhibits osteoclast apoptosis by regulating TNF-α-mediated osteoclast autophagy[J]. Exp Ther Med, 2020, 20(3): 1889-1898. doi: 10.3892/etm.2020.8903.

[3] Xu R, Shi G, Xu L, et al. Simvastatin improves oral implant osseointegration via enhanced autophagy and osteogenesis of BMSCs and inhibited osteoclast activity[J]. J Tissue Eng Regen Med, 2018, 12(5): 1209-1219. doi: 10.1002/term.2652.

[4] Sun K, Shen H, Liu Y, et al. Assessment of alveolar bone and periodontal status in peritoneal dialysis patients[J]. Front Physiol, 2021, 12: 759056. doi: 10.3389/fphys.2021.759056.

[5] Delatola C, Loos BG, Laine ML. Three periodontitis phenotypes: bone loss patterns, antibiotic-surgical treatment and the new classification[J]. J Clin Periodontol, 2020, 47(11): 1371-1378. doi: 10.1111/jcpe.13356.

[6] Ha J, Guan KL, Kim J. AMPK and autophagy in glucose/glycogen metabolism[J]. Mol Aspects Med, 2015, 46: 46-62. doi: 10.1016/j.mam.2015.08.002.

[7] Al-Bari MAA, Xu P. Molecular regulation of autophagy machinery by mTOR-dependent and-independent pathways [J]. Ann NY Acad Sci, 2020, 1467(1): 3-20. doi: 10.1111/nyas.14305.

[8] Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation[J]. Essays Biochem, 2017, 61(6): 585-596. doi: 10.1042/EBC20170021.

[9] Wang F, Cao M, Fan M, et al. AMPK-mTOR-ULK1 axis activation-dependent autophagy promotes hydroxycamptothecin-induced apoptosis in human bladder cancer cells[J]. J Cell Physiol, 2020, 235(5): 4302-4315. doi: 10.1002/jcp.29307.

[10] Lin M, Hua R, Ma J, et al. Bisphenol A promotes autophagy in ovarian granulosa cells by inducing AMPK/mTOR/ULK1 signalling pathway [J]. Environ Int, 2021, 147: 106298. doi: 10.1016/j.envint.2020.106298.

[11] Mizushima N, Levine B. Autophagy in human diseases[J]. N Engl J Med, 2020, 383(16): 1564-1576. doi: 10.1056/nejmra2022774.

[12] Galluzzi L, Green DR. Autophagy-independent functions of the autophagy machinery[J]. Cell, 2019, 177(7): 1682-1699. doi: 10.1016/j.cell.2019.05.026.

[13] Mizushima N. The ATG conjugation systems in autophagy[J]. Curr Opin Cell Biol, 2020, 63: 1-10. doi: 10.1016/j.ceb.2019.12.001.

[14] Bullon P, Cordero MD, Quiles JL, et al. Autophagy in periodontitis patients and gingival fibroblasts: unraveling the link between chronic diseases and inflammation[J]. BMC Med, 2012, 10: 122. doi: 10.1186/1741-7015-10-122.

[15] Ebersole JL, Kirakodu SS, Gonzalez OA. Oral microbiome interactions with gingival gene expression patterns for apoptosis, autophagy and hypoxia pathways in progressing periodontitis[J]. Immunology, 2021, 162(4): 405-417. doi: 10.1111/imm.13292.

[16] An Y, Liu W, Xue P, et al. Increased autophagy is required to protect periodontal ligament stem cells from apoptosis in inflammatory microenvironment[J]. J Clin Periodontol, 2016, 43(7): 618-625. doi: 10.1111/jcpe.12549.

[17] Aoki S, Shimizu K, Ito K. Autophagy-dependent mitochondrial function regulates osteoclast differentiation and maturation[J]. Biochem Biophys Res Commun, 2020, 527(4): 874-880. doi: 10.1016/j.bbrc.2020.04.155.

[18] Song L, Tan J, Wang Z, et al. Interleukin-17A facilitates osteoclast differentiation and bone resorption via activation of autophagy in mouse bone marrow macrophages[J]. Mol Med Rep, 2019, 19(6): 4743-4752. doi: 10.3892/mmr.2019.10155.

[19] Xue Y, Liang Z, Fu X, et al. IL-17A modulates osteoclast precursors´ apoptosis through autophagy-TRAF3 signaling during osteoclastogenesis[J]. Biochem Biophys Res Commun, 2019, 508(4): 1088-1092. doi: 10.1016/j.bbrc.2018.12.029.

[20] He S, Zhou Q, Luo B, et al. Chloroquine and 3-methyladenine at-

tenuates periodontal inflammation and bone loss in experimental periodontitis[J]. Inflammation, 2020, 43(1): 220-230. doi: 10.1007/s10753-019-01111-0.

[21] Li J, Sun Z, Lin Y, et al. Syndecan 4 contributes to osteoclast differentiation induced by RANKL through enhancing autophagy [J]. Int Immunopharmacol, 2021, 91: 107275. doi: 10.1016/j.intimp.2020.107275.

[22] Gavali S, Gupta MK, Daswani B, et al. Estrogen enhances human osteoblast survival and function via promotion of autophagy[J]. Biochim Biophys Acta Mol Cell Res, 2019, 1866(9): 1498-1507. doi: 10.1016/j.bbamcr.2019.06.014.

[23] Ke R, Xu Q, Li C, et al. Mechanisms of AMPK in the maintenance of ATP balance during energy metabolism[J]. Cell Biol Int, 2018, 42(4): 384-392. doi: 10.1002/cbin.10915.

[24] Yang J, Zhou R, Ma Z. Autophagy and energy metabolism[J]. Adv Exp Med Biol, 2019, 1206: 329-357. doi: 10.1007/978-981-15-0602-4_16.

[25] Kim J, Kundu M, Viollet B, et al. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1[J]. Nat Cell Biol, 2011, 13(2): 132-141. doi: 10.1038/ncb2152.

[26] Jia J, Abudu YP, Claude-Taupin A, et al. Galectins control MTOR and AMPK in response to lysosomal damage to induce autophagy [J]. Autophagy, 2019, 15(1): 169-171. doi: 10.1080/15548627.2018.1505155.

[27] Alers S, Löffler AS, Wesselborg S, et al. Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks[J]. Mol Cell Biol, 2012, 32(1): 2-11. doi: 10.1128/MCB.06159-11.

[28] Suvorova II, Pospelov VA. AMPK/Ulk1-dependent autophagy as a key mTOR regulator in the context of cell pluripotency[J]. Cell Death Dis, 2019, 10(4): 260. doi: 10.1038/s41419-019-1501-9.

[29] Li H, Zhang P, Lin H, et al. ETC-1002 attenuates *Porphyromonas gingivalis* lipopolysaccharide-induced inflammation in RAW264.7 cells via the AMPK/NF-κB pathway and exerts ameliorative effects in experimental periodontitis in mice[J]. Dis Markers, 2022, 2022: 8583674. doi: 10.1155/2022/8583674.

[30] Li H, Sun T, Liu C, et al. Photobiomodulation (450 nm) alters the infection of periodontitis bacteria via the ROS/MAPK/mTOR signaling pathway [J]. Free Radic Biol Med, 2020, 152: 838-853. doi: 10.1016/j.freeradbiomed.2020.01.184.

[31] Xing T, Liu Y, Cheng H, et al. Ligature induced periodontitis in rats causes gut dysbiosis leading to hepatic injury through SCD1/AMPK signalling pathway[J]. Life Sci, 2022, 288: 120162. doi: 10.1016/j.lfs.2021.120162.

[32] Portes J, Bullón B, Quiles JL, et al. Diabetes mellitus and periodontitis share intracellular disorders as the main meeting point [J]. Cells, 2021, 10(9): 2411. doi: 10.3390/cells10092411.

[33] Park-Min KH. Metabolic reprogramming in osteoclasts[J]. Semin Immunopathol, 2019, 41(5): 565-572. doi: 10.1007/s00281-019-00757-0.

[34] Qin X, Hoda MN, Susin C, et al. Increased innate lymphoid cells in periodontal tissue of the murine model of periodontitis: the role of AMP-activated protein kinase and relevance for the human condition[J]. Front Immunol, 2017, 8: 922. doi: 10.3389/fimmu.2017.00922.

[35] Cai ZY, Yang B, Shi YX, et al. High glucose downregulates the effects of autophagy on osteoclastogenesis via the AMPK/mTOR/ULK1 pathway[J]. Biochem Biophys Res Commun, 2018, 503(2): 428-435. doi: 10.1016/j.bbrc.2018.04.052.

[36] Tong X, Ganta RR, Liu Z. AMP-activated protein kinase (AMPK) regulates autophagy, inflammation and immunity and contributes to osteoclast differentiation and functionabs[J]. Biol Cell, 2020, 112(9): 251-264. doi: 10.1111/boc.202000008.

[37] Zhang B, Luo C, Xiao W. Induction of osteoclast formation by LOX mutant (LOXG473A) through regulation of autophagy[J]. Ann Transl Med, 2021, 9(18): 1474. doi: 10.21037/atm-21-4474.

[38] Dirckx N, Moorer MC, Clemens TL, et al. The role of osteoblasts in energy homeostasis[J]. Nat Rev Endocrinol, 2019, 15(11): 651-665. doi: 10.1038/s41574-019-0246-y.

[39] Al Saedi A, Stupka N, Duque G. Pathogenesis of osteoporosis[J]. Handb Exp Pharmacol, 2020, 262: 353-367. doi: 10.1007/164_2020_358.

[40] Zhang S, Xie Y, Yan F, et al. Negative pressure wound therapy improves bone regeneration by promoting osteogenic differentiation via the AMPK-ULK1-autophagy axis[J]. Autophagy, 2022, 18(9): 2229-2245. doi: 10.1080/15548627.2021.2016231.

[41] Ran D, Ma Y, Liu W, et al. TGF-β-activated kinase 1 (TAK1) mediates cadmium-induced autophagy in osteoblasts via the AMPK/mTORC1/ULK1 pathway[J]. Toxicology, 2020, 442: 152538. doi: 10.1016/j.tox.2020.152538.

[42] Yang Z, Gao X, Zhou M, et al. Effect of metformin on human periodontal ligament stem cells cultured with polydopamine-templated hydroxyapatite[J]. Eur J Oral Sci, 2019, 127(3): 210-221. doi: 10.1111/eos.12616.

[43] Ren C, Hao X, Wang L, et al. Metformin carbon dots for promoting periodontal bone regeneration via activation of ERK/AMPK pathway[J]. Adv Healthc Mater, 2021, 10(12): e2100196. doi: 10.1002/adhm.202100196.

（编辑　周春华）

官网